THE THYROID

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To

IRLDA

my wife companion and co worker

in appreciation of her

tireless effort and constant encouragement

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PREFACE

Several scientific advances have joined hands to improve our knowledge of the thyroid The contributions of many investigators each using tools best suited to his individual interests and capacities have created a wealth of material which properly digested should shed much light upon hitherto little understood processes within the thyroid gland

The major effort in this volume has been directed toward (1) a summarization of the more important contributions of recent years to make them readily available to undergraduate student investigator and internist alike (2) an expression of viewpoint whenever justified and an indication of preference on questions legitimately in dispute (3) a rationalization of the chemistry and physiology of the thyroid readily comprehensible for the purposes of the busy internist and sufficiently documented for the needs of the investigator and the student and (4) an analysis of the diseases of the thyroid in the light of our newer understanding of its chemistry and physiology

The bibliography has been designed primarily to enable the student and the investigator to turn to source material Moreover it has afforded a comprehensive background for our summarizations deductions and conclusions

The historical aspects have been segregated the surgical approach has been separately and briefly presented Attempt has been made to divide the purely chemical and physiological aspects from the discussion of the diseased states

Histological photomicrographs and drawings are best viewed at source or under referenced material therefore they have been omitted here

The classification used in the section on diseases is essentially that employed for the past several years by the Thyroid Committee of the New York Medical College Effort has been made to include major points related to pathological physiology under each disease so that the busy practitioner will have ready access to the information he requires for routine work Details of the histological chemical and physiological background of each disease are available in the second section and reference is often made thereto under the corresponding malady There are not infrequently repetitions of fact and of viewpoint These

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were considered necessary to maintain continuity of thought in some instances and to stress unusually important facts in others

Thanks are due to Dr Irma J Boyd for his reading and constructive criticisms of the entire manuscript to Dr Rulon Rawson for his review of all sections concerned with a discussion of radioiodine to Dr Daniel McGinty for his review of the section on anatomical chemical and physiological considerations to Dr George W Anderson for his help in the classification of antithyroid compounds to Dr Leon S Loiseaux for his reading of the sections relating to pregnancy and the thyroid to Miss Dorothy B Spear and to my brother Henry for their perusal of the entire manuscript with a view to ensuring simplicity and clarity of arrangement and sentence structure to Miss Dorothy B Spear for much of the library work and proofreading to my wife Freda and my daughter Daphne Durant, for their painstaking efforts in arranging headings and subheadings and in typing and retyping the manuscript to Mr Christopher Tritsch for all line drawings

It is hoped the work will fill the need for a condensed but comprehensive presentation of the existing factual material through which has been furthered an understanding of the fascinating and busy role in bodily economy of that factory for the production of thyroid hormone the thyroid gland

THOMAS HOYER MCGAVACK

New York NY

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History

Dorothy B Spear
and
Thomas Hodge McGavack

Chapter I

GOITER EARLY HISTORY AND FOLKLORE

Had the sciences of embryology and comparative anatomy been developed to a high degree by primitive man the origin of the thyroid as an offshoot of the upper portion of the digestive tract might have been determined early in the evolution of biological knowledge This could have led logically to a recognition not only of a close relationship between it and the processes of digestion but also to its dominant role in regulating the utilization of the products of digestion by the whole organism Thus the gland would have been demonstrated as the factory for the production of a hormonal regulator of body metabolism long before clinical disturbances in its activity were described In sharp contrast had biochemistry become highly developed in this earliest era of man's habitation of the world a recognition of the more or less universal capacity of living cells to iodinate protein possessing hormonal properties might have retarded significantly any serious investigation of the thyroid gland as a major source of the hormonally active iodine needed for the regulation of the metabolic processes of all vertebrate forms of life

As a matter of fact not only the recognition of goiter but the realization that certain substances such as burnt sponge were useful in reducing its size or causing its disappearance preceded by thousands of years any knowledge of its origin and any known description of a thyroid gland These early records can scarcely be regarded as scientific however for in them goiter was considered only as a swelling of the neck evidencing the characteristics of an endemic disease Curiously enough the majority of early references to this condition especially its endemic aspects were general observations in natural history rather than contributions to medicine Similarly much of the later information which has contributed to our knowledge of the thyroid problem can be credited to the concerted efforts of representatives of many branches of science natural

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History

Dorothy B Spear
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Chapter I

GOITER EARLY HISTORY AND FOLKLORE

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historians explorers geographers and geologists as well as to those of the medical profession and its related sciences

It is little wonder therefore that enlargements in the cervical region were called goiter a term believed by many historians to be a corruption of the Latin *guttur* meaning throat The word appears to have been applied indiscriminately by early physicians to all swellings of the neck and not alone to enlargements of the thyroid gland Thus considerable confusion exists in the early literature as to the authenticity of the cases of goiter to which reference is made

It is difficult to state exactly when the earliest written reference to goiter was recorded but many historians give credit to the *Atharva Veda* a collection of Hindu religious practices written in India before 1500 B C In this work is found an incantation recited by priests of Buddha for the cure of goitrous patients Another ancient reference from India was the description in the *Ayurveda* of Sushruta (1400 B C) of a case of goitre attended with difficult respiration a softening of the whole body weakness a non relish for food loss of voice This same author seems to have described several types of goiter and may have distinguished simple colloid goiter toxic nodular goiter and cancer of the thyroid

Early Observations Relating Iodine and Goiter—The ancient Chinese centuries before Christ probably around 1600 B C appear to have recognized goiter and the ameliorative effects of burnt sponge and seaweed in its treatment The action undoubtedly depended upon the iodine each of these substances contained It is not without interest that the patient was advised to take one of these remedies at least twice yearly namely in the spring and fall times at which it is now known that the strain upon the thyroid gland is greatest Furthermore such a suggestion is peculiarly in line with that of Marine and Kimball (1917) in their early investigations into the measures necessary to prevent the appearance of endemic goiter They advised that school children be given a good sized dose of iodine two or three times each year Their studies proved that the thyroid was capable of picking up concentrating and storing this material for slow release in the form of thyroid hormone not necessarily utilizing all of the surplus supply for several months after administration The scientific background of the ancient Chinese practice has therefore been well established but there is nothing in extant fragmentary information obtained from this early period of Chinese medicine to indicate that the procedure was based on other than chance observation and empirical methods of prescribing Some 1 200 1 800 and 2 500 years later Hippocrates Galen and Roger of Salerno respectively recommended the same remedies with no critical references to the origin or rationale of their suggestions However the repeated occurrence of the recommendation throughout the centuries is obvious tribute to the fact that results were obtainable through its use Thus the connection of preparations containing iodine and diseased states of the thyroid was established nearly four millenia prior to the discovery of iodine and equally long before the origin of the cervical swelling was identified

Goiter and Ovarian Function—The first mention of changes in the size of the neck in relation to sexual activity are ascribed to the Romans who recognized an increase in the size of the neck in newlywed women in relation to defloration and pregnancy They were apparently not aware that this enlargement had any direct connection with alterations in the thyroid gland Meckel (1806) was probably the first person to describe systematically the physiological enlargements of the thyroid in relation to adolescence menstruation defloration and pregnancy However it is only within very recent years that experimental

and clinical data have been developed in such fashion as to show the really close association that exists between thyroidal and ovarian function (Chapter XIV)

Exophthalmic Goiter—While there are probably allusions to manifestations which arose as a result of hyperthyroidism in the works of Hippocrates and possibly of other older writers the first practical association of bulging eyes nervousness ready fatigability and general physical debility was made by early Roman physicians They noted that slaves with prominent eyes were usually unsatisfactory assets because the symptoms just mentioned were so commonly present in connection with them Such early observations were actually not referred to the thyroid until the communication of Parry in 1786 wherein he described six cases of hyperthyroidism three with diffuse and three with nodular swellings of the neck all had cardiovascular manifestations of rather severe degree

Endemic Goiter and Dwarfism—It is difficult to say when records of the first cretins were made for amidst the folklore of every race and creed dwarfs have been described without too much attention being paid to the details which should distinguish one type from another The simple mindedness of cretinous dwarfs made them unacceptable as court jesters so that the Romans of Caesar's day were careful never to select as a favorite a dwarf from the Alpine regions especially if an enlargement of the neck was apparent

Notations regarding the prevalence of endemic goiter in various parts of the world are as old as the recorded history of the area Perhaps most is known of the Alpine peoples with this type of cervical enlargement Julius Caesar commented upon the big neck of the Gauls and looked upon it as a tribal or national characteristic Juvenal and Pliny both noted the prevalence of goiter and from Juvenal's query Who wonders at a swoln throat in the Alps? it may be assumed that goiter was endemic in that area in the first century Goiter in this region is further emphasized by the always medically minded Shakespeare in lines from *The Tempest*

> Who would believe that there were mountaineers
> Dew lapped like bulls whose throats had hanging at them
> Wallets of flesh or that there were such men
> Whose heads stood in their breasts?

Medical literature of the Middle Ages contained very few references to goiter endemic or otherwise The disease regarded as a divine visitation was referred to in the *Lives of the Saints* it is related that in the seventh century the Bishop of Emebert hurled an anathema at the despoilers of the tomb of St Gudulce the curse being that their offspring should be crippled and the women goitrous

The prevalence of goiter and the early belief that it enhanced the beauty of women are evidenced by the numerous paintings of the old Dutch German and Italian masters many of which depict madonnas with an enlarged thyroid

Early Concepts Regarding the Etiology of Goiter—One of the earliest etiological theories appearing in folklore and ancient literature of many countries is that goiter is caused by noxa in the drinking water Another ancient concept attributed it to water coursing through limestone deposits dissolving the calcium and rendering the water goitrogenic a fact not entirely unsupported by more modern experimental evidence (see action of thyroid hormone on electrolyte balance Chapter XIII)

During his travels in China in 1271 Marco Polo described the people in Yarkand They are in general afflicted with tumors of the throat occasioned by

the nature of the water they drink Further proof of this belief is contained in a sonnet written by Michelangelo while he was painting the Sistine Chapel

> I've grown a goitre while living in this den
> As cast from stagnant streams in Lombardy
> Or in what other land they hap to be

Thus centuries ago the belief prevailed in countries where goiter was endemic that men and animals acquired the condition from drinking water which was contaminated with some substance capable of producing swellings in the neck

Hellenistic scribes considered goiter as a deformity attributed to the drinking of snow water a theory which held sway for several centuries Since the centers of endemic goiter known to early European writers were usually confined to mountainous districts it is not surprising that the belief in the goitrogenic properties of water from melting snow or ice was prevalent until it became known that goiter was common in Sumatra where snow is never seen while Eskimos who drink nothing but melted ice were free from the disease

In the early sixteenth century Paracelsus the brilliant Swiss physician albeit also alchemist attributed goiter to mineral impurities in the drinking water with particular reference to the sulfide of iron marchasita Another theory regarding the etiological role of water was advanced by Heister in 1768 who believed that the chilling of the throat while swallowing cold water was responsible for goiter

Atmospheric conditions were also blamed by many of the early writers Fodere in 1800 observed that in endemic regions goiter was rarely found on high ground or open plains but in deep narrow valleys where heat is concentrated and the damp fertile soil is planted with fruit trees The warm humid atmosphere was believed to cause a state of chronic relaxation of the thyroid which became dilated and atonic with eventual obliteration of its mucin ducts In support of this theory Fodere claimed that goiter increased in the spring with the growth of foliage and decreased in the autumn

Another theory of historical interest was advanced in the same year by Moseley in his description of Alpine bronchocele He believed that frigid blasts descending upon towns during the warm seasons caused goiter and that the best preventive therefore was protection of the neck and throat In a memoir on goiter in North America among the Oneida Indians of New York Barton (1800) expressed the belief that the miasmata of the marshes were the casual factor Other ideas have been advanced to explain the etiology of goiter among them oxygen deficiency variable climate and high content of carbon dioxide in the air

Coindet in 1820 offered two possible explanations of thyroid enlargement (1) drinking of hard water (2) physical strain particularly in women at parturition and in those who carry heavy loads on their heads A similar theory had been expressed by Girard (cited by Wilmer in 1779) that women's efforts to restrain cries during labor set up an extreme tension in the trachea resulting in an inflation of the thyroid with air which had been forced backward through connecting ducts

In 1867 Saint Lager arranged the theories regarding goitrogenesis into 42 categories of which he summarily dismissed as untenable those that were unrelated to the water supply The problem is far from settled today for McCarrison (1937) has recently observed that faulty diet certain chemicals unsanitary conditions and infections may all have a predetermining influence upon the appearance and severity of goitrous swellings However with the advent of accurate methods for appraising thyroidal function the dominant role of iodine

and iodine deficiency either relative or absolute in the production of sporadic and endemic goiters begins to assume a proper setting against a background of a large number of other contributing or precipitating factors such as food physical and mental stress mineral imbalances vitamin deficiencies infections and so forth Early in the last century the isolation and purification of iodine and the discovery of its presence in agents long recognized as useful in the treatment of goitrous necks rose like a sunburst of light upon the remarkable relationship which may exist between a gland of the body and mineral metabolism a sunburst which has continued to throw its radiant beams into the elucidation of thyroid function up to the present day

the nature of the water they drink Further proof of this belief is contained in a sonnet written by Michelangelo while he was painting the Sistine Chapel

> I've grown a goitre while living in this den
> As cast from stagnant streams in Lombardy
> Or in what other land they hap to be

Thus centuries ago the belief prevailed in countries where goiter was endemic that men and animals acquired the condition from drinking water which was contaminated with some substance capable of producing swellings in the neck

Hellenistic scribes considered goiter as a deformity attributed to the drinking of snow water a theory which held sway for several centuries Since the centers of endemic goiter known to early European writers were usually confined to mountainous districts it is not surprising that the belief in the goitrogenic properties of water from melting snow or ice was prevalent until it became known that goiter was common in Sumatra where snow is never seen while Eskimos who drink nothing but melted ice were free from the disease

In the early sixteenth century Paracelsus the brilliant Swiss physician albeit also alchemist attributed goiter to mineral impurities in the drinking water with particular reference to the sulfide of iron marchasita Another theory regarding the etiological role of water was advanced by Heister in 1768 who believed that the chilling of the throat while swallowing cold water was responsible for goiter

Atmospheric conditions were also blamed by many of the early writers Fodere in 1800 observed that in endemic regions goiter was rarely found on high ground or open plains but in deep narrow valleys where heat is concentrated and the damp fertile soil is planted with fruit trees The warm humid atmosphere was believed to cause a state of chronic relaxation of the thyroid which became dilated and atonic with eventual obliteration of its mucin ducts In support of this theory Fodere claimed that goiter increased in the spring with the growth of foliage and decreased in the autumn

Another theory of historical interest was advanced in the same year by Moseley in his description of Alpine bronchocele He believed that frigid blasts descending upon towns during the warm seasons caused goiter and that the best preventive therefore was protection of the neck and throat In a memoir on goiter in North America among the Oneida Indians of New York Barton (1800) expressed the belief that the miasmata of the marshes were the casual factor Other ideas have been advanced to explain the etiology of goiter among them oxygen deficiency variable climate and high content of carbon dioxide in the air

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The Identification of Iodine as the Active Principle in Goiter Remedies—Immediately following the discovery of iodine medical investigators observed that many substances which formerly had been found useful in the treatment of goiter (kelp sponges mineral springs sea water of salt marshes and marine animals) contained large amounts of the new element iodine These investigations marked the real beginning of the study of iodine in relation to goiter

Contrary to the general opinion of many writers of medical history iodine for the treatment of goiter was first introduced in England by Prout in 1816 After testing it upon himself in the form of hydriodate of potash to determine its toxicity he recommended its use to Elliotson of St Thomas's Hospital London where it was prescribed three years later Prout did not publish his findings however until 1834 by which time the attention of the medical world had already been drawn to the value of iodine in goiter by Coindet's work

In 1820 Coindet collaborating with Dumas a chemist successfully tested the hypothesis that iodine was the active principle of the time honored burnt sponge remedy thus establishing the relation of the curative properties of iodine to that of seaweed and burnt sponge Giving iodine as an alcoholic tincture 10 drops three times daily Coindet observed that large long standing goiters began to soften and decrease in size within 8 to 10 days with complete disappearance within 6 to 10 weeks in some cases While credit for the introduction of iodized salt is usually given to workers early in the present century actually its use was recommended for the prevention of goiter in 1833 by Boussingault

Early Observations on Iodine Hyperthyroidism and Other Toxic Actions Iodine in Disrepute—In his second memoir on iodine published later in 1820 Coindet recognized the dangers involved and emphasized the need for caution warning against overdosage or administering it to ill patients or to those who could not be seen by their physicians daily

Untoward effects were noted in certain types of cases within a year after Coindet's introduction of iodine as a therapeutic measure for goiter Anxiety depression emaciation tremor diarrhea and nervous excitement were observed In spite of these reactions and Coindet's warnings however his early successes were so dramatic that people even began to carry small bottles of iodine around their necks like amulets

The blunders of Coindet's overenthusiastic followers and advances in the technic of surgical removal of goiter which rendered the operation less formidable combined to create a prejudice against iodine Thus this therapy which had begun so promisingly fell into disrepute Simultaneously there started a controversy which lasted until the end of the century when the full relationship between iodine and goiter was definitely established

Development of Present Day Concepts Regarding the Use of Iodine in Goiter—Since 1910 there has been a gradual return to the older views regarding the use of iodine in goiter due in large measure to the rational application of the numerous physiological facts gained by and since Baumann's discovery (1896) of the normal presence of iodine in the thyroid gland In collaboration with Oswald he found least iodine in the hyperplastic goiter most in the normal gland and an intermediate amount in colloid goiter

Iodine in Hyperthyroidism—Iodine was not used extensively in the treatment of thyroid disease however until Plummer's important investigations in 1922 and 1923 He championed the theory that iodine diminished the hypersecretion of hyperthyroidism but that it did not affect an abnormal secretion which he believed also occurred in Graves disease At this time he clearly showed the advantage of supplementing surgical treatment with a preliminary course of therapy with iodine

Chapter II

IODINE AND GOITER

Early Experiences With Iodine Containing Substance—Several points already mentioned in the preceding chapter may be stressed as illustrative of the successful albeit empirical application of therapy long before a scientific basis can be established. We refer to the unwitting use of iodine in one form or another in the treatment of goiter from the earliest times. The beneficial effect on goiter of substances now known to contain iodine was apparently recognized by the Chinese centuries before Christ. Of these iodine containing substances burnt sponge was the most widely used. Galen and Pliny referred to this type of therapy and it was used extensively in the time of Hippocrates. Roger of Salerno at the end of the twelfth century noted that the administration of ground sponges and seaweed benefited some of his patients who were suffering from goiter.

That early settlers in this country recognized the value of sea salt for treatment of goiter long before the discovery of iodine is revealed in an interesting reference to its use in Mrs. Lucy Crawford's *History of the White Mountains*. Commenting on the frequency of swelling of the thyroid in Coos County, New Hampshire at the close of the seventeenth century she relates that her grandfather brought sea salt 80 miles over the mountains on his back a bushel at a time. The almost exclusive use of game meat together with a lack of salt was generally believed by these early New England settlers to be the cause of swelling of the thyroid. They recommended large quantities of sea salt the only salt available to them.

Burnt sponge was not adopted in England until the middle of the eighteenth century when it appeared in a curious manner as the Coventry treatment, a secret remedy in the possession of a family in Coventry. A full account of this treatment of Derby neck was given by Wilmer in 1779.

Fodere (1800) accepted burnt sponge as a true specific in the therapy of goiter. At this time it was evidently regarded as a valuable if empirical remedy for the disease, the only objection being its liability to cause gastric disturbances.

The Discovery of Iodine—During the British blockade of France in the Napoleonic Wars there was a serious shortage of nitrate for the manufacture of gunpowder. The difficulty was met by cultivation of niter beds in which saltpeter was formed and treated with wood ashes. In 1812 Courtois a manufacturer of saltpeter substituted burned seaweed for wood ashes to decompose the calcium nitrate. With this change he noted that his copper vats were constantly corroding and on investigation traced the cause to the mother liquor obtained after the nitrates had been removed by crystallization. This mother liquor when heated with sulfuric acid produced a vapor of a superb violet color. When brought to the attention of Gay Lussac he showed it to be a new element having close affinities with chlorine and named it iodine from the color of its vapor. The iodide in the seaweed ashes had been oxidized to iodine which then crystallized in the vats.

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Iodine in the Prophylactic Treatment of Goiter—The use of iodine in the prevention of goiter dates from 1830 when Prevost of Geneva argued that goiter was an iodine deficiency disease due to lack of iodine in the water supply Shortly afterwards Boussingault influenced by his observations in the Andes recommended the official use of iodine as a prophylactic measure Others soon followed—Chatin (1852) suggesting that water supplies in goitrous areas be enriched with iodine Koesli (1885) proposing the use of iodized salt in Austria and Lombroso (1859) recommending that all goitrous persons of marriageable age be treated with iodine as a means of preventing cretinism

Experimental justification for the use of iodine as a prophylactic measure was presented by Marine's demonstration in 1907 that 90 per cent of the dogs in the vicinity of Cleveland showed some degree of thyroid enlargement All stages of thyroid hyperplasia and hypertrophy were found in these animals as well as in other domestic animals of the same locality Hyperplasia became detectable in these animals as soon as the glandular iodine fell below normal and the amounts of stainable colloid varied inversely with the hyperplasia and directly with the iodine content In 1910 Marine and Lenhart demonstrated that the addition of 1 mg of iodine per liter of water successfully prevented the development of thyroid hyperplasia in brook trout

The first large scale attempt to prevent endemic goiter by means of iodine was initiated by Marine and Kimball in 1917 among schoolgirls of Akron The successful outcome of this experiment led to its repetition in Switzerland especially in Zurich where by the use of an organic iodine preparation the incidence of goiter among school children was reduced from 90 to 28 per cent

Two theories regarding the cause of goiter have emerged from the vast amount of work on the production of experimental goiter by Marine Gaylord Sasaki and others The iodine deficiency theory i e a deficiency of iodine in water soil and food and the infectious or toxic theory Marine expressed the beliefs of most American investigators in this field in 1921 when he stated The ultimate cause of simple goiter is totally unknown The immediate cause is lack of iodine Within the past decade as a result of the advent of radioactive isotopes and antithyroid compounds our knowledge not only of the physiology of the thyroid gland but also of the influence of extrinsic factors upon it has unfolded with amazing rapidity so that at least some of these ultimate causes can be accurately designated (Chapters XVI XVII and XXVIII) Except in endemic areas of goiter where iodine deficiency plays a highly dominant role not one but several intrinsic as well as extrinsic factors are probably concerned in the evolution of any given case of the disease Foods having antithyroid activity are the extrinsic substances most frequently involved Disproportionately great increases in the requirements of the body for thyroid hormone head the list of the intrinsically acting group

Chapter III

ANATOMY, PHYSIOLOGY, AND CHEMISTRY

Early Concepts Laryngeal and Tracheal Lubrication.—The early medical literature contained no significant references to the normal thyroid gland Inconspicuous in shape and position it escaped the notice of most of the early investigators and prior to Wharton's systematic study in 1656 only a few scattered references are known Galen's work in the second century contains a rather vague description of the gland His contribution however is noteworthy since he was the first to ascribe any function to the thyroid considering its secretion a lubricant to the larynx and laryngeal cartilages for the facilitation of speech

The first significant work on the normal thyroid gland after the time of Galen was performed late in the fifteenth century by da Vinci anatomist and painter His drawings based upon animal dissections show a bilobed structure attached to the upper part of the trachea The frequency of the incidence of goiter in the fifteenth century is reflected in da Vinci's paintings many of which depict goitrous subjects

In Book VI of his *Fabrica* (1543) Vesalius described two glands glandulas ad laryngis radicem adnatas one on each side of the root of the larynx large funguslike flesh colored and covered with numerous vessels He suggested that the purpose of these glands was to moisten the lumen of the trachea

Eustachius in 1552 referred to the thyroid as the glandula laryngea and represented it as situated high upon the trachea and having a thick isthmus with poles extending well upward toward the base of the tongue

The moisture theory of thyroid function was again propounded by Bohelius (1585) who believed that nature had provided the gland to supply moisture for the trachea and lungs when dried by constant respiration speaking or shouting

The idea that the thyroid was a lubricating organ was later elaborated by Morgagni in 1719 and by Boerhaave in 1720 This theory was accepted provisionally by von Haller and in 1751 he wrote (as translated by Harington) The gland is full of a serous yellowish and somewhat viscid humour but whether it emits the same into the wind pipe or gullet is not yet determined at least there are no ducts certainly known to open into either of them Yet that the use of this gland is very considerable may appear from the largeness of the arteries which it receives from the carotids and lower subclavians Haller's cautious attitude in regard to the supposed ducts connecting the thyroid and trachea was not shared by authors of the time He gave an excellent description of the gland including the first mention of the thyroidea ima artery

The External Secretion Theory Disproved.—Casserius (1600) was the first to describe the thyroid as a single gland and pictured it as an oblong body lying across the top of the trachea Finding no excretory duct he concluded that the gland's chief significance was to enhance women's beauty by filling out the sides of the neck It remained for Cruveilhier (about 1840) after many dissections of men and animals to establish the fact that there was no duct connected with the gland

Attention was first called to the minute structure of the thyroid by Lalouette (1750) who observed that the vesicles seemed to communicate with each other a view which was later shared by Cruveilhier and Virchow

Wharton's Contribution —The first systematic treatise dealing with the glands of the human body was that of Thomas Wharton in 1656 In his Adenographia the term thyroid was first applied as descriptive of the shape of the gland (Greek *thyreos* oblong shield and *eidos* form) Wharton did not clearly distinguish the thyroid from the submaxillary glands but gave an excellent description of its location size and weight He noted a number of important characteristics of the gland among them the rich blood supply and firmness His theories on thyroid function were far advanced for his day he believed that its main use was to receive certain superfluous humors by way of the recurrent laryngeal nerves and to conduct them anew into the veins by way of the lymphatics He also speculated that the heat of the rich blood supply of the thyroid warmed up the colder cartilages to which it is attached that the larynx was lubricated by its vapors thus rendering the voice smoother and that it served to enhance the beauty of the neck Of this last function Wharton stated They contribute much to the roundness and beauty of the neck by filling up the vacant spaces around the larynx and by rounding the protuberances into a level and even surface Especially is this the case in the females in whom the glands are larger on this account and whose necks are so beautifully rounded Although incorrect in his theory in regard to the conduction of humors into the veins he apparently realized that the thyroid contributes some substance to the blood and in this theory was prophetic of later findings

The Vascular Shunt Theory of Function —A new school of thought developed among later investigators who were dissatisfied with Wharton's lubrication theory and especially impressed with the enormous blood supply of the gland First to connect the vascularity with function was Schreger (1791) who theorized that the thyroid served as a vascular shunt to prevent too violent access of blood to the brain This hypothesis was supported by such distinguished physicians as Benjamin Rush who in 1806 stated The design of this gland I believe to be to defend the brain from the morbid effects of all those causes which determine the blood into it with unusual force Rush based his arguments on (1) the situation and structure of the gland (2) its greater size in women (3) the effect of violent effort in causing pain in a goitrous gland and (4) the effect of thyroid disease on the brain To Rush is given the credit for the beginning of our knowledge of thyroid function in this country

A similar theory was propounded by Parry in 1825 the thyroid gland of which no use whatever has hitherto been hinted at by physiologists is intended in part to serve as a diverticulum in order to avert from the brain a part of the blood which urged with too great force by various causes might disorder or destroy the functions of that important organ

Apparently independently of Rush's early work the vascular shunt theory was revived in 1864 by Liebermeister and in a slightly different form by Forneris in 1858 Liebermeister had observed several cases of syncope occurring in healthy subjects on suddenly arising from a prostrate position His explanation of this phenomenon was that the thyroid was relaxed in the position of rest failed to adjust itself with sufficient rapidity to change of posture and thus became distended with the blood which should have been conveyed to the brain

During a period of late night work Forneris observed that his neck became swollen when the desire for sleep was almost uncontrollable A similar swelling was noticed on awaking in the morning He concluded that the thyroid served

as a diverticulum for the excess of blood not required by the relatively anemic sleeping brain

Early Histological Evidence Pointing to the Internal Secretory Nature of the Thyroid—Morphological evidence of an internal secretion from the thyroid was first presented by King of Guy's Hospital in 1836 He demonstrated that some of the colloid of the thyroid passed into the lymphatics and thence into the blood stream He also saw and described for the first time the elementary units of the gland—the colloid filled follicles He noted the lobular arrangement of the gland and acini and a gummy translucent fluid with a higher albumin content than that of blood serum That he nearly approached the true function of the gland may be inferred from his statement The influence which it exerts upon the circulating fluids may be more or less needful for the healthful subsistence of the entire animal

Further Early Theories Concerning Function—The situation of the thyroid and its muscular attachments led Merkel in 1857 and Martyn in the same year to advance the theory that it might play a mechanical part in voice production According to Martyn the thyroid gave rigidity to the vocal apparatus at the same time acting as a fulcrum to give the muscles more effective mechanical action The precise degree of tension could be regulated with resulting modulation of the vocal tone by the liberal blood supply to the thyroid

In researches on the function of the thyroid and the effects of its removal Horsley in 1886 attributed two functions to the gland the control of mucin metabolism and hematopoiesis

It can be seen therefore that by the middle of the nineteenth century several theories of thyroid function existed each with a certain amount of circumstantial evidence in its favor but none of them carrying any general conviction Writing of the period between 1860 and 1870 Fuhr stated in 1886 that the majority of physiologists at this time maintained the belief that although the thyroid might be of possible importance during fetal life it performed no essential function whatever in the adult In spite of the many speculations indulged in during the surgeons early struggles for a means of relieving goiter very little of scientific value was accomplished relative to the chemistry and physiology of the thyroid until late in the century

Experimental and Clinical Observations Which Led to the Discovery of the True Nature of Thyroidal Function—Descriptions of a cretinoid condition in middle aged women by Gull and Ord followed by the observations of Kocher the Reverdins and Schiff on a myxedema like syndrome following complete thyroidectomy were important milestones in the modern knowledge of thyroid function Results of total thyroidectomies in animals suggested to Schiff that the thyroid must be responsible for elaborating some substance which passed into the blood and served as an essential intermediate in the nutrition of the nervous centers Schiff's experiments (1859) finally received confirmation in the human being when Murray (1891) demonstrated that the parenteral administration of a glycerin emulsion of sheep's thyroid was satisfactory replacement therapy for subjects suffering from myxedema

The earliest observations that the thyroid affects the rate of metabolism were made by Hadden (1882) who noticed that in myxedema there was a diminution in excretion of urea which changed to an increase on injection or oral administration of thyroid Muller (1893) offered the first satisfactory explanation for the abnormal appetite in exophthalmic goiter In one of his patients he observed an increased rate of protein metabolism and concluded that thyroid hormone speeds the burning up or oxidation of food in the body thus increasing the rate of metabolism

Muller's theory was soon confirmed by Magnus Levy (1895) who influenced by Hadden's investigations observed that thyroid feeding materially raises the basal rate of oxygen consumption He further showed that the basal rate is notably elevated in hyperthyroidism and markedly depressed in *myxedema* The outcome of Magnus Levy's findings was the conception supported by all subsequent work that the thyroid's essential function is to maintain the general metabolic rate of the body at its proper level by the production of the necessary amount of a specific secretion or hormone

This knowledge with regard to metabolic activity was not put into general use until Benedict in 1918 developed a practical apparatus for measurement of gas exchange Methods of measuring the metabolic rate were perfected by Benedict Dubois and Lusk

Until it was demonstrated that the thyroid plays an essential part in the normal processes of the body no serious investigations of its chemistry were undertaken Earlier investigators had merely isolated a few of the more common extractives of no particular significance Almost simultaneously with the work of the Swiss surgeons who proved the essential nature of the gland Bubnow (1893) made a systematic biochemical study He confirmed the findings of previous observers as to the occurrence of xanthine creatinine and other substances but turned his attention particularly to the proteins of the gland believing that the so called colloid was protein in nature and a biochemically significant constituent He succeeded in isolating and analyzing three distinct proteins thyreoproteins and emphasized the fact that none could be regarded as mucin

The presence of iodine in the thyroid had been suggested by Kocher in 1893 and was confirmed in 1896 by Baumann who discovered large amounts of iodine combined with organic substances chiefly globulin which he called iodothyrin later thyroiodine His preparation iodothyrin was proved to have a physiological action similar to that of dried thyroid gland but much more powerful Administration of this substance to obese patients produced evidence of accelerated metabolism increased output of urea and loss of weight It was then demonstrated that all of the iodine in the gland was to be found in a protein fraction and was readily extractable Basing his line of reasoning on this experimental work Baumann then observed that persons living in goitrous areas were deficient in iodine and that the physiological action of the gland was due to a substance an important constituent of which was iodine

Baumann's investigations were soon followed by Oswald's careful study of the protein moieties of the gland (1899) He noted that goiters in which the increased size was due to cellular hyperplasia and in which the colloid was reduced as in Graves disease were almost iodine free On the other hand colloid goiter in which the follicles were distended with colloid contained large quantities of iodine From these studies it was demonstrated that the total iodine content of the thyroid increased directly in proportion to the amount of colloid in the follicles

The next important contribution in this field was Marine's demonstration in 1907 that iodine is essential for normal functioning of the thyroid

These early studies on the chemistry of the gland prompted the extensive biochemical investigations which led to Kendall's epoch making discovery of thyroxin in 1915 and to its subsequent synthesis by Harington and Barger in 1927 Kendall isolated in crystalline form from the thyroid a compound thyroxin containing 60 per cent iodine and apparently having the full physiological activity of the whole gland (Chapter IX) He thus provided the final and long sought after proof of the essential role of iodine in thyroid function

Chapter IV

HYPOTHYROIDISM

I CRETINISM

Definition—The name cretinism is so old that many theories have been offered as to its derivation According to one theory it is a twisted form of the French chretien or the Swiss patois crestin or cretin referring to imbeciles regarded as Christian and innocent creatures although physically and mentally deformed There is little support for this interpretation however A much sounder theory arises from the gravish white pasty complexion characteristic of this condition with the name linked to words meaning chalk the French craie German Kreide and the Latin creta Others have associated the expression simply with the word creature with the Austrian Swiss Kreidling and the Rhaeto Romanic cret meaning dwarf

The use of the term apparently dates to Felix Platter's work in 1614 although the *Oxford Dictionary* gives William Coxe credit for the first use of the English word cretin in 1779 Platter's short description of cretins referred to the deaf and dumb dwarfish and mentally deficient individuals so frequently observed in the Canton of Vallais Platter's original account in 1602 while not containing the term cretin is a classical description translated by Mettler and quoted in part as follows Many infants are often affected in addition to their innate simple mindedness the head is sometimes malformed the tongue is large and swollen they are dumb frequently have a struma at the throat and display a deformed appearance

Early Notes on the Association of Cretinism and Goiter—The first suggestion of a causal connection between cretinism and goiter is attributed to Paracelsus a discovery based upon his personal observations in the Salzburg region and published posthumously in 1603 This relationship was clearly recognized by Fodere (1800) and de Saussure (1804) However it was not until the middle of the nineteenth century that the nature of this relationship was fully established Fodere had observed that goitrous women although intelligent frequently gave birth to cretins but he did not understand the implication possibly due to the fact that conspicuous goiters are not usually present in cretins Goitrous himself he pointed out that goiter is the first degree of a degenerative process in which the last step is cretinism

Many writers described the clinical picture of cretinism and noticed its coincidence with endemic goiter especially in the Alpine countries A high incidence of undoubted cretinism in a goitrous village of Somersetshire was reported in 1848 by Norris He too expressed the belief that the cause of cretinism in addition to the accompanying goiter was a combination of circumstances among them intermarriage inferior water and impure air All of the cretins he described had goiters as indeed did the majority of the noncretinous inhabitants of the village

Early Investigations Into the Causes of Cretinism—A growing awareness of the prevalence of cretinism is suggested by the commissioning of Ipohofen by the Saxon government (1808) to investigate the question of cretinism His findings reported it to be "an imperfect development of the human body due to a deficiency of vital power and its predisposing cause in the electrical state of the atmosphere

A commission appointed by the French government attributed the development chiefly to the heat produced by rays of the burning sun concentrated and reflected by the rocks which enclose the narrow Alpine valleys They also mentioned as contributing factors the influence of the winds use of lime charged water indolence of the inhabitants lack of education unhealthy dwellings bad food drunkenness and debauchery In an early account of the disease (1657) Hofer had attributed it to faulty diet and mode of living

Early Attempts at Treating Cretinism—Numerous attempts were made to improve the fate of the victims of cretinism by a change in environment Napoleon in 1811 introduced dictatorial health measures by taking a census of cretins in the Canton of Wallis His attempt to transplant the goitrous population to healthier sections was defeated by the desire of the people to remain in their own homes

The first and most persistent attempt to improve the life of cretins is attributed to a Swiss physician Guggenbuhl in 1835 whose publications attracted world wide attention

During the period from 1850 to 1852 Chatin tried unsuccessfully to introduce the use of iodine for prophylaxis of goiter but in spite of his extensive investigations and remarkably accurate observations he failed to arouse the interest of the medical world

The Recognition of Sporadic Cretinism and Its Close Relationship to Endemic Forms of the Disease—In 1850 an English pathologist Curling established for the first time the fact that absence of thyroid tissue was the cause of a peculiar condition similar to endemic cretinism In a report to the Royal Medical and Chirurgical Society of London he described two cases of sporadic cretinism—a term which he originated to distinguish the condition from the endemic type Both subjects showed the typical characteristics of cretinism including swellings at the outer sides of the neck Autopsy examination revealed that these swellings were fatty and no trace of the thyroid gland could be found in either case

Although a scientific basis for an understanding of the growth deficiency was laid by Virchow's pathological studies of cretinism in the middle of the nineteenth century it did not become a well established morbid entity until the key position of the thyroid was discovered

One of the most outstanding contributions to the development of our knowledge of hypothyroidism was that of Fagge of Guy's Hospital in London In a report (1871) of four cases of sporadic cretinism he noted the similarity of this disease to endemic cretinism except for the constant absence of goiter He also observed the fat pads above the clavicles which he described as soft movable inelastic swellings apparently connected with the subcutaneous tissues Such he believed to be a common characteristic of sporadic cretinism which was not present in common idiots

The essential characteristics of sporadic cretinism as described by Curling and Fagge were "body stunted head round face broad eyes widely separated by a flat nose alae nasi thick nostrils round mouth large and usually open lips thick hands and feet short and broad" In the congenital form there was a deficiency in mental powers in the endemic form goiter in the sporadic type a wasting or absence of the thyroid The latter type might occur in offspring of normal parents

Fagge considered that sporadic cretinism always showed the presence of fatty tumors and the absence of or a small thyroid Furthermore he thought it could be distinguished from the endemic form by the absence of symptoms until after the period of infancy Yet he recognized in his experience with one child who had been normal until eight years old that the condition can be acquired This case led him to speculate as to the character of the disease should it arise in adult life—a prophetic recognition of myxedema Without ever seeing a case he gave a good description of adult myxedema the coarseness and thickness of the soft parts of the face especially of the lips and possibly of the subcutaneous tissues of the hands and feet supraclavicular fatty tumors and possibly a wasting of the thyroid body

Experimental production of cretinism was first approximated by Halsted in 1896 when he found that puppies born of partially thyroidectomized mothers possessed thyroid glands which showed a high degree of hyperplasia

II ADULT MYXEDEMA

Sir William Gull physician to Queen Victoria first described in 1873 the condition now known as myxedema This short paper marked the real beginning of our modern knowledge of thyroid function although the full significance of the contribution was not appreciated at the time Gull fulfilled Fagge's prophecy by describing two cases of a cretinoid condition in middle aged women characterized mainly by a progressive change in the appearance of the features which became coarse and thick by a spadelike appearance of the hands and by mental retardation He observed that the thyroid glands of these patients were not enlarged but his communication added nothing further to our knowledge of the pathology of the condition

Four years later Ord reporting on the same condition observed that you will find little or no trace of a thyroid body and a decided resilient fulness on both sides of the neck above the clavicles Ord agreed with Gull as to the essentially cretinoid nature of the affection He was particularly impressed by the jellylike swelling of subcutaneous tissue which he believed to be due to an accumulation of mucin and which led to his proposal of the term myxoedema to describe the condition The symptoms were ascribed to padding of the peripheral nerve endings by the mucin with consequent suppression or diminution of sensory stimuli This led to retrogression of nervous and mental faculties in the adult form of the disease and to failure of development of these faculties in the congenital form of cretinism Ord's greatest contribution to the knowledge of myxedema was the report of the postmortem examination of one of his patients the first demonstration of the association of myxedema with atrophic changes in the thyroid The thyroid was revealed as profoundly abnormal the alveoli were obliterated rather than being filled with colloid and the normal glandular epithelium was replaced by an overgrowth of fibrous tissue

Until 1880 when Savage reported a case of myxedema in a male patient this disease like other affections of the thyroid gland which were regarded as occurring far more commonly in females was believed to be confined entirely to women

The valuable report of the London Myxoedema Commission (1888) headed by Gull and Ord summarizes well the early history of myxedema There is strong evidence that myxoedema sporadic cretinism endemic cretinism cachexia strumipriva and the operative myxoedema of animals are species of one genus and that the one pathological fact common to all these conditions is the occurrence of morbid processes involving destruction of the thyroid gland

III THYROID REPLACEMENT THERAPY

Although the employment of thyroid replacement therapy did not come into general use until the end of the nineteenth century preparations of sheep thyroid as soup are believed to have been known to the Chinese 4 000 years ago and Pinsuti in 1800 proposed the administration of thyroid juice

That symptoms of cachexia thyropriva could be prevented by a previous graft of thyroid substance or by hypodermic or oral administration of thyroid was demonstrated by Schiff whose data were summarized in 1884 These epoch making experiments over a twenty eight year period gave him the distinction of being a pioneer in the doctrine of internal secretions and a prophet in the future use of thyroid therapy Thus with this new information the dwarfish imbeciles afflicted with thyroid deficiency were given hope of a normal status in life

In the next few years rapid strides were made in the field of substitution therapy Bircher (1889) grafted a piece of human thyroid into the abdominal wall of a patient with temporary benefit Relief of symptoms by the graft of half a sheep's thyroid under each breast was reported by Bettencourt and Serrano (1890) Experimentally Vassale (1891) found that the intravenous injection of an extract of their own thyroid glands into dogs prevented cachexia strumipriva

Reports of the beneficial effects in thyroidectomized animals of thyroid grafts encouraged Murray a pupil of Horsley to inject subcutaneously a glycerol extract from sheep thyroid into a woman with myxedema (1891) Startling results were observed The death of this woman at the age of 71 was recorded by Murray in 1920 For nearly 30 years she had remained in excellent condition with daily injections of this thyroid preparation proving conclusively that myxedema was due to a deficiency of thyroid secretion

In the same issue of the *British Medical Journal* in which Murray's original article appeared Fenwick also reported the subcutaneous administration of thyroid juice in a case of myxedema Marked diuresis occurred in this patient however and Fenwick did not recommend further employment of this method of therapy

The remarkable success of thyroid therapy in Murray's patient attracted considerable attention from the medical profession The importance of his observations was fully realized when Fox and Mackenzie independently demonstrated a year later that the oral administration of thyroid gave equally good results Both observed symptoms of hyperthyroidism when dosages were too large Fox cooked his preparation without any apparent loss in its activity These successful results of Schiff Murray and others removed any possible doubt as to the fundamental significance of the function of the thyroid gland

Accounts of successful thyroid treatment of myxedema in the next few years appeared frequently in the medical literature The majority of workers adopted the convenient method of oral administration of the fresh or lightly cooked gland A few however adhered to Murray's method of injecting thyroid extract subcutaneously In 1923 Albert Kocher revived the thyroid graft treatment insisting upon the importance of keeping the patient under the influence of thyroid extract both before and after the transplantation Otherwise the graft was simply eaten up by the subthyroid patient In a number of his cases the graft apparently was active for many years According to Kocher the patient's own thyroid became active as a result of the treatment and cure ensued in most cases

At the present time the desiccated thyroid gland of sheep represents the most commonly employed medicament for the control of hypothyroidism and

is highly effective when given by mouth It is possible that it may be replaced shortly by artificially iodinated proteins of high potency which are also effective when taken per os Thus myxedema has become the first of the endocrine diseases to be successfully treated by a substitution therapy which can be easily and effectively administered by way of the gastrointestinal tract

Chapter V

HYPERTHYROIDISM

As early as A D 100 the Romans recognized exophthalmos a symptom of toxic goiter as an indication of impaired health Experience had taught them that any slave with this affliction tired easily and was worthless as a servant Consequently any contract for *buying or* selling slaves was *invalidated* when ever exophthalmos was detected The first intimation of any recognition of a logical relationship between goiter and palpitation as evidences of Graves dis ease appears to have been offered by Richard Wiseman physician to Charles II in 1668 No written account of exophthalmic goiter however is known to have been made until 1802 when Flajani described two cases Despite his accurate descriptions Flajani did not associate the dyspnea extraordinary pal pitation emaciation and goiter he observed as integral manifestations of a single disease entity

Recognition of Hyperthyroidism as a Di ea e Entity—Caleb Parry preceded Fla jani s publication by observing a case in 1786 but his report was published posthumously in 1825 His description is clearer and more complete than *that of Flajani In his case the following symptoms and signs were observed* palpitation especially during exercise increased force and frequency of the heart beat irregular pulse nocturnal attacks of dyspnea and constriction in the chest with spitting of a small amount of blood violent pain beneath the sternum large bilateral swelling of the thyroid distention of the carotids and exophthalmos Although impressed with the possible relationship between the violent heart action and goiter Parry did not establish an association between the cardiac condition and bronchocele until 1813 twenty seven years after describing his first case of this condition However in his *Elements of Pathology and Therapeutics* he mentioned the frequent coincidence whether as cause or ef fect between enlargement of the thyroid and cardiac disease

No further accounts of exophthalmic goiter appeared until those of Graves in 1835 and of von Basedow in 1840 The four cases reported by the latter were *described in considerably more detail than were those of his predecessors* The coincidence of affections of the heart and enlargement of the thyroid chiefly impressed Parry and Graves and each cited a case in which exophthalmos was also present Like Wharton Graves recognized the extreme vascularity of the *thyroid and believed that the heart action* was purely functional In his 1835 lecture Graves described three cases of violent and long continued palpitations in females in each of which the same peculiarity presented itself viz enlarge ment of the thyroid gland The well known connexion which exists be tween the uterine functions of the female and the development of the thyroid observed at puberty renders this affection worthy of attention particularly *when we find it* closely related by sympathy to those palpitations of the heart *which are of so* frequent occurrence in hysterical and nervous females

The increased sweating asthenia wasting sensation of warmth increased appetite and all the other classic symptoms except tremor were *mentioned for*

the first time in Basedow's report. His four cases exhibited what has been known ever since as the Merseburg triad, i.e. exophthalmos, goiter and palpitation. He also observed diarrhea and nervousness as additional symptoms. So complete was his description of the disease that little has been added since. The use of mineral waters containing iodide and bromide of sodium was recommended by Basedow for the therapy of the disease.

Elaboration and Attempted Clarification of the Hyperthyroid Syndrome.—The period from 1802 to 1840 has been designated by Means and Richardson as the period of discovery, the first of the three periods in the history of exophthalmic goiter described by these authors. The second period, 1841 to 1886, is characterized as one of further description and interpretation, much of it erroneous. During this period the French school (Charcot, 1856 to 1889; Trousseau, 1867; Marie, 1883) emphasized particularly the nervous symptoms, regarding the whole syndrome as one of nervous origin, either a type of hysteria or associated with a definite but undetermined nervous lesion. Enlargement of the thyroid was considered merely as a secondary phenomenon. Marie however pointed out that an affection of the vegetative nervous system alone was insufficient to account for all of the manifestations and preferred to regard it as a neurosis of the entire nervous system.

The incomplete or fruste forms of Flajani's disease were described by Trousseau in 1860. The term fruste was originally applied by coiners to defective coins or medals, and Trousseau compared a case of the disease commonly characterized by exophthalmic goiter but without goiter or exophthalmos to a defaced coin lacking some of the necessary marks for recognition. He made a distinction between the rudimentary cases in which signs had not developed and the formes frustes in which one or more of the chief signs were effaced.

An important contribution in the study of exophthalmic goiter was made during this period in Stokes' (1854) recognition of four outstanding features of the disease: (1) increased force and rapidity of the action of the heart without fever and of long continuance; (2) excited action of the carotid and thyroid arteries; (3) enlargement of the thyroid varying with the force of the heart; and (4) enlargement of the eyeballs without any disease of the orbits or brain.

An attempt to produce exophthalmic goiter experimentally was made by Filehne in 1879. Believing that the manifestations of the disease suggested an abnormality of the sympathetic nervous system, he theorized that the cause must lie either in the peripheral ganglia or in the brain. By incising or cauterizing the upper quarter of the inner portion of the corpora restiforma in rabbits he claimed that signs of Basedow's disease were produced. Tachycardia and exophthalmos were usually present, occasionally goiter, but all three were never produced successfully in the same animal. He believed that all changes were either vagus or vasomotor in origin and attributed the exophthalmos to engorgement of the vessels at the back of the orbit, the goiter to engorgement of the thyroid.

The view that the sympathetic system plays at least an important role in the production of exophthalmic goiter was supported in 1914 by Cannon's experiments in which fusion of the phrenic and cervical sympathetic nerves in cats was followed by tachycardia, emaciation, irritability, increased sweating, elevated metabolism and in one case unilateral exophthalmos.

By 1880 over 270 communications on the subject had appeared and were comprehensively reviewed by Sattler. The numerous symptoms described in these early publications however served rather to confuse the picture than otherwise.

The next important advance in the study of this disease was the recognition by Marie in 1893 and confirmed by Charcot in 1885 that tremor is a constant *sign in exophthalmic goiter* Added to the Merseburg triad this sign is often considered the fourth cardinal manifestation of the disease Several other symptoms now well known were also stressed by Marie—the urinary manifestations paroxysmal diarrhea increased perspiration insatiable appetite angina pectoris tachycardia nonproductive cough and skin manifestations Charcot agreed with Marie in general but claimed that the tremor differed from all others seen in neuropathology

The second period in this phase of the history of the *thyroid ended in* 1886 with Moebius description of one of the important signs—an insufficiency of convergence known as the Moebius sign Another significant sign the so called lid lag a stationary condition of the upper eyelid when the eyeball *is rolled up or down had been described by von Graefe in 1864*

Recognition of the Role of Thyroid Over ecretion in the Genesis of Hyperthyroidism The third period in the history of hyperthyroidism was marked by the development *of the thyrotoxic theory of the disease That an excess secretion* of the thyroid might be the cause of Graves disease was suggested by Rehn in 1884 This was followed in 1886 by Horsley s theory that the thyroid body is affected first in exophthalmic goiter and that all symptoms can be explained *by an altered function or dysthyroidism*

In the same year Moebius expressed the definite view that pathologic alteration in the thyroid was the primary factor in the causation of exophthalmic goiter He disagreed with the French theories as to the neurogenous origin of the disease although he admitted that persons with neuropathic natures were more likely than others to develop the disease His thyrotoxic concept appeared to account for certain hitherto unexplained features of the condition namely its higher incidence in women and its frequent termination in myxedema Moebius views were incontestably supported by the results of replacement therapy which began with Murray s observations in 1891

From clinical and postmortem studies of 5 cases of exophthalmic goiter Muller (1893) described nearly every phase of the disease and demonstrated thyroid hyperplasia as manifested by high columnar epithelium and diminished lumina of the acini He believed that two factors were essential for the production of exophthalmic goiter a neurogenous and a thyrogenous factor or in other words an hereditary or acquired neuropathic nature and disease of the thyroid The first satisfactory explanation for the abnormal appetite and loss of weight was also offered by Muller in his theory that the thyroid hormone speeds the burning up of food in the body thereby increasing the metabolic rate *Muller s theories in regard to metabolism were confirmed* in 1895 when Magnus Levy s studies of gas exchange showed a physiological antithesis between myxedema and exophthalmic goiter in a characteristic drop in energy metabolism in the former and a rise in the latter

Three other contributions of great importance in our knowledge of hyperthyroidism were made during this period (1) Plummer s recognition in 1913 of two distinct types of toxic goiter—one a true hyperplasia with thyrotoxicosis the other hyperthyroidism associated with adenomatous tumors of the gland *Prior to these observations all types had been grouped* together under the designation of Graves or Basedow s disease This separation added further light to our knowledge of the physiology of the thyroid and has had an important bearing on the management of the thyrotoxic patient While Plummer s contribution was important *it tended to differentiate* sharply two types of goiter which may often merge imperceptibly the one into the other Moreover the development of goiter in any given instance is a somewhat continuous process

in which phases of simple hypertrophy and hyperplasia are later succeeded by nodule formation (2) Cannon's experimental production (1914) in cats of a syndrome closely resembling exophthalmic goiter and (3) Plummer's demonstration in 1922 and 1923 of the specific detoxifying action of large doses of iodine

Modern Approaches to Hyperthyroidism.—To the three periods in the history of hyperthyroidism outlined above may now be added a fourth the discovery experimental development and clinical application of the goitrogenic agents in the treatment of the disease and the use of radioactive iodine in the study of the physiology of the thyroid gland and in the treatment of its diseases (Chapter VI)

Chapter VI

SOME RECENT DISCOVERIES NEWER TOOLS FOR INVESTIGATION AND THERAPY

In the several years just past new cytological and cytochemical technics have been adapted to a study of the nature formation storage and secretion into the tissues of thyroid hormone Some of the results have been well and critically summarized (De Robertis 1949 Dempsey 1949) When such technics are applied in conjunction with recently discovered agents capable of modifying thyroidal activity such as thyrotrophin antithyroid compounds radioiodine and the like much of value has been accomplished in elucidating and correlating the histology histochemistry and physiology of the gland Indeed it is fair to conclude that as a result of present day knowledge and facilities more progress has been made in our understanding of thyroid function in the past fifteen years than had been achieved in the preceding fifteen centuries

I THYROACTIVE IODINATED PROTEINS

Ever since the discovery by Baumann (1895) of iodine in organic combination within the thyroid gland research on the nature of the thyroid hormone has never ceased and has finally resulted in not only the discovery of an active fraction of this hormone but also the production of artificially iodinated proteins having several times the activity of desiccated thyroid substance (Data supporting this statement have been summarized in the excellent reviews of Reineke 1946 1949)

As a matter of fact since 1876 it has been known that iodine is capable of combining with protein (Blum and Vaubel) but until the discovery of iodine in the thyroid gland some twenty years later little attention was paid to the observation The intensification of interest following Baumann's observations was so great that within four years there was proof that the active principle of the thyroid was actually an iodoprotein a combination of iodine and thyroglobulin (Hutchinson 1898 Oswald 1899) Simultaneously many attempts were made to synthesize iodinated proteins possessing thyroidlike activity but claims for most of these were rapidly abandoned It was not until 1914 (Morse) that the characteristic effect of thyroid hormone upon the metamorphosis of tadpoles was demonstrated for an artificially iodinated protein However some toxicity was observed as a result of the administration of such preparations and despite the fact that all of a series of iodinated proteins tested shortly thereafter showed some thyroidal activity in tadpoles (Rogoff and Marine 1917) their more general application was not attempted

Further attack upon the problem logically proceeded from Kendall's isolation of crystalline thyroxin in 1915 and progressed hand in hand with the succession of brilliant investigations from which the chemical configuration of thyroxin was hypothecated in 1926 (Harington) and the synthesis of l thyroxin accomplished a year later (Harington and Barger)

While prior to such synthesis of thyroxin it had been recognized that iodination of the tyrosine in the protein molecule occurred in the process of iodination it was equally clear that more iodine was absorbed than could be thus accounted for This additional iodine has been found bound to histidine by way of its imidazole grouping As soon as the identity of thyroxin was proved further study of artificially iodinated proteins became concerned with the hydrolysis concentration and isolation of their hormonally active material or materials The first successful experiment of this kind was reported in 1931 (Brandt Mattis and Nolte) Much credit should be accorded a number of workers for subsequent developments but the final isolation of thyroxin in crystalline form from artificially iodinated protein was first reported by Ludwig and von Mutzenbecher (1936 1939) thus supplying the final link of evidence proving that the active hormonal principle of such protein was identical with that of the thyroid gland

It was difficult at first to reconcile the above discovery with the apparent failure of iodinated proteins to cause metamorphosis of the tadpole Reineke and his associates reinvestigated this problem and showed that these iodinated proteins were potent when administered orally (Reineke and Turner 1941) Later they proved that the addition of them to the surrounding waters medium was ineffectual only because of their insolubility (Reineke Williamson and Turner 1942)

Many practical applications of this clear demonstration of the activity of artificially iodinated proteins were obvious and served as further stimulus for investigation of the methods best suited for the production of material of optimum potency at low expense Again tribute must be paid to Reineke and his associates who have now produced artificially iodinated proteins with several times the potency of desiccated thyroid substance (Reineke and Turner 1943a b 1946) In connection with these studies a considerable fund of knowledge has been added not only to the methods best suited for the production of hormonally active material but also to the nature of the reactions concerned with the formation of thyroxin and to the formation of this material *within the protein molecule* The role of pH of temperature of catalysts such as manganese of oxygenation of the basic protein employed and so forth are fully summarized in Reineke s latest review (1949)

The principles discovered in the synthesis of iodinated proteins have materially aided in our understanding of the manner in which the thyroid may act to produce thyroxin and iodothyroglobulin in vivo The synthesis of a protein containing hormone is a tremendous step forward in the preparation of endocrine substances for it is the first instance in which an hormonally potent compound of protein nature has been produced from raw materials which themselves lack any incretional effects While the processes here concerned are relatively simple it is pertinent to make the point that other metallic protein combinations may be found later which also possess hormonal properties not shared by any single constituent used in their preparation

In summary as a result of the discovery of artificially iodinated proteins investigators have gained an opportunity to study closely the various steps in the production of thyroxin have further demonstrated the ubiquitous nature of the reactions involved have elucidated the optimum conditions under which they occur and have established means of obtaining practically unlimited quantities of thyroidally active material for use in both industry and medicine

II THYROID STIMULATING HORMONE OF THE PITUITARY (THYROTROPHIN OR TSH)

While Rogowitsch's observation (1888) that the pituitary hypertrophies following thyroidectomy can be looked upon as the first positive evidence of an interrelationship between the pituitary and thyroid glands it was the classical work of P E Smith in 1927 some thirty nine years later that established conclusively the dependence of thyroid activity upon stimulation from the hypophysis Two years later (1929) Loeb and Bassett and Aron working independently were able to produce hyperplasia of the thyroid of the guinea pig by the use of pituitary extracts However it was not until 1935 that Collip and Anderson obtained a relatively pure active extract of the thyroid stimulating principle of the pituitary (TSH) and demonstrated the specificity of its action upon the thyroid cells Since that time more than a thousand papers dealing with this material or some phase of its activity have appeared (Albert 1949) Further refinements in its preparation have been described although the particular chemical groups within its structure upon which specific activity depends are still unidentified (Albert 1949)

It was noted early that TSH induced a rise in the basal metabolic rate concomitantly with the hypertrophy and hyperplasia of the thyroid epithelium In 1938 Rawson and Starr related the activity of TSH quantitatively to the increased height of the thyroid acinar cell Shortly after radioiodine became available it was noted (Hertz 1938) that the elevation in the basal metabolism the increase in the size of the follicular cell and increase in the uptake of radioiodine by the gland paralleled each other Later Keating and his associates (1949) and Rawson (1949) observed that the first action of TSH upon the thyroid was probably an extrusion of organically bound iodine and that the increased uptake of iodine might therefore actually be induced secondarily by iodine want From the earliest observations regarding thyrotrophin many workers have contributed to show the integration of pituitary and thyroid function through the interaction of thyrotrophin iodine and thyroid hormone (see Chapter XII)

A relationship between thyrotrophin and exophthalmos was postulated in the early thirties (Marine and Rosen 1934) but it was not until twelve years later than Dobyns (1946a b) demonstrated the effects of thyrotrophin upon various parts of the body and showed that disturbances of a lipoid nature were widely spread throughout the fat depots skeletal and cardiac musculature the liver the kidneys and structures of the reticuloendothelial system At about this same time the manner of inactivation of TSH was established (Rawson Sterne and Aub 1942) so that a further step forward in our understanding of the proptosis of hyperthyroidism was made and a rational explanation given for its frequent aggravation following control of the toxic manifestations of hyperthyroidism (see Chapter XXXIX)

The availability of thyrotrophin for research purposes not only has advanced our knowledge of its action but also has been highly illuminative in delineating the metabolism of iodine and the effects of antithyroid compounds For this work much tribute must be paid to a long succession of workers prominent among whose names must be those of Collop Dobyns and Rawson

III ANTITHYROID COMPOUNDS

In its broadest sense an antithyroid compound is one which suppresses the formation of thyroid hormone by the thyroid gland or interferes with the action of hormone already formed There is no evidence to favor the concept that substances of the second type are of clinical importance today although

structural analogues of thyroxin such as those originally described by Woolley (1946) belong in this class of compounds (Chapter XVI)

Of the antithyroid compounds a classification of which is made in Chapter XVI thyroid hormone and iodine are unique by virtue of their prominent position in the normal activity of the thyroid Furthermore when present in excess they acquire a remarkable capacity for inhibiting the thyroid activating hormone of the pituitary Conversely a deficiency of either of these substances may result in overaction of the pituitary Indeed our present day knowledge of the interdependence of the thyroid and the pituitary probably begins with the observation of Rogowitsch (1888) that total thyroidectomy is followed by pituitary hypertrophy In quick succession came the isolation of iodine in pure form from the thyroid gland (Baumann 1895) the recognition that the active principle of the gland contains iodine in organic combination (Baumann 1896) the brilliant work associating iodine deficiency and goiter (Marine 1907) and considerably later the application of iodine in large doses for the relief of hyperthyroidism (Plummer 1922)

All of the above epoch making events have been dealt with historically in earlier chapters (q v) There remain several groups of antithyroid compounds —including foods thiocyanates aniline derivatives and mercapto—and thio heterocycles—which recently have proved to be excellent investigative tools and in some instances powerful therapeutic agents Despite differences in their origin their chemical structure and characteristics and their point of attack upon the physiological processes through which the synthesis of thyroid hormone normally occurs the sequence of events following the administration of any one of them presents an over all pattern of considerable uniformity In order there occur (1) a deficiency of thyroid hormone (2) an increased production of thyroid stimulating hormone (thyrotrophin) of the anterior pituitary and (3) hypertrophy and hyperplasia of the thyroid gland which if unchecked eventu ally assumes the proportions of goiter There is indeed a morphological ac tivation without physiological effect (Anderson 1949)

While the work of Marine (1907) linked a deficiency of a substance iodine with the formation of goiter widespread interest in positive goitrogenic ma terials that is in those producing goiter when administered in excess stems from the observations of Chesney Clawson and Webster in 1928 who described the development of goiter in rabbits maintained on a dietary consisting chiefly of cabbage and demonstrated the fact that such lesions were associated with a diminished production of heat

In the years that followed other vegetables were added to the list of sub stances proved goitrogenic in laboratory animals—brussels sprouts and cauli flower in 1929 (Marine Baumann and Cipra) kohlrabi (Stiner) and soybeans and peanuts (McCarrison) in 1933 turnips and chard and the seeds of many Brassica species including rutabaga soft and hard turnip cabbage mustard and rape by Purves and his associates from 1936 onward (Hercus and Purves 1936 Kennedy and Purves 1941 Griesbach Kennedy and Purves 1941 Purves 1943) radish in 1940 (Indina) and kale red cabbage lentils and peas in 1942 (Blum) Recently Astwood and his associates (Stanley Greer and Astwood 1948 Astwood 1949a) have quantitatively appraised in man the antithyroid effect of these vegetables and other foods through the use of tracer doses of radioiodine

The antithyroid effect of these various foods has been variously ascribed to the presence of mustard oils and cyanides (Marine Baumann Spence and Cipra 1932) acetonitrile being particularly active to thiourea or its derivatives (Kennedy 1942) and to the thiocyanate ion and certain aromatic amines (Astwood 1949b) Recently a pure chemical material (1-5-vinyl-2-thiooxa-

done) has been isolated from the antithyroid food most potent in man (yellow turnip or rutabaga) This agent is sufficiently active to account for the observed suppression of thyroid activity which follows consumption of rutabaga (Astwood Greer and Ettlinger 1949) Thus has been successfully forged the final link which connects the goitrogenic action of foods and the pharmacologically demonstrable effect of pure chemical compounds upon the *formation of thyroid* hormone

Major impetus was given to this entire subject in 1941 by a number of apparently unrelated events (1) Griesbach Kennedy and Purves observed that rape seed goiters were associated with changes in the pituitary gland similar to those caused by thyroidectomy Moreover no goiter developed unless the pituitary was intact (Griesbach Kennedy and Purves 1941) As an outgrowth of these observations Purves (1943) later showed that iodine might partially relieve the hyperplasia but that thyroid hormone was capable of suppressing it entirely (2) while searching for an improved rat poison Richter and Clisby (1942) observed that phenylthiourea caused a marked hyperplasia of the thyroid (3) in the course of testing the antibacterial effects of sulfonamides in rats the Mackenzies (1942 and 1943) found incidentally that sulfaguanidine enlarged the thyroid by inducing hypertrophy and hyperplasia They also observed that this effect could not be prevented by the administration of iodine but could be obviated by giving thyroxin

These early studies with their chief emphasis on goitrogenesis were soon followed by the publications of Astwood (1943a b) and of the Mackenzies (1943) and McCarty and his coworkers (1945a b) which directed attention to the more important effect of these compounds as inhibitors of thyroid function This shifting of emphasis from goitrogenic to antithyroidal activity resulted in widespread researches on compounds which depress thyroid function In a study of over 200 substances Astwood and his coworkers found two types of chemical structure associated with antithyroidal activity the thiocarbonamide grouping of the thiouracil derivatives and the aminobenzene group of the sulfonamides The latter substances proved to be only a fourth as active as the thiouracil derivatives The results of these investigations led Astwood to select thiourea and thiouracil for clinical trial in the therapy of hyperthyroidism and his first report appeared in June 1942 This marked the beginning of the present era of chemotherapy in the management of the thyrotoxic patient a rapidly unfolding era which despite tremendous strides may still be in its infancy

IV RADIOACTIVE IODINE

Valuable tools for the study of intermediary metabolism were made available to the medical profession with the discovery of artificial radioactivity by Joliot and Curie in 1934 the building of the cyclotron by Lawrence and his associates between 1936 and 1939 and the development of the uranium chain reacting pile in 1946

Because of the unique ability of the thyroid gland to collect iodine selectively in relatively large quantities as first shown by the investigations of Marine and his associates (1910 1916) studies with radioactive isotopes of iodine first prepared by Fermi in 1934 have proved readily applicable to the study of thyroid physiology Cooperative investigations started in 1937 at the Massachusetts Institute of Technology and the Massachusetts General Hospital were soon followed by similar studies at the University of California and other institutions As a result of these investigations certain principles of thyroid function have been amplified progress has been facilitated toward the solution of the steps involved in synthesis of the natural thyroid hormone the mode

of action of some of the goitrogenic thyroid inhibiting agents has been clarified and the knowledge of iodine metabolism in Graves disease has been advanced

Using various isotopes of radioactive iodine chiefly a mixture of I and I as tracers for studying thyroid function Hertz and other investigators found that in untreated hyperthyroidism the thyroid may take up as much as 80 per cent of a small dose (less than 2 mg) of iodide within a few hours after its oral administration Shortly after these earliest observations it was possible for the same and other workers (Hamilton and Lawrence 1942) to demonstrate the tissue distribution of iodine and its rate of excretion when following the administration of tracer doses of radioiodine

Within two years radioactive isotopes of iodine were widely employed in the investigation of the steps by which the thyroid synthesizes thyroid hormone The technic of radioautography as applied to isotopes of iodine was first employed in 1940 (Hamilton Soley and Eichorn) In the succeeding year reports of the work of Chaikoff and his associates (see Morton Perlman and Chaikoff 1941 Perlman Morton and Chaikoff 1941) began to appear in which the reactions of thyroid tissue slices toward various environmental conditions were intensively analyzed Our present knowledge of the oxidative enzyme systems involved in the conversion of iodide to thyroxin are an outgrowth of the studies initiated from these two directions In 1942 Leblond and Mann first connected antithyroid compounds and thyroid function by way of radioactive iodine when they demonstrated an increase in the affinity for iodine of the thyroid gland of animals fed an iodine deficient diet following the administration of soybeans Properly modified and standardized their procedure has now become a reliable method for the standardization of the activity of such compounds in animals (McGinty and associates 1948) and human beings (Stanley and Astwood 1947)

A correlation of histological changes and the capacity of the thyroid to pick up iodine following the administration of thyrotrophic hormone was first made by Rawson and his associates in 1915 (Keating Rawson et al 1945) That thyrotrophic hormone of the pituitary not only prepares the thyroid histologically but also functionally to absorb iodine and transform it into hormone was first adduced with the aid of radioiodine when Rawson and his associates (1945) carefully correlated in a quantitative manner the rate of iodide concentration with the magnitude of hypertrophic and hyperplastic changes taking place in the gland

From these early observations with radioiodine has developed much of our present knowledge of the intimate details of thyroid physiology all of which has laid the background for the rationalization of present day chemotherapeutic methods

Not only does radioiodine afford us a standardized method of evaluating the effectiveness of antithyroid agents but also is itself an effective weapon in the control of certain hyperthyroid states The first reports of its use in this connection were made in 1942 by Hamilton and Lawrence using I^{131} and by Hertz and Roberts employing a mixture of I^{130} and I It is doubtful that such therapy will ever be employed in the majority of cases of hyperthyroidism but the numerous contributions to therapy which have occurred since these first reports indicate a place for it in the management of selected cases of the Graves type of thyrotoxicosis

From the first studies made in cases of malignancy of the thyroid (Hamilton Soley and Eichorn 1940) the outlook for therapy with radioiodine has not been very promising although isolated instances in which the primary growth and/or its metastases were capable of taking up large quantities of the material are now on record (see Chapter XVII)

done) has been isolated from the antithyroid food most potent in man (yellow turnip or rutabaga) This agent is sufficiently active to account for the observed suppression of thyroid activity which follows consumption of rutabaga (Astwood Greer and Ettinger 1949) Thus has been successfully forged the final link which connects the goitrogenic action of foods and the pharmacologically demonstrable effect of pure chemical compounds upon the formation of thyroid hormone

Major impetus was given to this entire subject in 1941 by a number of apparently unrelated events (1) Griesbach Kennedy and Purves observed that rape seed goiters were associated with changes in the pituitary gland similar to those caused by thyroidectomy Moreover no goiter developed unless the pituitary was intact (Griesbach Kennedy and Purves 1941) As an outgrowth of these observations Purves (1943) later showed that iodine might partially relieve the hyperplasia but that thyroid hormone was capable of suppressing it entirely (2) while searching for an improved rat poison Richter and Clisby (1942) observed that phenylthiourea caused a marked hyperplasia of the thyroid (3) in the course of testing the antibacterial effects of sulfonamides in rats the Mackenzies (1942 and 1943) found incidentally that sulfaguanidine enlarged the thyroid by inducing hypertrophy and hyperplasia They also observed that this effect could not be prevented by the administration of iodine but could be obviated by giving thyroxin

These early studies with their chief emphasis on goitrogenesis were soon followed by the publications of Astwood (1943a b) and of the Mackenzies (1943) and McGinty and his coworkers (1943a b) which directed attention to the more important effect of these compounds as inhibitors of thyroid function This shifting of emphasis from goitrogenic to antithyroidal activity resulted in widespread researches on compounds which depress thyroid function In a study of over 200 substances Astwood and his coworkers found two types of chemical structure associated with antithyroidal activity the thiocarbonamide grouping of the thiouracil derivatives and the aminobenzene group of the sulfonamides The latter substances proved to be only a fourth as active as the thiouracil derivatives The results of these investigations led Astwood to select thiourea and thiouracil for clinical trial in the therapy of hyperthyroidism and his first report appeared in June 1942 This marked the beginning of the present era of chemotherapy in the management of the thyrotoxic patient a rapidly unfolding era which despite tremendous strides may still be in its infancy

IV RADIOACTIVE IODINE

Valuable tools for the study of intermediary metabolism were made available to the medical profession with the discovery of artificial radioactivity by Joliot and Curie in 1934 the building of the cyclotron by Lawrence and his associates between 1936 and 1939 and the development of the uranium chain reacting pile in 1946

Because of the unique ability of the thyroid gland to collect iodine selectively in relatively large quantities as first shown by the investigations of Marine and his associates (1915 1916) studies with radioactive isotopes of iodine first prepared by Fermi in 1934 have proved readily applicable to the study of thyroid physiology Cooperative investigations started in 1937 at the Massachusetts Institute of Technology and the Massachusetts General Hospital were soon followed by similar studies at the University of California and other institutions As a result of these investigations certain principles of thyroid function have been amplified progress has been facilitated toward the solution of the steps involved in synthesis of the natural thyroid hormone the mode

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Since first made available fifteen years ago radioiodine has become an indispensable tool for weaving the background against which the hitherto ill defined picture of thyroid physiology has been detailed with considerable accuracy so that its fundamental features stand out in bold relief Less dramatic is its contribution to our therapy of thyroid disease although it seems likely that some permanent place will be accorded it in the treatment of Graves disease

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SECTION II

Anatomical, Chemical, and Physiological Considerations

Thomas Hodge McGavack

Chapter VII

THE METABOLISM OF IODINE

Iodine is one of the essential raw materials concerned in the hormonal function of the thyroid. Therefore its movements into and out of the body and its behavior within the tissues under normal and abnormal conditions are of paramount importance in assessing physiological and pathological states of activity of the thyroid gland. This is a simple statement but its application to the problems in hand is often beclouded by the fact that many gaps still exist in our knowledge and that too often data collected by one method are erroneously compared with those obtained by means of an entirely different discipline. Nevertheless the story of iodine metabolism is a fascinating one, challenging all of the skills and interests of the scientist as well as those of the philosopher. Later knowledge of the subject derived from a variety of newer techniques—histodissection, vital and supravital staining, microchemistry, radioactive tracers, antithyroid compound activity, and so forth—have broken through the mists of doubt illuminating the picture of thyroidal activity to a greater extent in the past decade than in the preceding ten centuries. One may now agree that a chief function of the thyroid gland is to convert inorganic iodine (iodide) to a state of higher oxidation equivalent to elementary iodine (Salter, Karandikar, and Block, 1949). In the presence of protein containing tyrosine, elemental iodine will *combine to form* thyroxin, an action which will readily occur even in vitro. It is probably for this reason that metamorphosis of amphi-

brians was achieved by the administration of elemental iodine even though the animal was thyroidectomized (Swingle 1919a b) or thyroidectomized and hypophysectomized (Allen 1919) More recently it has been shown that iodine by injection or iodocasein by mouth will prevent the dwarfing effects of hypothyroidism produced by methylthiouracil (Nelson and Hines 1949) When injected subcutaneously elemental iodine has a thyroxin like effect (Purves and Griesbach 1946a b Dvoskin 1947a Nelson and Wheeler 1948a b Nelson and Hines 1949 Ferguson and Sellers 1949 Barker and Lipner 1949) Barker and Lipner observed no change in the basal metabolism of normal rats nor of thiouracil treated rats when the doses of iodine were small (1 mg) but saw considerable elevation of the blood protein bound iodine in all groups of their animals

Dvoskin was unable to demonstrate a thyroxin like effect when the elemental iodine was given orally which led him to conclude that proteins can be readily iodinated by elemental iodine whereas the more stable iodide absorbed following ingestion of the *element* or its salts lacks this action While such a conclusion illustrates the point in question one must not ignore the work of Chapman (1941b) who reported thyroxin like activity in thyroidectomized rats given iodide in their drinking water His data indicate that under proper conditions the tyrosine containing protein of all cells is capable of being iodinated to thyroxin or other hormonally active material In any event the conversion of iodide to iodine and thence to a thyroidally active material appears to be an ubiquitous reaction shared by all cells The thyroid gland is a specialized factory for the efficient manufacture of this material capable of rapidly regulating the rate at which it is produced stored and distributed to the tissues This is a simplified statement of the rather complex events which occur daily in relationship to the ingestion distribution and excretion of iodine Some detail of these steps in iodine metabolism are essential for the further elucidation of thyroid status in health and disease

The Daily Requirement of Iodine —It is not easy to determine accurately the daily requirement of iodine as this involves a type of balance study not readily performed Particularly difficult has been the estimation of iodine in the food However the minimum requirement for normal health has been set at the order of 15 micrograms per day (Salter 1940a b) and the optimum probably lies in the neighborhood of 200 micrograms per day The latter represents approximately 300 micrograms of thyroxin which Means and Lerman (1938) found to be approximately the amount necessary for the maintenance of the myxedematous individual For the human being such a turnover of thyroid hormone is confirmed by recent studies using newer and more accurate technics (Salter Johnston and Gemmel 1948 Stanley 1949) Fur-

thermore the figure corresponds fairly well with observations upon rats (Astwood and Bissell 1944) dogs (Iamrog Chaikoff and Intenmann 1947) and goats (Schultze and Turner 1945) It seems quite likely that the body is capable of reclaiming *a portion of the iodine liberated in* the catabolism of thyroid hormone (Albert and Keating 1949)

Sources of Iodine, Routes of Absorption, and Temporary Storage — The amounts of iodine available to the individual depend for the most part upon the *quantity and quality of the foodstuffs consumed the* water drunk and the air absorbed Thus the actual amount introduced into the body is entirely uncontrolled by the individual quite in sharp contrast to the ingestion of the second halogen chlorine the quantities of which are regulated by the individual according to taste

While iodine may enter the body in a number of ways as for instance through any mucous membrane or even through the unbroken skin by far the major portion is taken up from the intestinal tract in the form of inorganic iodide Approximately 80 per cent of orally administered *iodine or its salts is absorbed within two hours or less* (Salter 1940) Using radioiodine as a tracer Keating and Albert (1949) found that the rate of absorption is of the order of 5 per cent per minute and they considered absorption virtually complete in 2 hours or less

If the amount of iodine ingested is large temporary storage takes place in the liver skin and lungs If not taken up by the thyroid gland quickly most of this temporarily stored material is rapidly excreted by way of the kidneys lungs and feces It is somewhat difficult to say *what constitutes a large and what a small dose of iodine* However Keating and Albert (1949) noted that amounts up to 85 gammas did not appear to disturb the normal urinary excretion rate significantly whereas doses of 1 000 gammas or more caused the urinary excretion of larger amounts of the tagged iodine

The Distribution of Iodine in Body Tissues — (1) Tissue analysis Sturm and Bucholz (1928) found iodine to be distributed in the body as follows muscles 50 per cent skin 10 per cent skeletal structure 7 per cent thyroid 20 per cent other endocrine organs and the central nervous system combined 13 per cent From *these figures it follows* that the concentration of iodine within the thyroid gland is more than a thousand times that of its concentration in muscle and ten thousand times that of the blood Subsequent investigators have not confirmed the observation of Sturm and Bucholz that iodine is more highly concentrated in other endocrine glands than in the tissues at large In fact King (1940) feels that the iodine content of the pituitary and of the central nervous system is unusually low However in this connection the nature of the iodine containing material must be taken into account as Keating and Albert (1949) have recently observed a rela-

tively high concentration of organically combined radioiodine in the pituitary as compared with that of the tissues of the body in general and with other endocrine organs aside from the thyroid in particular

The important role of the thyroid in iodine metabolism and the functional significance of iodine itself may be surmised from the fact that of the body's total normal supply of iodine amounting to from 20 000 to 50 000 micrograms the thyroid ordinarily contains one fifth although its mass as compared with that of the body is 1 to 500 Expressed in another way the thyroid gland contains 0 01 per cent of iodine by wet weight or 0 2 per cent by dry weight By contrast if outside the thyroid iodine were evenly distributed to all tissues then in the average normal adult its concentration will represent approximately 0 00008 of 1 per cent of the body weight From the above it is clear that there are two great tissue reservoirs for iodine in the body the thyroid and the skeletal musculature differing widely in concentration but each accounting for nearly 50 per cent of the body's total store of the element

(b) Disposition of iodine following absorption The rates at which absorbed inorganic iodine disappears from the blood concentrates in the thyroid accumulates in the extracellular fluid and tissues and is excreted in the kidneys are all interrelated In other words the exponential rate at which inorganic iodide disappears from the blood is the sum of the individual rates of its removal by the thyroid kidneys and other tissues Following a tracer dose of radioiodine the length of time required for the absorption and the establishment of tissue equilibrium varies with the status of thyroid function it being shortest in hyperthyroidism and longest in myxedema Keating and Albert (1949) found the duration of this distribution phase for inorganic iodide to be from 6 to 12 hours in euthyroid individuals 12 to 24 hours in hypothyroid subjects and less than 6 hours in hyperthyroid patients During this period in each of the three groups an average of 12 per cent of the total amount of labeled iodide was disposed of in tissues other than the kidneys and the thyroid the rate of such accumulation varying from 1 to 2 per cent per hour

Thyroid Gland Iodine—Under normal conditions inorganic iodide is accumulated by the thyroid at a rate of approximately 2 5 per cent per hour It may rise to ten times that figure in subjects with hyperthyroidism and will fail to concentrate at all in the completely myxedematous subject When tracer doses of radioiodine are given with small amounts of carrier for instance not exceeding 100 micrograms the curves of accumulation by the thyroid in euthyroid subjects follow a rather uniform and characteristic pattern rising rapidly at first and reaching a plateau at the end of 24 to 48 hours roughly corresponding to a total accumulation of about 20 per cent of the ingested dose The thyroid glands of hyperthyroid subjects pick up the iodine more rapidly

thermore the figure corresponds fairly well with observations upon rats (Astwood and Bissell 1944) dogs (Taurog Chaikoff and Entenman 1947) and goats (Schultze and Turner 1945) It seems quite likely that the body is capable of reclaiming a portion of the iodine liberated in the catabolism of thyroid hormone (Albert and Keating 1949)

Sources of Iodine, Routes of Absorption and Temporary Storage — The amounts of iodine available to the individual depend for the most part upon the quantity and quality of the foodstuffs consumed the water drunk and the air absorbed Thus the actual amount introduced into the body is entirely uncontrolled by the individual quite in sharp contrast to the ingestion of the second halogen chlorine the quantities of which are regulated by the individual according to taste

While iodine may enter the body in a number of ways as for instance through any mucous membrane or even through the unbroken skin by far the major portion is taken up from the intestinal tract in the form of inorganic iodide Approximately 80 per cent of orally administered iodine or its salts is absorbed within two hours or less (Salter 1940) Using radioiodine as a tracer Keating and Albert (1949) found that the rate of absorption is of the order of 5 per cent per minute and they considered absorption virtually complete in 2 hours or less

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normally plays in the elaboration of iodothyroglobulin In a remarkably short space of time the inorganic iodine (iodide) normally brought to the gland enters into organic combination so that under ordinary circumstances about 90 per cent of the iodine in the thyroid is organically bound (Schachner et al 1941)

Thus far it has only been possible to isolate from the gland two forms of organic iodine diiodotyrosine and thyroxin although in the process of producing the thyroid hormone certain intermediaries may be found (Fig 1) The constancy with which the thyroxin accounts for one half as much thyroid iodine as does diiodotyrosine is certainly significant These two amino acids contain approximately 65 and 59 per cent of iodine by weight respectively and under normal conditions account for 30 and 60 per cent respectively of the iodine present in the thyroid What if any significance this may have in relation to the mechanism concerned in the elaboration storage release and tissue activity of the thyroid hormone is not clear but it is difficult to believe that the constancy of the relationship is sheer coincidence

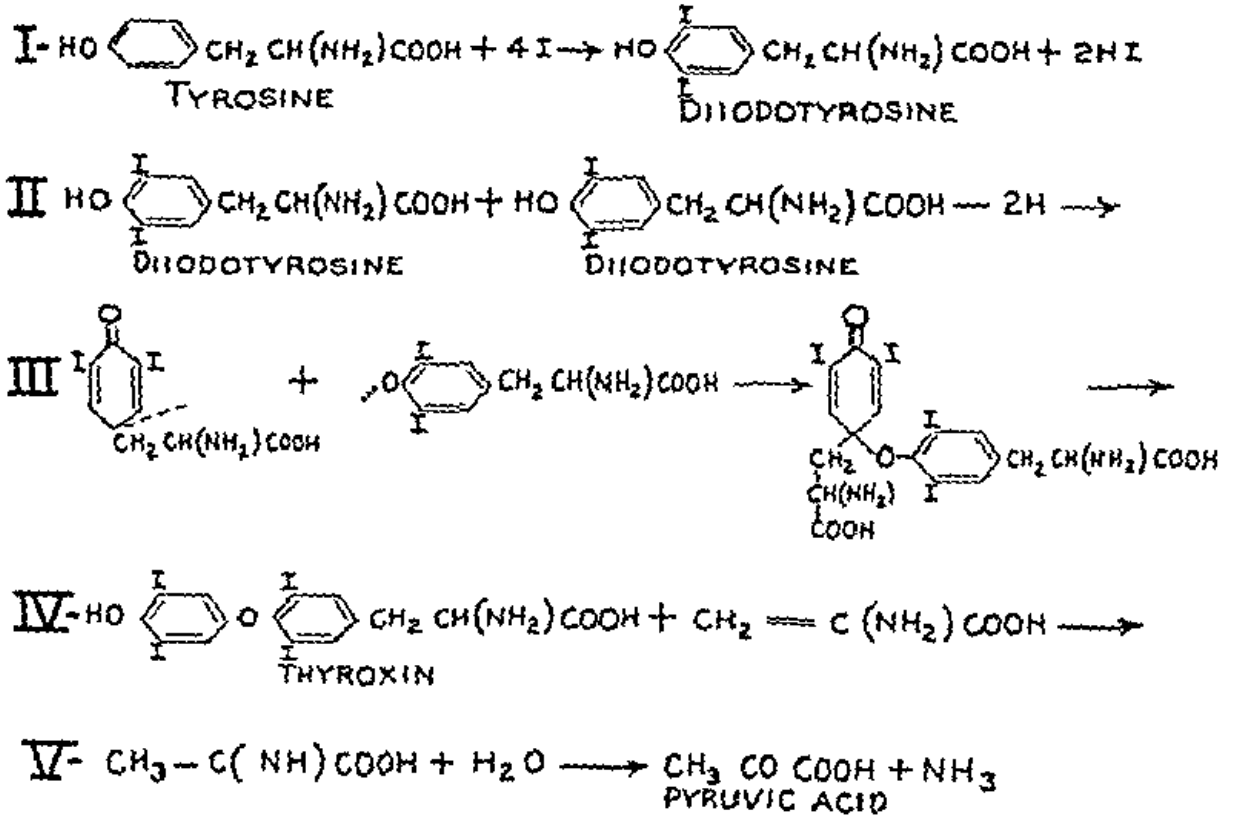


Fig 1—S l mat r pre nt tion of a n e hanism f r th onversion of i dine and tyro in i dii d ty in and thyr xin The synth si f thy oxin from dij Iotyrosine i that propo ed by Johnson and T wk sb ry (1914) D t and da h s pre nt un sti fi d bond and indicat th positi n withi th c mpound at whi h activity i pr sum d to o cu Many interm diary t p a e nitted nd many ar not known However th end p odu ts of th e r action appear t b thyr xin pyruvic eid and ammonia St ps H t V f this r a tion will o cur simply by in ubating diiodoty sine under suitable conditi s an i do n t requ the intervent n of a biol gi al nzym s t m In the i dination of p t i and p bably al in the formati n f thy xin by the thy oid gland it is b lieved that thyr xin i f rm d *within th prot in mol ule*

and reach a much higher plateau (for instance 15 per cent accumulation in 6 to 12 hours) As aforesaid completely myxedematous subjects fail to show appreciable collection of the material given When small physiological amounts of radioiodine are being thus taken up by the thyroid the accumulation curve probably reflects with considerable accuracy the rate of synthesis and storage of the labeled iodine in the thyroid as thyroid hormone (Keating and Albert 1949)

This is confirmed by Stanley's (1949) method of direct measurement of total iodine accumulation by the thyroid through the use of which he found that euthyroid individuals who had not received added iodide showed an average uptake by the thyroid of 10 micrograms per hour This corresponds well with the even earlier calculations of daily turnover of iodine under optimum conditions of intake namely 200 micrograms per day In thyrotoxic patients this concentration of uptake of iodine by the thyroid may be increased ten or twelvefold

When a large amount of carrier for instance 100 mg of iodine are given along with tracer doses of radioiodine the uptake curves in the thyroid are quite different The quantity taken up by the gland rises sharply to a peak within one to two hours and then declines rapidly in an exponential manner closely paralleling the behavior of the iodine within the blood stream With such doses it is evident that the first sharp rise of radioiodine within the gland probably measures the ability to concentrate iodine without relation to its capacity for converting this into organically combined material Stanley (1949) believes that in general the inhibition of organic binding by the administration of iodide appears to be determined by the level of iodide in the thyroid cell which in turn is a function of both the ability of the cell to concentrate iodide from the serum and the amount of iodide available in the serum

To approximate thyroid function more closely Keating and Albert (1949) have proposed the calculation of thyroidal iodide clearance which can be derived by multiplying the rate of accumulation of iodide in the thyroid by the volume of distribution of iodide If by direct measurement the accumulation rate alone were determined it is obvious that the data obtained would not accurately measure thyroid function as no consideration would be given to the renal status or to the extrathyroidal rate of disposal and tissue distribution of iodide Calculation of thyroidal iodide clearance takes account of these factors and therefore arrives at the most appropriate method for measuring the ability of the thyroid to accumulate iodide While every cell in the body is believed to contain iodine (Salter 1940) its concentration within the thyroid emphasizes the important role which the element

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The volume of distribution of iodine is here defined as the volume of fluid in the body occupied by iodine in equilibrium with the blood assuming a concentration uniformly the same as that in the serum Slight variations in concentration may exist this concept is hypothetical not real but it may nevertheless have some usefulness (Keating and Albert 1949) As *defined* the volume of distribution of iodide may be roughly approximated when the ingested dose of radioiodine and the serum concentrations of radioiodine in relation to time are known

inversely (Fig 2) Other workers have failed to demonstrate any satisfactory correlation (Skanse 1918 Beierwaltes et al 1948) In general it may be said that the rapidity with which tracer doses of iodine are excreted varies inversely with the functional status of the thyroid gland However as reported by a single observer the percentage of the tracer dose excreted in the urine by normal individuals has varied widely from subject to subject Moreover results have differed considerably from observer to observer In Sl uses (1918) patients the 18 hour urinary excretion varied from 53 to 81 per cent of the administered dose with an average of 67 per cent Werner and his associates (1948) noted that from 10 to 70 per cent of a tracer dose was excreted during the first 24 hours while Beierwaltes and his co workers (1948) found that from 19 to 42 per cent of the dose was lost in the urine during a similar period of time Therefore it might be emphasized that urinary excretion curves following tracer doses of radioiodine must not be taken as a sole index of thyroidal activity as many extrathyroidal factors influence them nor do such curves afford us a true picture of the turnover of iodine within the body

These seemingly contradictory data may be readily brought into relationship with one another if serum and tissue concentrations of iodine and rate of accumulation in the thyroid are simultaneously determined (Keating and Albert 1949) In normal individuals these workers found the urinary excretion rate of tracer doses of iodide to be about 6 per cent per hour or equivalent to a renal clearance of 38 c c per minute The renal clearance is more or less independent of the serum concentration suggesting that at or near physiologic concentrations inorganic iodide is passively reabsorbed by the renal tubules Approximately 2 per cent of a tracer dose of radioiodine is excreted in the feces within 24 hours of its ingestion

Blood Iodine—Following its absorption from the intestinal tract iodide disappears from the blood at an exponential rate which is the sum of the individual rates of its removal by the kidneys thyroid and other tissues Keating and Albert (1949) have estimated the average disappearance rate in normal subjects receiving tracer doses of radioiodine to be about 9 5 per cent per hour However the rate of removal through the various channels indicated will vary in any given subject in direct proportion to the concentration of iodine attained within the blood stream Thus the size of the administered dose is always one determining factor in the speed of disappearance

While it is now well recognized that every organ tissue and secretion of the body contains iodine values for various fractions of blood iodine are useful to the clinician as an indicator of the status of thyroid function Salter (1940) states that by the majority of methods now available the total blood iodine of normal subjects is rarely less than 5 gamma per 100 c c or more than 20 gamma per 100 c c Methods

Within the thyroid the ratio of colloid iodine to parenchymal iodine is normally approximately 6 to 1 This can be altered by a low or a high ingestion of iodine For instance when the concentration of iodine within the thyroid falls below 10 mg per 100 Gm that is to one fourth of its average normal value hyperplasia of the gland ensues and goiter may subsequently develop (Kimball 1916)

The Excretion of Iodine – The amount of iodine excreted depends primarily upon the amount ingested *Under ordinary circumstances* 10 to 60 per cent of the excreted iodine passes through the urine while the feces account for another 25 per cent and the skin and respiratory tract the remainder

As a result of studies with tracer doses of radioiodine it is believed by some (Keating et al 1947 Werner et al 1948) that the rate of the urinary excretion of iodine when ingested in physiological amounts may be used as an index of thyroidal uptake and activity the two varying

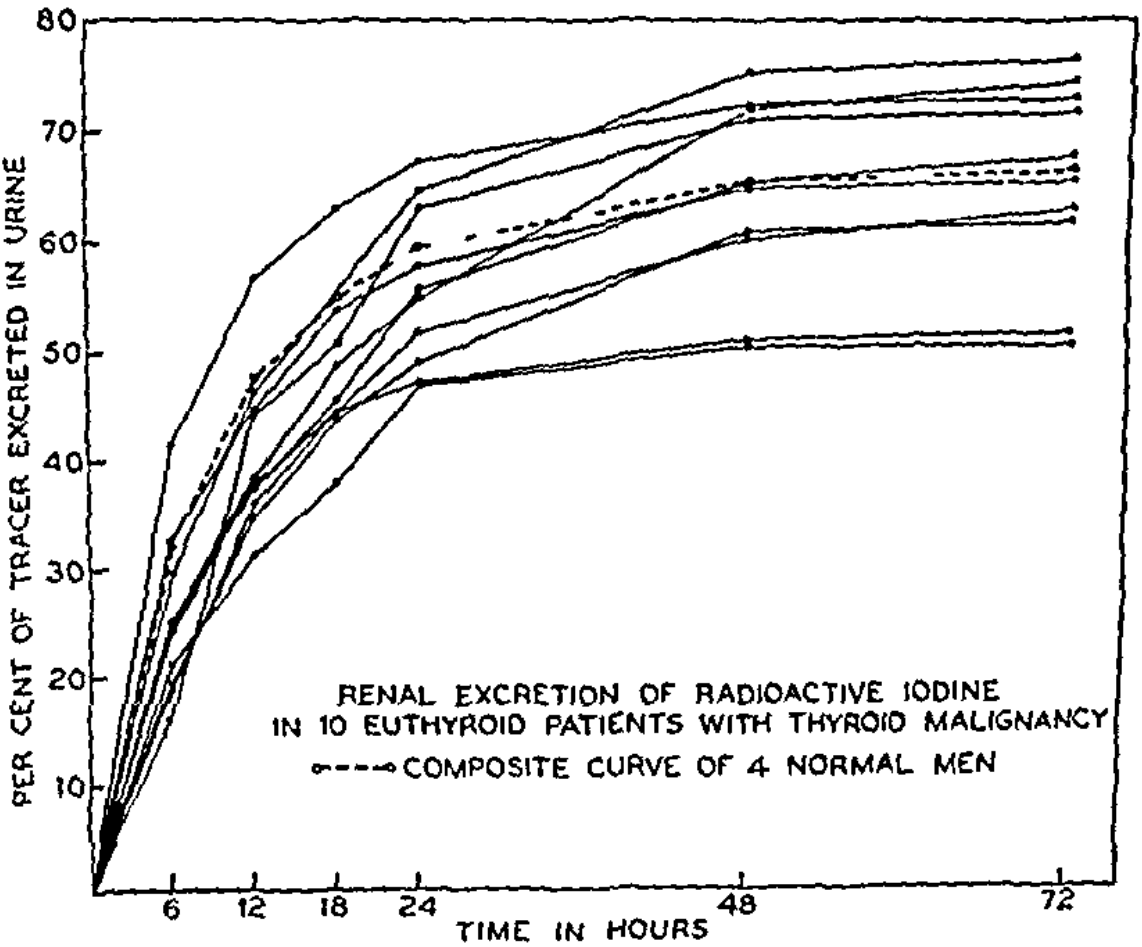


Fig 2—Rate of urinary excretion of radioiodine in euthyroid subjects While there is considerable variation from subject to subject in the height of the plateau approached and the time required to reach it it has been suggested that the early and similar data indicate that the rate of urinary excretion is an exponential function when plotted against time (After Keating Power Berkson and Haines 1947)

inversely (Fig 2) Other workers have failed to demonstrate any satisfactory correlation (Skanse 1918 Beierwaltes et al 1948) In general it may be said that the rapidity with which tracer doses of iodine are excreted varies inversely with the functional status of the thyroid gland However as reported by a single observer the percentage of the tracer dose excreted in the urine by normal individuals has varied widely from subject to subject Moreover results have differed considerably from observer to observer In Skanses (1918) patients the 48 hour urinary excretion varied from 33 to 81 per cent of the administered dose with an average of 67 per cent Werner and his associates (1948) noted that from 40 to 70 per cent of a tracer dose was excreted during the first 24 hours while Beierwaltes and his co workers (1948) found that from 49 to 52 per cent of the dose was lost in the urine during a similar period of time Therefore it might be emphasized that urinary excretion curves following tracer doses of radioiodine must not be taken as a sole *index of thyroidal activity* as *many extrathyroidal factors influence* them nor do such curves afford us a true picture of the turnover of iodine within the body

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and adaptations of methods vary considerably from laboratory to laboratory The nature of the fractionating agent and the manner of isolating and determining the iodine present in each fraction have caused considerable differences in the end results It therefore seems wise to pay attention not so much to absolute figures but to the range of values to be expected under the conditions employed in each group of tests It is far outside the scope of the present discussion to analyze different methods critically Because of its practicality and ready adaptation for clinical laboratories figures will be given for the methods employed by Salter and his associates (Bassett Coons and Salter 1911 Salter Bassett and Sappington 1911 Salter 1910) Fasting normal values for these different fractions are shown in Table I It cannot be too strongly stressed that the values in Table I are not necessarily true or absolute but afford an accurate basis for comparison if the same methods are used in determining the iodine of the blood of subjects with normal and altered thyroid function The use of plasma in preference to whole blood for these estimations seems logical in view of the fact that the iodine content of red cells varies comparatively little as compared with the iodine content of the plasma (Salter 1910) Bassett Coons and Salter (1911) believe that the inorganic iodine content of the plasma is extremely constant unless this substance is supplied from the outside In one instance studied by them iodine was applied to the skin preparatory to lumbar puncture whereupon the inorganic iodine fraction of the plasma rose to 2000 micrograms per 100 c c

TABLE I

VALUES FOR IODINE FRACTIONS IN THE BLOOD PLASMA OF NORMAL FASTING SUBJECTS

IODINE FRACTION	GAMMA PER 100 C C		APPROXIMATE PERCENTAGE OF TOTAL PLASMA IODINE
	RANGE	AVERAGE	
Inorganic (I)	0 3–5 0	2 0	27 7
Protein bound (I)	3 9–8 1	5 2	72 3
(a) Thyroxine like (T)		3 6	50 0
(b) Duodotyrosine like (D)	1 0–1 8	1 6	22 3
Protein bound (P) fraction in			
(a) Hyperthyroidism	8 0–22 0	>8 0	
(b) Hypothyroidism	0 0– 4 0	<4 0	

Values for iodine fractions of the serum of fasting subjects It is wise for each laboratory to establish its own standards as the values are easily distributed by local factors for which a constant deviation can be determined (After Bassett Coons and Salter 1911 and Salter Bassett and Sappington 1911)

Radiopaque preparations containing iodine may affect the values for blood iodine and for relatively long periods of time For example those employed in performing intravenous pyelography may influence the figure for from one to seven weeks (Salter 1949b Man and Peters 1950) those used in bronchography for from one to several years (Jakob and Wachsmann 1947 Man and Peters 1950) and those employed for visualization of the gall bladder for not less than three months (Man and Peters 1950)

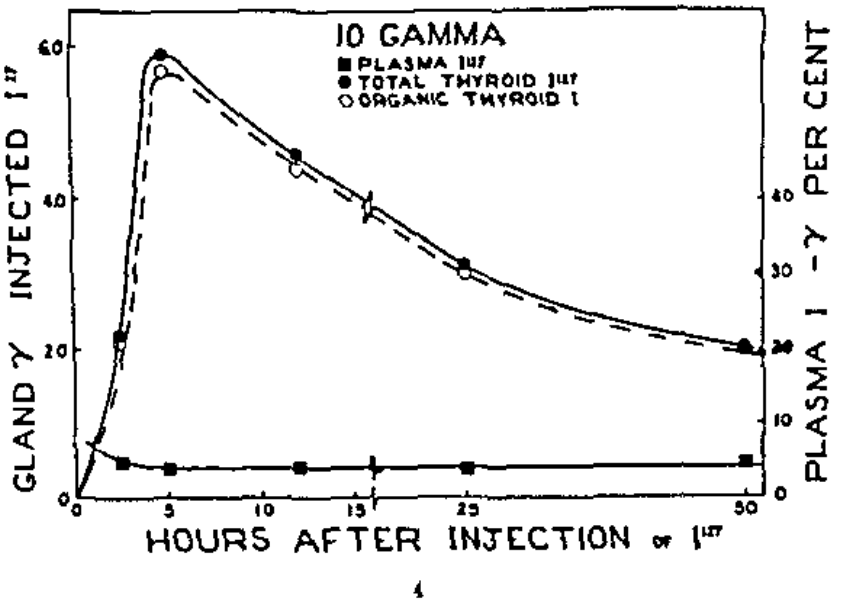
A Significance of the Protein Bound Fractions of Blood Iodine — The protein bound iodine lies mostly in the traditional albumin fraction of the plasma but small amounts are attached to fibrinogen and to globulin as well as to other albumin fractions Indeed the highest *concentrations* have been observed in relation to the alpha and beta globulins In connection with any determination of protein bound iodine it must be remembered that an increase in the inorganic iodine in the plasma may simultaneously raise the protein bound fraction This is due to the fact that under the conditions obtaining in the serum and extracellular tissues of the body inorganic iodine when present in excess is capable of forming a loose combination with protein and may be precipitated with the hormonally active iodine fractions if special precautions are not taken (Salter Karandikar and Block 1949) Therefore when iodine is being administered values for protein bound iodine may become meaningless (Bassett Coons, and Salter 1941)

In the normal subject the diiodotyrosine fraction of plasma iodine constitutes from 5 (Chaikoff 1949) to 30 (Salter, 1940) per cent of the protein bound iodine of the plasma, the former figure probably being more nearly correct (Salter 1940) However with alterations in the functional activity of the thyroid gland the T or the thyroxin like fraction is more affected than the 'D or the diiodotyrosine moiety Salter estimates that every five liters of human blood should contain approximately 0 5 mg of thyroxin If thyroid function is increased as in thyrotoxicosis or following the administration of thyroid stimulating hormone of the pituitary gland it is the thyroxin fraction of blood iodine which rises most and causes the major increase in the iodine of the blood Conversely it is the thyroxin fraction which suffers most in hypothyroidism

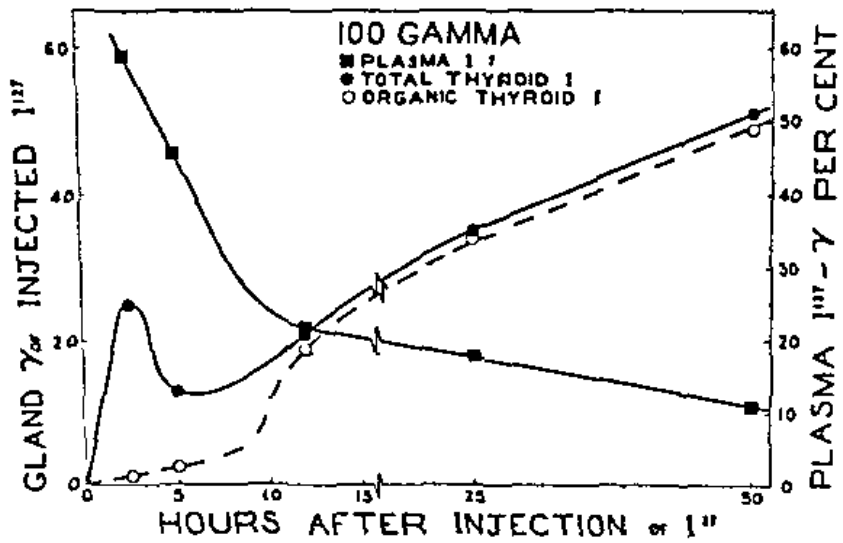
That disturbances in thyroid activity affect *the thyroxin like fraction* of plasma iodine has been further confirmed by the work of Morton and his associates (Morton Perlman and Chaikoff 1941 Morton et al 1942) In hypophysectomized rats these investigators have shown that only a small quantity of ingested radioactive iodine in an organic form is found in the blood plasma at the end of 96 hours as contrasted with 80 per cent of the ingested iodine in this form in normal rats The formation of diiodotyrosine under these conditions is less disturbed It is their conclusion that the mechanism for diiodotyrosine formation is

altered slightly or not at all by hypophysectomy but that such a proced ure prevents its transformation into thyroxin (Morton Perlman, An derson and Chaikoff 1942) Conversely following the administration of thyroid stimulating hormones of the pituitary these same workers (Mor ton Perlman and Chaikoff 1941) found a higher percentage of the blood iodine as thyroxin than was to be observed in normal or control ani mals That is at the end of 26 hours after the radioactive iodine had been administered 80 per cent of the total iodine contained in the plasma of the hormone treated animals was present as thyroxin *in comparison* with 50 per cent in the plasma of normal animals In more recent work where tracer doses of radioiodine have been employed it has been concluded that the circulating thyroid hormone is in the form of a small thyroxin like molecule loosely attached to protein (Tre vorrow 1939 Taurog and Chaikoff 1947b Chaikoff and Taurog 1949) Inasmuch as organically bound iodine in the thyroid is distributed about 60 per cent to the diiodotyrosine fraction and 30 per cent to the thy roxin moiety and in the plasma conditions are reversed with thyroxin accounting for from 90 to 95 per cent of the acetone insoluble iodine it is clear that there is a preferential discharge of thyroxin from the thyroid gland A fall in the level of the protein bound iodine of the plasma promptly follows thyroidectomy On the other hand thyro *trophic hormone administered to normal or hypophysectomized rats* rapidly raises it (Taurog Chaikoff and Tatenman 1947) In the cases of Salter Bissett and Sappington (1941) hypothyroid individuals had a protein bound iodine of blood which never exceeded 10 micrograms per 100 cc whereas none of their hyperthyroid patients showed a value for protein bound iodine of less than 8 micrograms per 100 cc (Table I) In hyperthyroidism the elevation of the blood protein bound iodine was roughly proportional to the basal metabolic rate and in only one of their 38 subjects was the figure below 8 micrograms per 100 cc Lowenstein and his associates (1941) made substantially similar observations in a study of 32 thyrotoxic patients and concluded that the protein bound iodine of the plasma (*P* iodine) is directly correlated to the basal heat production They further noted that this relation ship holds true regardless of age sex thyroid disease *Lugolization* or thyroidectomy Talbot Butler and Saltzman (1945) working with various groups of children stated that the concentration of protein bound iodine in serum is a useful direct index of thyroid activity

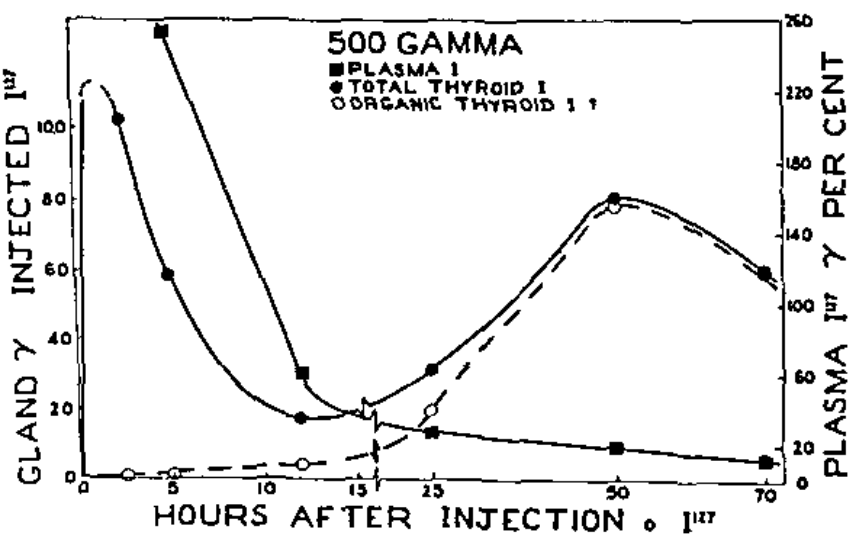
That thyroglobulin as such is not present in the circulating blood seems now to have been well established (Leman 1940 1941) Fasting blood iodine levels vary more or less directly with the thyroid iodine but the range over which these changes take place is much more narrow (Elmer 1938) Variations in the fasting blood iodine due to age sex and seasons have been both claimed (Burger and Mobius 1934 Curtis Davis and Phillips 1933 Seidell and Fenger 1913 Fenger 1913 Ito



A



B



C

Fig 3 *A B* nd *C*—The b havi r f pl sma nd thy oid i din in e p t th dmini t ti n of ying sl gl d e f iodid Note the inhib t ry influe of ing st d iodin up n th o g ni binding of i dine by th thy id gland (After W lff nd Chaikoff 1948b)

1938 Baumann and Metzger 1937 Veil and Sturm 1925 Kato 1936) and denied (Leipert 1931 Lohr 1936 Elmer 1931 Curtis and Lertman 1913)

From the clinical point of view therefore it would seem important to emphasize the usefulness of determining the protein bound fraction of plasma iodine and particularly the thyroxin like moiety thereof Under satisfactory laboratory conditions such estimations represent an accurate index of the activity of the thyroid gland

B Regulatory Action of Blood Inorganic Iodine —When an excess of inorganic iodine is present in the plasma it interferes with the enzymatic conversion of iodide to the organically bound forms diiodotyrosine and thyroxin (Wolff and Chaikoff 1918a b d Chaikoff and Taurog 1949 Stanley 1949) Organic binding of iodine by the thyroid can be prevented by raising the value for plasma iodine above a certain critical level which has been determined for the rat to be somewhere between 20 and 35 gammas per 100 cc and for euthyroid human beings between 6 and 12 gammas per 100 cc (Fig 3A C) This inhibitory effect is not permanent as the formation of diiodotyrosine and thyroxin is again resumed as soon as the inorganic iodine of the plasma falls below the lower limit of the range mentioned While almost completely blocking the organic binding of iodine by the thyroid the high plasma levels do not affect the ability of the gland to concentrate inorganic iodide (Fig 3A C) On the contrary in Wolff and Chaikoff's experiments (1918 a b) the normal thyroid blood ratio of from 100 to 300 was maintained throughout the period of inhibition

These observations confirmed earlier ones which emphasized the fact that the normal thyroid possesses a mechanism for the concentration of iodide which is independent of its conversion to organic compounds Indeed it is the high level of inorganic iodine within the gland which probably acts to inhibit the thyrotrophic hormone present for at times under the influence of antithyroid compounds from 2 to 10 mg of iodide may be present in the rat thyroid per 100 Gm of thyroid tissue This influence of iodine seems adequate to account for the salutary action of Lugol's solution and other inorganic iodine preparations in the management of thyrotoxicosis It may also account for the escape from iodine control not infrequently seen in hyperthyroidism for it has been reported that the organic binding of iodine will be resumed after a certain lapse of time despite the maintenance of a high level for total plasma iodine even as high as 200 gammas per 100 cc (Wolff Chaikoff Goldberg and Meier 1949)

It becomes clear that iodine metabolism plays an important role in regulating the activity of the thyroid gland and equally clear that any further discussion of iodine activity within the body will be illuminated by some discussion of the nature and function of that structure

Chapter VIII

ANATOMY AND HISTOCHEMISTRY OF THE THYROID GLAND

The thyroid is a somewhat U shaped endocrine gland located in the neck near the junction of the larynx and trachea charged with the function of forming storing and extruding the hormone iodothyroglobulin which has as its major action a regulatory effect upon the energy exchanges of the body A similarly formed and similarly acting material can be produced by many if not by all living cells and by synthesis in vitro when the necessary raw materials are brought together under proper circumstances The seemingly ubiquitous nature of this function in no way detracts from the very important position which the thyroid occupies among the glands of internal secretion in the human being a point well emphasized by merely recounting some of its unusual attributes

The thyroid is the largest of the wholly endocrine glands varying in weight in the adult from 25 to 40 grams Its blood supply per unit of weight surpasses that of any other organ in the body This is not surprising for every tissue and cell requires the thyroid hormone iodothyroglobulin in order to function properly It is little wonder therefore that the flow of blood through this gland is greater per unit of weight than that of any other bodily structure When thus measured the amount of blood traversing each unit of the thyroid is only slightly greater than that to the adrenal but is from four to five times that to the kidney and approximately eight times that to the intestines

The thyroid is one of the most labile organs of the body fluctuating in size and histological appearance in relation to many physiological stresses such as age social state pregnancy and environmental influences including diet habitation and temperature It responds even more vigorously to abnormal stimuli such as infection emotional crisis chronic wasting disease and so forth Indeed the variations in the anatomy and the histology of the gland may be so great under physiological as well as pathological conditions that even the most expert may have difficulty in distinguishing the normal from the abnormal

These variations within the thyroid are predicated upon the bodily requirements for thyroid hormone at any given time It is therefore not the nature of the hormone itself that is such a remarkable feature

of thyroidal activity but the ability of the gland to produce large quantities of this material rapidly in response to physiological needs We may well liken the thyroid to the governor on an engine designed to regulate the speed with which *the over all exchanges of energy in the* body shall take place It accomplishes this by an action directly upon each and every one of the tissues and cells of the body without the mediation of any other gland or structure of any sort Thus each cell *reflects its deficiencies and its* excesses *and no part of the* body escapes its all important control

GROSS APPEARANCE

The thyroid gland is located in the anterior cervical region beneath the infrahyoid muscles and upon the anterior and lateral surfaces of the thyroid and cricoid cartilages and the upper part of the trachea It extends from opposite the junction of the middle and lower third of the thyroid cartilage above to the level of the fifth or sixth tracheal ring below While thyroid means shield (*thyreos* shield plus *eidos* form) or shieldlike the shape of the gland is actually more like that of the letter U The two lateral lobes form the arms of the U and the isthmus which is missing at times acts as its base When present the isthmus lies over the third and fourth tracheal rings Each of the two lateral lobes surrounded by an outer areolar capsule and an inner true capsule is about 5 cm in length 3 cm in breadth and 2 cm in thickness

Anteriorly the capsule of the thyroid is a smooth glistening peritoneum like structure which permits the gland to glide back and forth freely under overlying tissues *Here the two capsular layers are readily* distinguishable while posteriorly they become thinned out to merge with the tracheal fascia A marked condensation of fascial tissue occurs mesially near the posterior margin of the tracheal surface of each lobe This connective tissue forms a firm band extending to the thyroid and cricoid cartilages By some authorities this condensation of connective tissue is recognized as a suspensory ligament for the thyroid gland which insures a movement of the gland with the larynx while at the same time not fixing it firmly to that structure or to the trachea The ramifications of this ligament enter each lateral lobe to spread between the lobules and follicles thus forming a supportive framework for the gland The lobulation is complete when these septa meet with and join the inner portion of the capsule in all parts of the gland However in many instances these connective tissue septa are poorly differentiated so that the gland substance appears to be broken into ill defined masses of irregular shape and size

It is believed that the attachments of the capsule particularly the connection with the pretracheal fascia are important factors in the development of intrathoracic goiter

The overall structure and arrangement of the thyroid somewhat resemble that of a compound alveolar gland On cross section the ultimate unit of the gland the follicle can be discerned by the naked eye the sharpness of its outline depending upon the respective amounts of colloid and interfollicular stroma present

THE BLOOD SUPPLY

In proportion to its size the thyroid possesses a richer blood supply than any other organ in the body This is so abundant that the blood volume of a normal man (about 5 liters) moves through his thyroid once every hour (Lerman 1941) To be sure injection experiments (Williamson 1926) suggest that only a small fraction of the blood entering the gland at any one time passes through its intimate interfollicular spaces A great proportion seems to be shunted directly through the venous radicles and thence to the larger surface veins (Modell 1933)

The superior and inferior thyroid arteries branches from the external carotid and subclavian arteries respectively receive blood for the thyroid In about one out of every 10 persons a small proportion of the blood supply is derived from the *thyroidea ima* artery which varies in origin sometimes arising from the arch of the aorta and other times from the innominate the subclavian or the common carotid artery The points at which these major arteries of the thyroid enter the gland are remarkably constant a fact of no little aid to the surgeon The superior thyroid artery enters at or near the upper pole the inferior thyroid vessel posterolaterally along with the nerve and lymphatic supply to the organ and the *thyroidea ima* through the posteroinferior surface

The arteries of the thyroid are not terminal in type on the contrary rich anastomoses exist between them They form a widespread extraglandular plexus of vessels over the surface of the thyroid and upon penetration of the glandular substance break up into many branches eventually forming a profusely rich capillary bed about each alveolus

The blood from these intraglandular veins is collected by venules which course along with the arteries in the interfollicular spaces These drain into the superior and middle thyroid veins which empty into the internal jugulars and into the inferior thyroid veins which connect with the left innominate vein

THE LYMPHATICS

Our knowledge of the lymph vascular system of the thyroid is still meager It is known that immediately outside the follicular capillaries there is a network of very fine lymph spaces which completely surrounds the follicle From this network lymph is drained into the lymphatic vessels of the interlobular connective tissue through which

it passes into the larger trunks that finally unite to form the subcapsular plexuses. The majority of efferent vessels pass to the deep cervical lymph nodes and a few to the pretracheal lymph glands. Lymph finally reaches the right lymphatic duct by way of the cervical and thoracic lymph glands.

Since the classical work of Carlson and Woelfel (1910) little has been done to determine the amount of lymph secreted by the thyroid. In dogs they observed the amount of thyroid lymph to be remarkably small under normal conditions and increased in amount only when the gland was much enlarged. Surprisingly they found that lymph from the thyroid did not contain any larger quantity of thyroid hormone than lymph from any other source.

THE NERVE SUPPLY

The close connection between some functions of the thyroid gland and the autonomic nervous system may well be inferred from the fact that nerves supplying the gland are derived from the superior laryngeal and recurrent branches of the vagus as well as from the middle and inferior cervical branches of the sympathetic ganglia. All of these pass into the thyroid along with the lymphatics and blood vessels. It is believed that they are uniformly distributed to all parts of the gland, some to terminate in the blood vessel walls and others in the loose tissues around the follicle. Thus the thyroid is supplied by a rich network of autonomic nerve fibers, the sympathetic arising from the cervical ganglia and the parasympathetic from the vagus. The function of these nerves appears to be chiefly vasomotor in character, through such control a secondary reaction upon secretory activity may be exerted, although this has not been proved (Nonidez 1935, Uotila 1939a, Lindgood and Cannon 1939, 1940).

Nervous regulation of thyroid secretion may also be influenced indirectly by impulses beginning in the hypothalamus and extending over the hypothalamicohypophyseal pathways to the pituitary. Under normal circumstances, at least in some animals, this action may not be demonstrable (Uotila 1939b), but under certain stresses such as exposure to cold or mental or emotional upset these influences may play an important role in the disturbances seen in thyroid function.

THE INTERFOLLICULAR (INTERSTITIAL) TISSUE

The interfollicular spaces of the thyroid are occupied by a loose connective tissue through which are distributed the capillaries, smallest lymph and blood vessels, and the nerves. We have already implied in the preceding paragraphs that alterations in this stroma result from the combined action of blood vessels and nerves in response to various physiological stimuli (Nonidez 1932, Modell 1933, Lerman 1941). That such changes play an *important role in the capacity of*

the follicle to carry on its specific functions is indicated by certain cytochemical techniques (Dempsey and Astwood 1943 Dempsey 1944 Dempsey and Singer 1946 De Robertis and Nowinski 1946 De Robertis 1948 1949)

Extensive investigations into the nature of the argyrophilic reticulum or network of this stroma have led Dempsey and Singer (1946) to the conclusion that such stromal tissue contains a protein or proteinlike material to which active carbonyl groupings are attached This material decreases with an increase in thyroid activity and is found in greatest quantity in the stroma lying between the least active follicles It is therefore logical to conclude that it represents a metabolite or metabolites useful for the performance of some of the intermediary steps in the development of thyroid hormone or it may be the source upon which the thyroid cell draws for readily available energy in periods of stress Its exact function has not been determined

Alterations in the phosphatases of the endothelium of the thyroid capillaries occur concomitantly with variations in the amount of argyrophilic stromal reticulum It may be that both are similarly concerned with the nutritional status of the acinar cell Dempsey and Singer (1946) suggest that regions containing the enzyme may transmit across the endothelial barrier materials which are denied passage by other regions lacking the enzymatic mechanism Furthermore these changes in endothelial phosphatase may provide a qualitatively different pabulum to the parenchymatous cells of the active as opposed to the inactive gland

THE THYROID FOLLICLE, PRIMARY FUNCTIONING UNIT OF THE THYROID

The thyroid follicles alveoli or acini are the ultimate and essential functioning units of the thyroid gland These as well as the surrounding stroma alter considerably in appearance pH and staining reactions under different physiological and pathological conditions

Each acinus is an irregularly oval or spherically shaped body which is approximately 300 microns or less in diameter and is lined by a continuous secretory epithelium one layer deep When cut perpendicularly to the lumen of the follicle the outline of each cell section is roughly square in the normally active gland When cut tangentially it is circular The size and shape of these cells and the amount of colloid alter considerably during the various phases of acinar activity

Each follicle is a secretory unit in which the lining cells and the colloid play equally important parts (Jackson 1931 Wilson 1927) nor indeed must the surrounding supporting stroma be forgotten It was aptly remarked The cells of the follicle make the thyroid colloid the lumen is the storehouse (Lerman 1941) This is a dramatic albeit extremely useful oversimplification of the matter for in order to

integrate the activity of the thyroid with all other bodily structures many qualitatively and quantitatively varied biochemical reactions proceed continuously within both cells and colloid

Concomitantly with these *wide variations in function* equally striking histological alterations occur in the normal gland the interpretation of which has baffled the most astute histologists and pathologists These were stressed a quarter of a century ago by Crawford and Hartley (1925) More recently other workers (Portmann 1931 Holt 1931 Smith Pool and Olcott 1931) have emphasized the tremendous variation to be found in the histological picture of the normal gland by carefully analyzing cases mistakenly diagnosed as carcinoma of the thyroid and conversely others in which the same diagnosis was missed

It was Uhlenhuth (1923) who first demonstrated in rabbits a complete and definite cycle of thyroidal activity which could be divided into not less than two distinct phases—*a colloid storage phase* and *a colloid release phase*—the whole gland undergoing activity or involution simultaneously By observing thyroid follicles implanted in rabbits ears Williams (1937) was able to divide this cycle into four distinct stages *There is good reason to believe that such stages occur in the individual* follicles of the human being (Fitzgerald and Foote 1919) but at no time are all follicles in any single phase even in the highly hyperplastic gland (Wahlberg 1916 1917) In any event Williams classification affords a convenient though somewhat arbitrary method for describing the chemical and physiologic changes taking place These stages are respectively those of (1) secretion (2) secretion and colloid release (3) partial collapse and (4) recuperation For the rabbit data regarding these secretory phases are briefly summarized in Table II

1 **Secretion** -During the recuperative phase the cell which was flat in the resting stage becomes cuboidal or columnar in type being approximately as high as it is wide (about 15 microns) The Golgi apparatus hypertrophies and the number and size of the mitochondria increase The nucleus assumes a more nearly central position than before and granules appear in the cytoplasm both at the base and at the apex of the cell At least two types of granule can be distinguished at the base of the cell argentaffin and oxidase The former can be demonstrated in all phases of activity except that of collapse Popoff (1913) believes that it is probably concerned with the rejuvenation and vitality of the acinar cell (Popoff 1913 Dempsey and Singer 1936) thus resembling in mode of formation and functional significance similarly appearing cells within the gastrointestinal tract The oxidase granules described by Olkels (1931) also occupy the basal portion of the cell during the recuperative and early secretory phases of activity Under the influence of thyrotrophic hormone from the pituitary, these granules may become exceptionally numerous invading all parts of the

TABLE II

CYCLIC CHANGES OCCURRING IN THE THYROID FOLLICLE

PHASE	CHARACTERISTICS OF THE FOLLICLE	RELATIVE LENGTH OF PHASE (APPROX.) %
I Secretion	Thick wall Secretion towards follicle Thyroxin rich colloid	17
II Secretion and colloid release	Irregular wall Secretion to and from follicle Thyroxin rich colloid Diam. up to 300	50
III Collapse	Follicle almost completely disappears Little or no thyroxin	3
IV Recuperation	Wall thickens Small amount of colloid Little thyroxin Diam. up to 80	30

The changes observed in living transplanted thyroid tissue of the rabbit (From the data of R. G. Williams 1937.)

cell the colloid and even the interfollicular spaces. Their functional significance is not entirely clear but undoubtedly their increase with an increase in colloid formation and release is more than coincidental.

The apical inclusions are of two types: enzymic granules and colloid droplets. The enzymic granules are concerned with the elaboration of colloid and appear in all types of acinous epithelium except in the flat endothelioid form seen in the third and early part of the fourth stages of follicular activity (Popoff 1943).

Colloid droplets first make their appearance in close proximity to the enlarged Golgi reticulum (Severinghaus 1933). In this phase secretion takes place wholly or at least predominantly toward the lumen of the follicle (De Robertis 1942, 1948, 1949; Popoff 1943; Williams 1944) which begins to fill with colloid having a high thyroxin content (Dempsey 1944; Wahlberg 1947). However, the intrafollicular space is relatively free of colloid until the mixed phase of secretion and release begins (De Robertis 1942; Dempsey 1944; Williams 1944; Chapman and Higgins 1944; Keating, Rawson et al. 1945).

2. **Secretion and Colloid Release.**—In this stage the follicles become distended with colloid in which by the use of proper staining

technics proteolytic enzymes can be demonstrated in a precipitated form (Popoff 1913 Wahlberg 1916 1917 De Robertis 1918 1919) Toward the end of this stage, apical secretion granules disappear the cells become more vacuolated and show the presence of much proteolytic enzyme like that earlier demonstrated within the colloid itself (Popoff 1913)

From our present knowledge of the histophysiology of the follicle it appears that the secretions produced by the cell may under varying circumstances migrate in one of several ways Early in the phase of secretion and colloid release the predominant direction is toward the lumen of the follicle while later it is mainly toward the base of the cell (Herman 1911 Herman and Salter 1936 Means 1937 McClendon 1939 De Robertis 1911 1912 1918a 1919 Popoff 1913 Williams 1911 De Robertis and Nowinski 1916, Dempsey and Singer 1916 Wahlberg 1916 1917) If the thyroid is hyperactive secretion from the base of the cell directly into the subjacent capillaries has been demonstrated (Wahlberg 1916 1917) In certain states of cellular hyperactivity the secretion may proceed in both directions When the secretory stream is predominantly toward the base of the cell as in certain hyperthyroid states or following the use of the thiourea and its derivatives it can be reversed by the use of iodine (Wahlberg 1916 1917 De Robertis 1919)

Whether release of hormone occurs through or between the acinar cells has long been a moot question Today most workers accept an intracellular route of reabsorption (Severinghaus 1933 De Robertis 1912 1918 1919 Williams 1937 1911 Dempsey and Singer 1916 Wahlberg 1917) with a pre release breakdown of the large iodothyroglobulin molecule or at least a splitting off and extrusion of thyroxin as a single unit while the remainder of the molecule is reduced to polypeptides or smaller groups for circulation and resynthesis within the tissues

Many methods of tissue manipulation and a wide variety of stains have been used in correlating the histological and physiological changes which take place within the follicle Statements regarding staining reactions may be readily misleading unless the conditions of fixation the pH of the tissues and the stain the reagents used and so forth are recorded Therefore whenever their use would be ambiguous we shall avoid insofar as possible such terms as acidophilic cosinophilic basophilic blue staining red staining and so forth with which the clinician has really little concern Instead an attempt will be made to speak of active or inactive responsive or unresponsive cells droplets and colloid

The more active colloid appears to lie at the periphery of the individual follicle and is rich in thyroxin in a readily assimilable and soluble form as well as in vacuolar proteolytic enzymes (Popoff 1913)

These ferments are believed to break down iodothyroglobulin preparatory to delivery of thyroid hormone through the acinar cell and capillary wall into the blood stream for it is clear that unchanged thyroglobulin with a molecular weight of approximately 675 000 never enters the blood stream nor circulates through the body (Lerman 1940 1941) Interference with such release may give rise to soft and anatomically defective adenomatous glands (Popoff 1943)

In the larger acini a second type of colloid is centrally located and represents the older inspissated colloid of a more or less inactive type However this colloid is also subject to enzymic activity which can usually be recognized histologically by the appearance of a solitary central vacuole from which proteolytic enzymes can be precipitated This solitary vacuole spreads as if by pseudopodal formation until such a time as the proteolysis reaches the acinar epithelium That resorption of this colloid takes place directly though the cells seems to be unmistakably proved by the fact that degradation products of inspissated colloid are demonstrable in the epithelial cells and that the proteolytic enzymes are also present in the cells themselves (Popoff 1943 Wahlberg 1947 De Robertis 1948a 1949) While such colloid is as rich in thyroxin as that seen at the periphery of the follicle its thyroxin exists in a relatively inactive insoluble I eto form (Popoff 1943)

Not only may a single follicle take on two different types of staining reaction peripherally and centrally located which indicate the presence of active and inactive colloid respectively but also it is equally possible to find some follicles which are relatively inactive or quiescent and others in which all of the colloid is active as well as the cellular structure The former are more common at the periphery of the thyroid while centrally placed acini are more likely to be in the latter group This concept is further supported by the demonstration of relatively large amounts of radioiodine in the peripheral follicles of the normal gland for a relatively long period of time as compared with the rapid turnover in the centrally located follicles (Leblond 1943 a b Morton and others 1941 1942 De Robertis 1941 Lerman 1941 Leblond and Gross 1948a b) This relationship between the two types of colloid as shown by their responses to special stains is still further emphasized by the fact that most of the follicles in animals treated by anterior pituitary extracts are basophilic in reaction to the ordinary polychrome methylene blue stains such as hematoxylin and eosin azan stain etc whereas those of hypophysectomized animals tend to be more acidophilic (Leblond 1944) Therefore in stage two one finds predominantly basophilic follicles containing large amounts of fresh colloid with multiple vacuolization (Leblond 1944) The high enzymic content of this type of follicle reflects the intensity with which the secretory and release phases of colloid activity are carried forward (Lerman 1941 De Robertis 1941 1948 1949 Leblond 1944)

It would appear that both acidophilic (inactive) and basophilic (active) follicles can receive iodine from the blood stream with equal readiness but organic iodine is more readily released from the stimulated presumably basophilic follicles so that by the end of 15 hours Leblond (1941) showed more radioactive iodine in the former than in the latter From these observations and the work of others (Morton et al 1941 1942 De Robertis 1941 1945 1949 Lerman 1941) it is quite clear that in stages one and two of follicular activity it is possible for the thyroid to pick up inorganic iodine much more readily from the blood and to return it to the tissues in an organic form more rapidly than at other times (Leblond and Sue 1941) Interference with the intracellular resorption of colloid results in a large number of follicles containing central vacuoles and the absence in the epithelial cells of the products of digestion of inspissated colloids Morphologically such disturbances resemble those seen in the thyroid gland of an aged person and when present in a high degree indicate a senile gland (Popoff 1913) The high level of the enzymic activity of the follicular colloid in stages one and two is further attested by a rise in its oxidation reduction potential (De Robertis and Gonçalves 1945)

It has been further shown by staining technics that the cytoplasm of the follicular cells and intrafollicular colloid contain proteolytic enzymes ribonucleoprotein and an argyrophilic protein material the reactions of which are characteristic of active carbonyl groupings (Dempsey and Singer 1946 Dempsey 1949) Glycerophosphatases are present in the follicular cells and simple sugar phosphatases are concentrated in the capillary endothelium

The ribonucleoprotein is highest in amount in the cells and colloid of the inactive follicles and decreases in direct proportion to the activity undergone by the follicle Both the ribonucleoprotein and the argyrophilic protein are highest in concentration in the peripheral inactive cells and follicles and decrease in direct proportion to the increase in function of the gland It would appear from these facts that not one but several proteins are involved in the formation of colloid and that while thyroxin is an important constituent colloid may be manufactured in its absence Such a conclusion is amply borne out by experimental evidence as a colloid deficient in thyroid hormone has been produced by hypophysectomy (Astwood and Bissell 1944) and by the administration of thiouracil (Astwood Sullivan et al 1943)

Alkaline glycerophosphatases are observed in highest concentration in the inactive peripheral follicles almost disappearing completely from the central active follicles Moreover an increase in the activity of the thyroid is associated with a loss of them from all follicular cells and colloid Acid phosphatases behave in an exactly opposite fashion The hexosephosphatases which show a strong predilection for the capillary endothelial cells but which can also be demonstrated in the follicular

epithelium fluctuate widely in amount with activity of the tissues It seems probable that the dominant role of phosphatase is its participation in the intermediary carbohydrate metabolism of the thyroid gland (Dempsey and Singer 1946 Dempsey 1949) This concept is well supported by the fact that polysaccharide complexes have been found in the colloid in all states of thyroidal activity (Gersh 1947 Dempsey 1948) Gersh believes these may consist chiefly of hyaluronic acid a suggestion questioned by Dempsey who is of the opinion that the mucopolysaccharide fraction of the colloid is neutral in reaction

If we turn from a study of fixed stained tissues to a study of conditions in vivo finer morphologic details—shall we say scientific artefacts (Dvoskin 1947b)—are lost but the sequence of events within the follicle is clarified In continuous observation of individual follicles through all stages of development and regression Williams (1937) has never seen secretion take place toward the base of the cell though not denying that this may take place Nor does he believe it necessary to postulate the existence of intercellular canaliculi as distinct morphologic entities In fact the tremendous activity of the cells and their rapidly changing contours lead him to doubt the presence of such structures He believes that colloid release by diffusion through compressed cells is an extremely active process but does not deny the possibility of intercellular release as well Throughout stage two a rapid succession of changes concerned with the formation and release of colloid was observed by him in the cells of the follicular wall and in the colloid itself It is during this stage that cellular secretion reaches its height and begins to decline Not all cells are in the same stage of secretory activity Some cease to function sooner than others Such cells will be compressed due to the increased pressure produced by the continued secretion of other still active cells A thin point will therefore develop in the wall at the site of such a cell against which colloid will be forced The free ends of the adjacent active cells will close or tend to close this partial defect thus leaving a colloid droplet entirely within the wall to diffuse slowly through the flattened inactive cell or perhaps between it and the adjacent cell In this connection it must be emphasized that the colloid droplet as such never appears in the interfollicular spaces Hence it seems likely that a slow diffusion perhaps associated with enzymic activity (Dempsey and Singer 1946 Dempsey 1949) takes place in the transport of the colloid across the thinned out cell (described by Williams as never less than 2 microns thick) to the interfollicular spaces and blood stream At times droplets are not formed for if a relatively long stretch of the cellular boundary of the follicle becomes thinned out absorption into the blood stream will be more rapid Droplets will not be seen for the remaining active cells are unable to repair the defect or squeeze off the particles of colloid

From his study of living autogenous implants into the rabbit's ear Williams (1937) observed that during stage two of follicular activity both colloid formation and release occur simultaneously As long as the thinned out portions of the wall are small formation (or colloid manufacture) and extrusion into the follicle predominate with continuing distention and possibly increased pressure within the lumen but when large stretches of the wall become thinned out then colloid release is rapid cellular activity ceases and the acinus enters a stage of partial collapse

In summary various types of histological study of the thyroid follicle during the stage of its greatest and most prolonged activity stage two reveal that secretory activity takes place at first toward the lumen of the follicle and later goes in both directions Probably under normal conditions and certainly in states of hyperactivity secretion occurs directly toward the base of the cells and into the capillaries Centrally placed follicles are more active than those peripherally located In the larger follicles the less active portion of the colloid is centrally located and while containing thyroxin probably holds it in a less readily available form than the peripheral portions of the acinus More than one protein is concerned in the formation and hormonal potency of colloid as in addition to thyroglobulin, ribonucleoprotein and protein material with active carbonyl groupings are also present The intensity of the energy exchanges within the acini is suggested by the behavior of phosphatases which vary quantitatively and qualitatively in response to a changing activity of the thyroid tissues After a certain amount of intense secretory activity the acinus becomes temporarily refractory to further stimulation by pituitary thyrotrophic hormone and enters a resting or collapse phase

3 **Partial Collapse** —All follicular activity vanishes during this stage The poorly stained cytoplasm of the follicular cell disappears from view and only the flattened nucleus remains to indicate its location Indeed had the position of the follicle not been demonstrated during phases one and two one might well question its existence as a structural entity (Williams 1937) This is a stage of exhaustion or rest in which the follicle becomes refractory to stimuli normally capable of eliciting specific activity

4 **Recuperation** —The resting stage of thyroid follicular activity is very short and often not as striking as pictured above During the recuperative stage tremendous changes occur The indistinct flattened endothelioid appearing follicular cell with a shrunken elongated nucleus changes to a sharply defined cuboidal or low columnar structure in which all the elements of nuclear and cytoplasmic material are readily discernible During this stage the cells reach their highest morphological development that is attain full potential activity (Williams

1937) The follicular wall is markedly thickened but the intrafollicular space is small or negligible so that the longest diameter of the follicle rarely exceeds 80 microns Response to thyrotrophic hormone is maximal in preparation for another cycle of intense secretory activity During this stage and the early part of the secretory phase the iodine content of the follicle is low A long time ago Marine and Lenhart (1909a) emphasized the fact that under normal conditions the amount of iodine present in the follicle varies inversely as the degree of hyperplasia of the lining cell This is probably the reason that during this phase the response of the follicle to thyrotrophic hormone is maximal for it is well known that iodine opposes directly the action of thyroid stimulating hormone (Rawson and McArthur 1917)

DURATION OF THE FOLLICULAR CYCLE

Little or nothing is known of the duration of the follicular cycle in man and it is undoubtedly true that the secretory and release phase phase two may continue indefinitely Williams (1937) stated that the shortest cycle observed in rabbits was 19 hours and the longest 21 days (Table II) In prolonged cycles phase two occupies the major portion of the time Phase three is always short rarely continuing more than one to two hours in the rabbit In general stages one and two combined represent from 60 to 90 per cent of the entire length of the cycle

Many influences are brought to bear upon the thyroid follicle in the course of its cyclic activity each concerned in some way with the elaboration of its specific secretion Before discussing these regulatory factors in detail (Chapter XI) we will focus our attention upon the manner in which the gland probably produces this important secretion the thyroid hormone

Chapter IX

THE SYNTHESIS AND NATURE OF THYROID HORMONE

The only known function of the thyroid gland is the elaboration storage and delivery to the body of thyroid hormone a special substance which is mainly concerned with the functions of growth and metabolism In the production of this material which contains iodine in organic combination the thyroid behaves under normal conditions like a well ordered factory in which executive dispatches (pituitary) are predicated upon supply (thyroid hormone) demand (physiological conditions such as cold exercise etc) the availability of raw materials (iodine tyrosine globulin) and their influence upon the economic balance of the community (various metabolites such as uracils cyanates blood and tissue levels of iodine as affecting thyrotrophic hormone thyroid cell etc)

We may conveniently separate the work of the thyroid factory into five major categories (1) iodide concentration (2) iodine binding to amino acids and protein (3) the secretion of thyroid protein into the follicle (4) the digestion of stored hormonally active protein and (5) the secretion or extrusion of thyroid hormone into the blood stream

Some of the influences of the hypothalamus thyrotrophin (TSH) thyroid hormone and several antithyroid substances are graphically summarized in Figs 1 to 11 inclusive to which from time to time more detailed reference will be made

THE RAW MATERIALS

In order to synthesize thyroxin iodine and the amino acid tyrosine must be brought together under proper conditions For completing the formation of thyroid hormone at least as stored in the follicular colloid thyroxin enters into a loose combination with globulin to form iodothyroglobulin

Although experimentally it is possible to produce hormonally active material when there is partial or complete substitution of bromine chlorine or other halogens for the iodine (Danilewsky 1917 Leblond and Gross 1948 Baumann et al 1919 b Kennedy and Griesbach 1919 Lerman and Harington 1949 Richards Brady and Riggs 1949) and replacement of the thyronine grouping (Frieden and Winzler 1948 a) such preparations are far inferior to thyroxin in activity and are of little

or no importance for the over all functioning of the human thyroid in either health or disease

Ever since the early work of Marine and Lenhart (1909b) it has been well known that a deficiency of iodine results in a colloid or en-

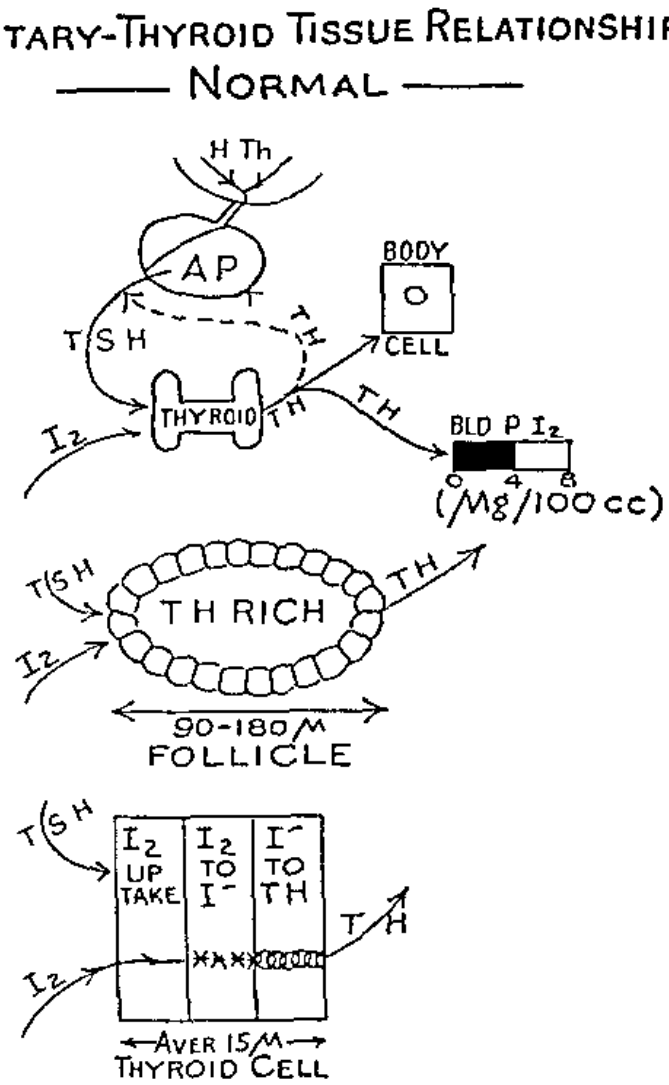


Fig 4—S h m tic rep sentati n of v al mai r n rmal pituit ry thyr id tis u relation hips The balan d a t n of the hypothalamu tl e ant or pituitary thy otrophin iodine and thyr d horm ne re ults in a norn lly i d normally funct oning thyroid with cellular and foll cular units l m tically depi ted Th ee t ps of thyroid h rmon development within the ll ar p es nt d f r pu p e of c mpari n witl ub equ nt figu es und varied conditions In th s and Γ g 5 11 in lusiv the f llowing bbr vi tion a e employed

H Th — Hypothal n u
A I — Ant ri pituit ry gland
T H — Thyro d ho m ne
I— — I d d
I — Na e t i di
Bld P I — Bl d prot n b und jo line

Sol d lin rep sent t mul tion a i brok n lin s inh biti n of th indi ted activity Na cent i dh is rep s nt d by os s (xxx) d o ani ally b und i dine by int locking circles Th ell a e hem tically mpartn ntalized to illustrat th lterations in the fu ct n ubb t d Wl ile the fi ur a not d av n to x ct ale a comp red the one with noth ff t has be n mad to ner e de as the i e of lin glandular utline cellular wall and c mpa tment in uch a m n e a to lend vi ual aid to th concept illustrated

demic type of goiter Under ordinary circumstances iodine is introduced into the body by way of the gastrointestinal tract and is delivered to the thyroid only in the form of the inorganic iodide The thyroid is capable of meeting its needs with as little as 15 micrograms of iodine per day (Salter 1940) but optimally has a turnover along its 'production line' of something like 200 micrograms per day

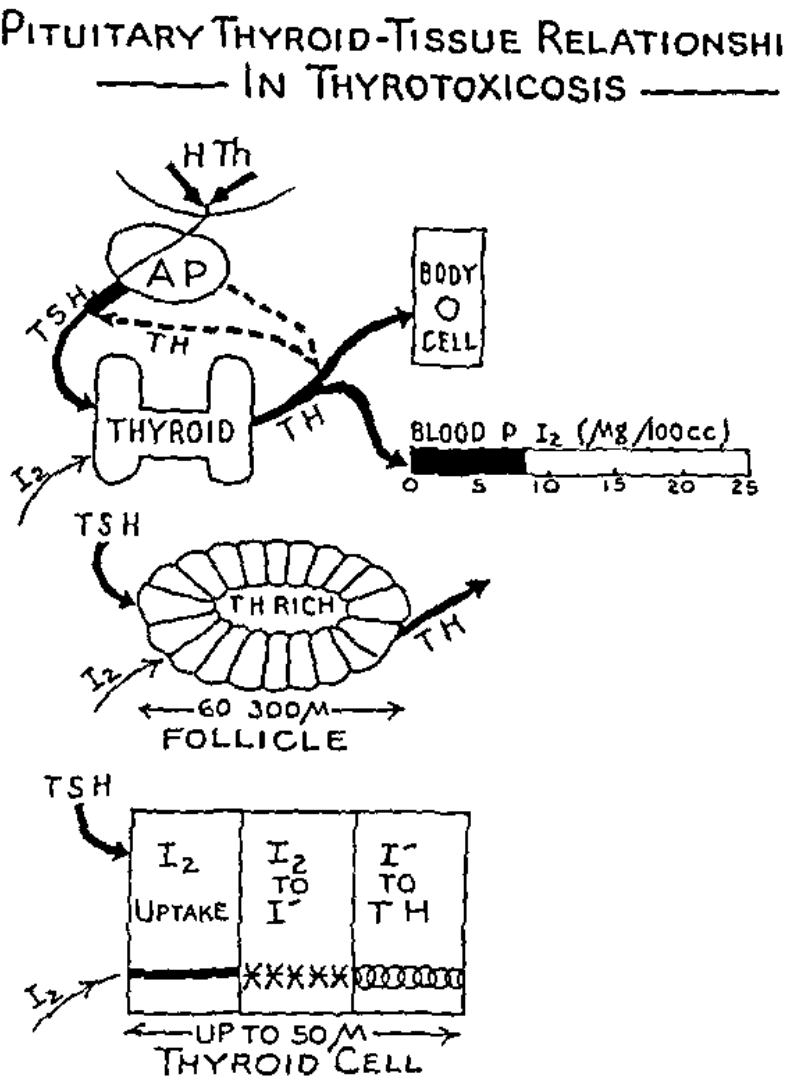


Fig —Pituitary thyroid tissue relationship in thyrotoxicosis The primary fault is probably nervous and emotional acting by way of the hypothalamus to the pituitary The increased amount of thyrotrophin produced stimulates the thyroid cells causing hypertrophy and an overproduction of thyroid hormone Even this increased amount of thyrotrophin hormone is not capable of controlling the excessive secretion of the pituitary or of sufficiently inactivating the additional thyroid stimulating hormone formed Note the excessive uptake phase of the work of the thyroid cell

Tyrosine is widely distributed in nature it is therefore doubtful that deficiency ever occurs in man unless it be in connection with starvation or the most advanced types of destructive pancreatic disease It is of interest that Hinton Morton and Weeks (1934) were

able to produce colloid goiter by ligation of the pancreatic ducts of dogs thus depriving the animals of important protein split products particularly tyrosine Pal and Bose (1913) decreased the thyroid hyperplasia of rats fed a deficient diet by the administration of *l* tyrosine However following ingestion tyrosine is rapidly incorporated into the protein of most tissues particularly the intestinal mucosa kidney, plasma liver and spleen (Frieden and Winzler 1948a b) Wherever it goes it retains its identity for long periods of time as shown by radioactively tagging the beta carbon atoms of the amino acid side chain Slow degradation is accompanied by the incorporation of the tagged

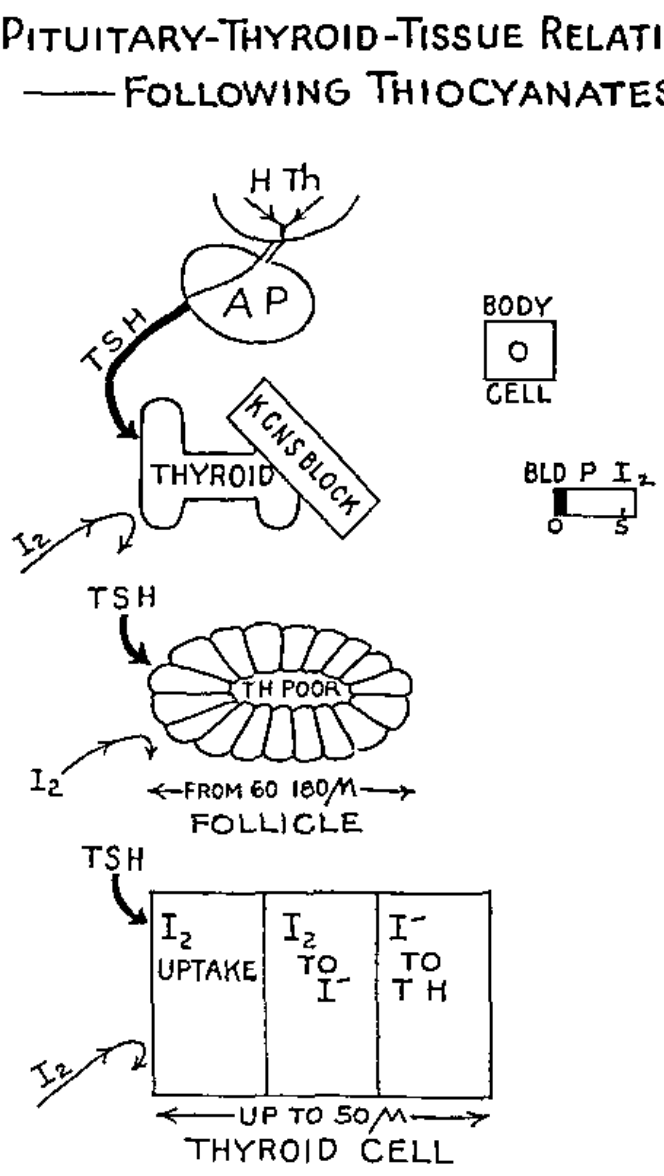


Fig 6—Pituitary thyroid tissue relationships following the administration of thiocyanate to normal subjects Note that the entry of iodine into the cell is completely blocked As a result thyroid hormone is not formed that the stimulatory action of TSH on the thyroid cell and follicle stands unopposed to u hyp tr phv hyp pla a and g iter

atoms into glycerine dicarboxylic acids urea creatinine hippuric acid and ketone bodies (Winnick Friedberg and Greenberg 1948) The larger portion which is not thus destroyed may be used over and over again Therefore it is reasonable to assume that the thyroid factory is rarely without a satisfactory supply of tyrosine even though its immediate precursor phenylalanine is one of the essential amino acids

Globulin is the third substance necessary for the completion of thyroid hormone for it is as iodothyroglobulin that this secretion exists within the follicles of the thyroid gland The ability of this material to

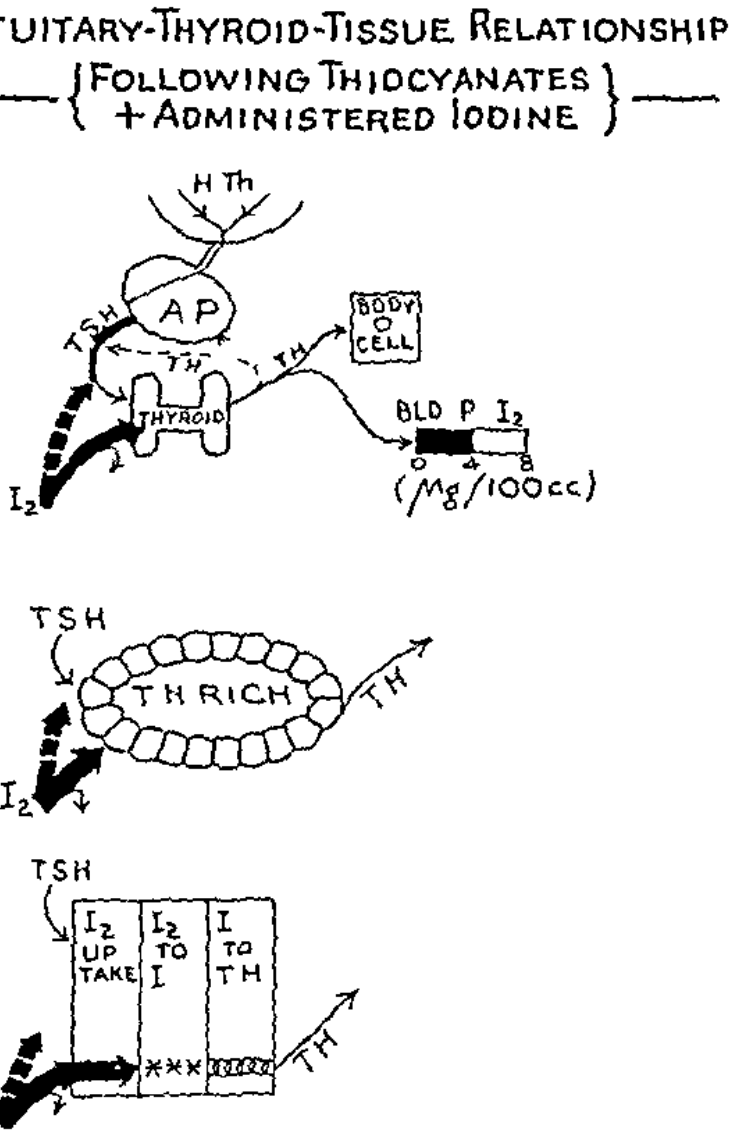


Fig 7—Pituitary thyroid tissue relationships following the administration of thiocyanates and iodine The block to the entry of iodide (Fig 8) can be effectively broken by large doses of iodine which act in a twofold manner (1) to inactivate thyrotrophin and (2) to increase the ability of the thyroid to concentrate iodide Simultaneously the gland returns to normal function and if goiter has occurred it may recede

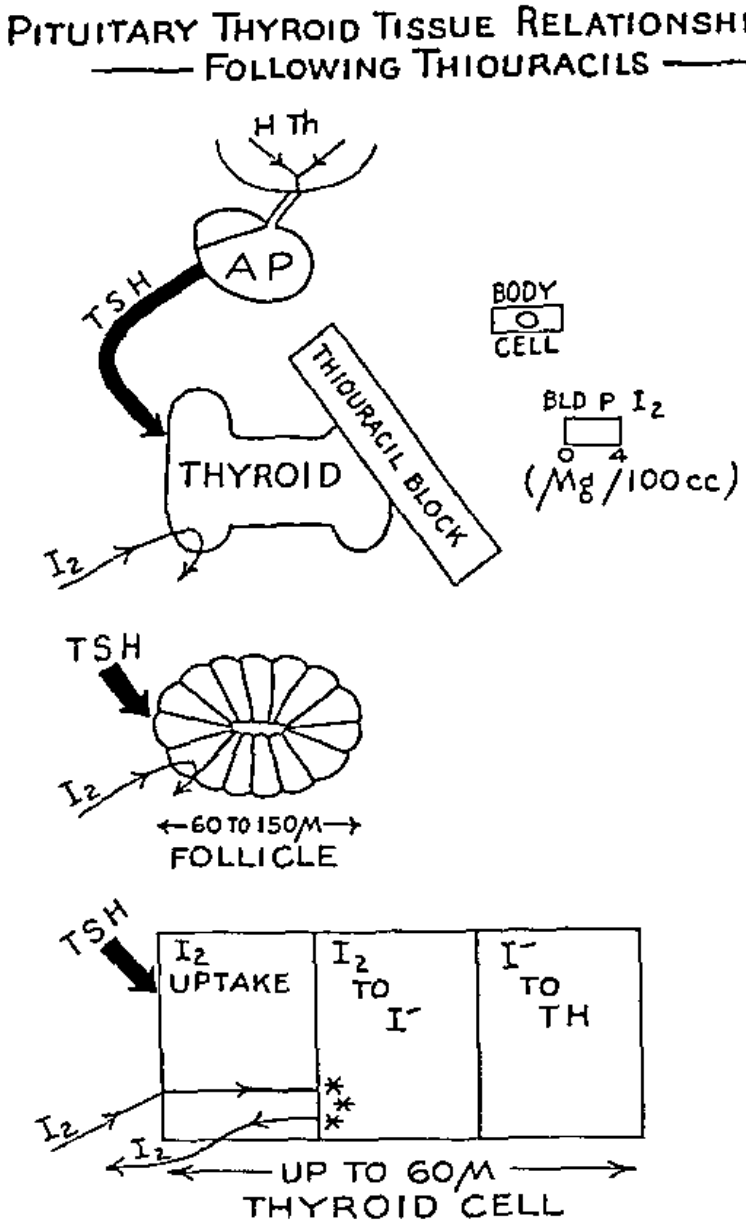


Fig. 8—Functional thyroid tissue relationships following the administration of the thiouracils and iodide. Substances which inhibit the ability of the gland to bind iodine organically depress active transport uptake. This may be an early effect of the drugs but the mechanism is still far from clear. Note the uncoupling of TSH with the secondary production of hyperplasia and hypertrophy, the failure in thyroid analysis of the steps through which the intermediate forms of thyroid hormone

raise rapidly the oxygen consumption of tissue distinguishes it physiologically from thyroxin (Williams and Whittenberger 1947).

Other protein fractions, various enzymes, and inositol (Meyer 1946) complete the list of raw materials needed by the thyroid for its elaboration of thyroid hormone. There is no unequivocal proof that metallic catalysts play any role in the production of thyroid hormone in the intact animal. Moreover the absence normally of any increased concentration within the thyroid of such common metallic catalysts as zinc

cobalt copper manganese and magnesium (Astwood 1949) is negative evidence that they are not concerned normally in the elaboration of thyroid hormone Nevertheless manganese particularly in the form of its tetroxide has proved to be of catalytic value in the synthesis of the hormonally active iodinated proteins (Remeke and Turner, 1945 1946 Ray and Devsach 1942 Remeke 1946 1949) Furthermore when fed to normal animals there is a tendency for manganese to concentrate in the thyroid (Ray and Devsach 1942 Devsach and Ray 1949) so that a possible role in thyroxin formation in vivo must not be dismissed too lightly

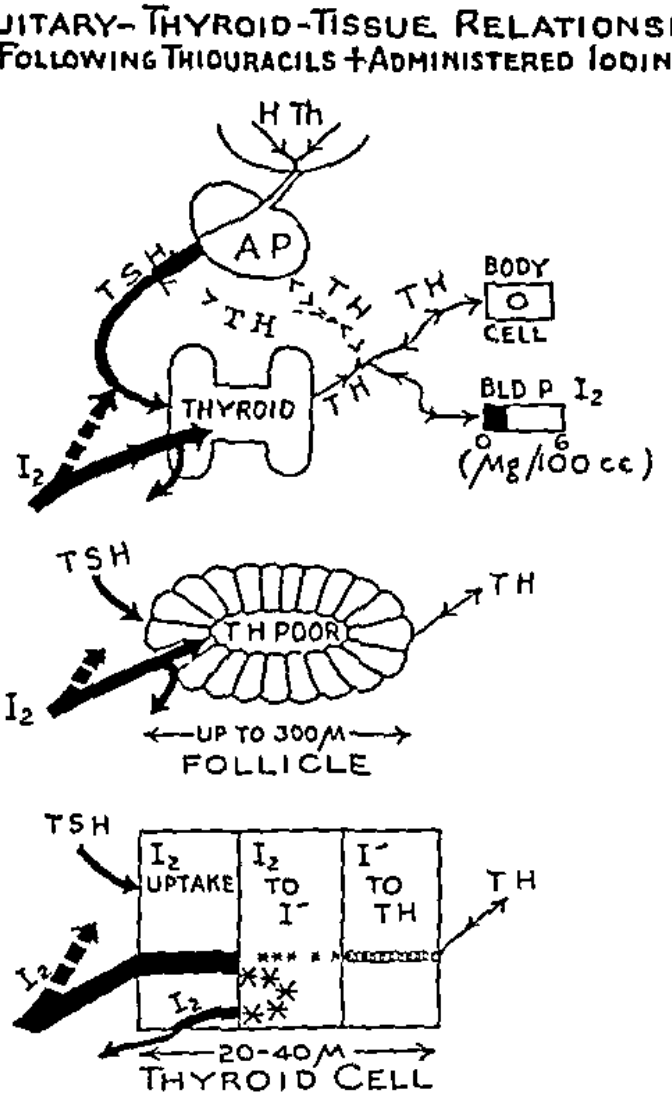


Fig 9—Pituitary thyroid tissue relationships following the administration of thiouracils and iodine The mass action of iodine opposes that of thiouracil with the result that a small amount of TH is formed TSH is partially inhibited chiefly by the iodide action cellular hypertrophy and hyperplasia are checked and a TH poor colloid is collected This suggests a reason for the usefulness of iodine in conjunction with antithyroid drugs as a part of preoperative therapy for subjects with hyperthyroidism

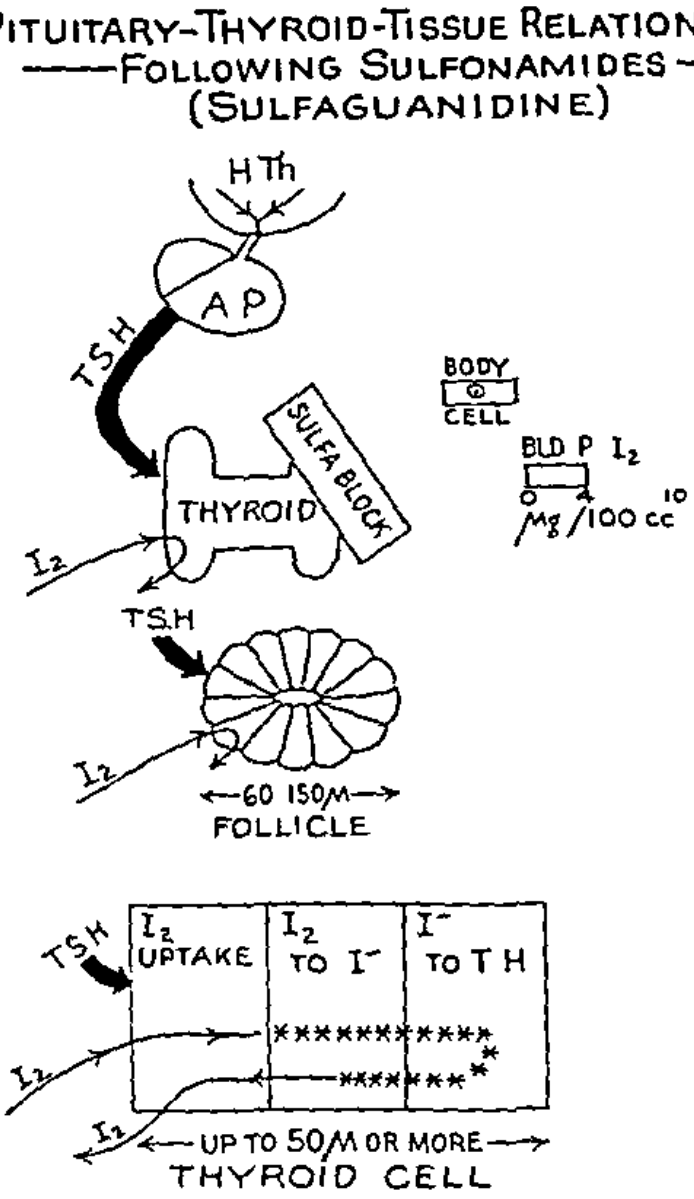


Fig 10 – Pituitary thyroid tissue relationships following administration of the sulfonamide The net result is the same for this as all but it may be that the point of attack of these substances is different Presumptively the action is one of inhibition of the enzymatic oxidative process responsible for the conversion of ingested iodine to the organic forms diiodotyrosin and thyroxin

IODINE CONCENTRATION WITHIN THE THYROID

Except under experimental conditions iodine is always received by the thyroid gland in the form of the iodide (I⁻) Iodide is rapidly fixed by the gland at first in an inorganic state (Chaikoff and Taurog 1949) as little as 10 minutes being sufficient for the concentration of an organic iodide to reach its maximum following an orally administered dose of radioiodine (Hertz et al 1939 1940 Hertz 1941 Leblond 1943)

The ability of the thyroid cell to collect and concentrate iodine is more or less independent of its capacity for organically binding this

iodine to amino acids and protein in the synthesis of thyroid hormone Therefore no constant or fixed relationship exists between the amount of inorganic and organic iodine contained in the thyroid gland at any *given moment* There is indeed some mechanism in the thyroid gland for concentrating inorganic iodine which is not dependent upon its conversion to diiodotyrosine thyroxin or thyroglobulin (Schachner et al 1941 Astwood 1939) The nature of this mechanism is unknown but the iodine so trapped is in the form of the iodide (Chaikoff and Taurog 1949)

When the amount of iodine ingested is varied over a wide range of dosage the plasma iodine is rapidly affected the larger the dose of

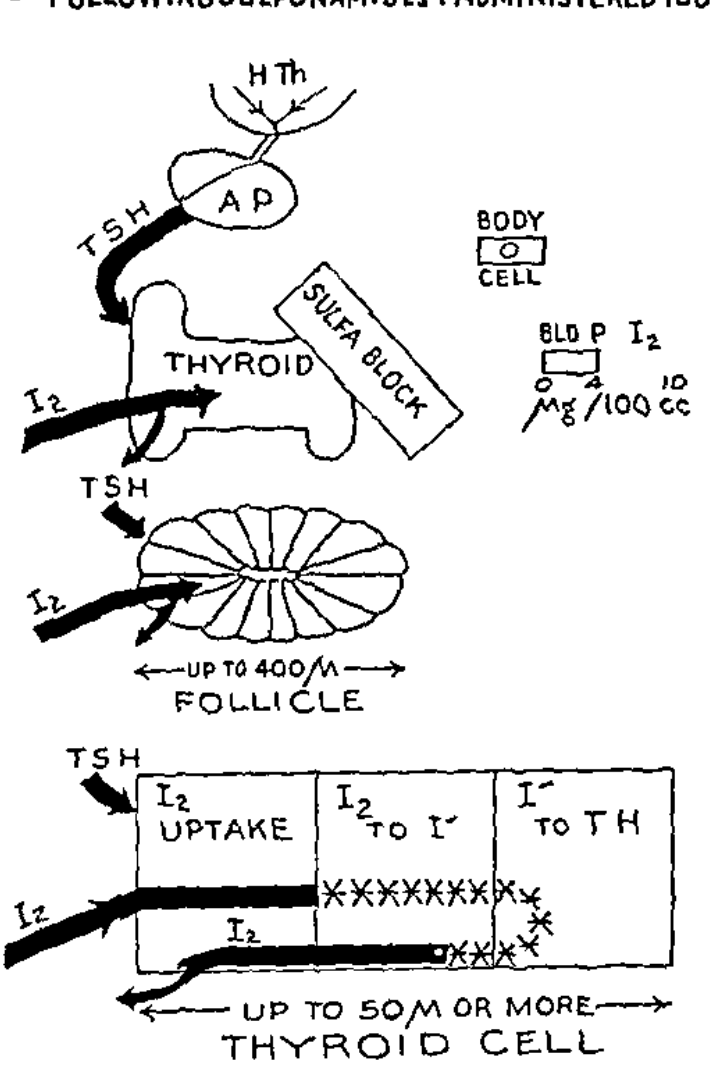


Fig 11—Pituitary thyroid tissue relationships following the administration of sulfonamides and iodine Sulfaguanidine in subnarcotic doses was the drug actually used for the experiments described It will be noted that the hypertrophy and hyperplasia caused by sulfaguanidine above have actually been increased by the addition of iodine

iodine the greater the plasma values The iodine trapped by the thyroid appears to vary directly with the height of the blood iodine This is however not a matter of simple equilibrium for the concentration within the thyroid is manyfold that in the blood having been found to vary in normal subjects from 31 to 91 when tracer doses of iodine are fed (Stanley and Astwood 1949)

Inasmuch as this general relationship between the iodine of the thyroid and that of the blood is subject to alteration by many extrinsic factors no single constant can be used for its mathematical expression under all conditions Iodine deficiency as for instance in goitrous areas is followed by a higher than usual ratio as soon as adequate quantities of the element are administered For a considerable period of time following the depletion of thyroidal iodine by thiouracil or a closely related derivative the capacity of the gland for the uptake of iodine is increased (VanderLaan and VanderLaan 1947 McGinty 1949) Thyrotrophin and thyrotoxicosis both dramatically augment this function of the gland for concentrating iodine (Stanley and Astwood 1948 1949) Thiocyanate not only blocks the entry of iodide into the thyroid (Fig 6) but also actually favors its discharge thus lowering the thyroid to blood ratio After such a block sufficiently large doses of iodine will restore the iodide concentration to normal Under specific conditions these actions of thiocyanate and thyrotrophin may be reversed (Raben 1949)

In summary the iodide concentrating capacity of the thyroid varies roughly with the blood levels for that element except under the special conditions above mentioned Thiocyanates lower the thyroid blood ratio thus decreasing or inhibiting the uptake and diminishing both the concentration and amount of iodide within the gland Thiouracil and its derivatives and the sulfonamides interfere little if at all with uptake of iodine by the thyroid except in the release phase when the capacity of the thyroid cell for inorganic iodide is greater than normal Hyperthyroidism and the thyrotrophic hormone of the pituitary dramatically augment the amount of iodide packed into the gland and thus raise the ratio of thyroid to blood iodine

IODINE BINDING TO AMINO ACIDS AND PROTEIN

Oxidative processes are involved in converting inorganic to organic iodine within the thyroid cell In the normal gland a large percentage of a small dose of tracer iodine may be organically bound in as little as 15 minutes after administration (Chaikoff and Taurog 1949) The first step or steps involved in such a change is the oxidation of iodide to hypoiodous acid and nascent iodine in which states it is capable of combining the tyrosine to form 3 5 diiodotyrosine directly (Li 1942) or in successive steps by way of monoiodotyrosine (Finkel and Fink 1948 Taurog Chaikoff and Tong 1949)

TABLE III

SOME FACTORS KNOWN TO BE NORMALLY CONCERNED IN THE SYNTHESIS STORAGE AND DISTRIBUTION OF THYROGLOBULIN

AT LEVEL OF	SUBSTANCES CONCERNED	RESULTING PRODUCT	SPEED OF MAXIMUM FIXATION BY THYROID OF RATS	HORMONAL ACTION		
				CALORIGENIC	RELIEF OF MYX	QO_2 OF TISSUE
Intestinal villi blood and other extra thyroidal tissue	Iodides Tyrosine or Thyronine		10 min			
Thyroid cell	Iodides + Enzyme (*Peroxidases?*)	Hypoiodous acid				
	Hypoiodous acid + Enzyme + Tyrosine	Di iodo-tyrosine		Slight	0	?
Cell and Colloid	Di iodo tyrosine + Enzyme	*Di iodo thyronine (?)*		+	4% Thyroxin	0
	Di iodo thyronine + Enzyme	Thyroxin	Cell 8 hr	+	Complete	0
Colloid	Thyroxin + Colloid Globulin	Thyroid hormone (Iodo thyro globulin)	Colloid 40-48 hr	+	Complete	+
Colloid cell and blood	Thyroglobulin + *Proteolytic enzyme* or thyroxin	Thyroxin + Split globulin products (?)	Same as thyroxin			
Tissues	Thyroxin + Globulin	Thyroid hormone	Same as thyroglobulin			

It now appears as earlier contended by Harington (1935 1944), that 3 5 diiodotyrosine is the normal precursor for the formation of thyroxin (Fig 1) (Chaikoff and Taurog 1949 Reinecke 1949) and that oxidative enzymes are responsible for the conversion of one to the other Such enzymes are believed to be similar to or identical with those which effect the conversion of inorganic iodide to diiodotyrosine (Schachner et al 1943) (Fig 1 and Table III)

In the final synthesis of the active hormone thyroxin from indifferent proteins the iodine and the tyrosine are equally important When only two atoms of iodine are added as in diiodotyrosine the thyroidlike action is approximately 1 per cent of that of the fully formed hormone In thyroxin two molecules of tyrosine are combined with the disappearance of the propionic acid side chain in such a way as to form a diphenyl ether (Fig 1) If these phenyl groups of thyroxin are directly linked to carbon rather than through a connecting oxygen atom (diphenyl ether combination) then the material becomes hormonally inert despite the presence of four iodine atoms

When all the known facts are considered they are in consonance with the view that thyroxin is probably formed *within the protein molecule* by the oxidative coupling of two diiodotyrosine radicals with the splitting off of one amino propionic acid side chain (Fig 1)

THE ENZYME SYSTEMS PROBABLY INVOLVED IN THE FORMATION OF THYROID HORMONE

As indicated above at least three steps are concerned in the synthesis of thyroxin by the thyroid gland (1) the oxidation of iodide to nascent iodine (2) the iodination of tyrosine to form diiodotyrosine and (3) the coupling of two molecules of diiodotyrosine to form tetraiodothyronine (thyroxin) All three steps appear to be dependent upon enzymic oxidative phenomena (Li 1942 Johnson and Tewkesbury 1942 Schachner et al 1943 Harington 1944 Harington and Pitt Rivers 1945 Cruz Colee et al 1947 Wolff and Chaikoff 1948a b Swenson and Curtis 1948 Chaikoff and Taurog 1949 Astwood 1949 Leblond and Gross 1949)

Evidence has accumulated which indicates that the cytochrome cytochrome oxidase system may be concerned in thyroid hormone synthesis despite the fact that it is probably not blocked by antithyroid compounds of the thiourea type Chaikoff and Taurog (1949) have summarized some of the facts upon which this statement is based as concluded from a study of the formation of diiodotyrosine and thyroxin by thyroid tissue slices Evidence that oxidative enzymes are involved was obtained by a study of the effects of anaerobiosis and of substances that are inhibitors of cytochrome oxidase Sulfide azide and cyanide in low concentrations had strong inhibitory effects on the formation of thyroxin and diiodotyrosine Only 5 to 15 per cent of the normal

synthesis occurred in the presence of these agents The complete absence of oxygen or the presence of a high concentration of carbon monoxide also had a marked inhibitory effect (which for carbon monoxide) was partially reversible in the presence of strong light The evidence strongly suggests that the cytochrome cytochrome oxidase system is involved in the formation of these iodine compounds by the thyroid gland

That other oxidative enzyme systems are probably more important than the cytochrome cytochrome oxidase system in the production of thyroid hormone is conclusively shown by the fact that the inhibition of oxidation produced by thiourea thiouracil and sulfa preparations is not mediated through the cytochrome cytochrome oxidase system (Lerner and Chaikoff 1945 McShan Meyer and Johnsson 1946 Glock 1946b DuBois and Irwin 1946 Upton and Nixon 1946 Astwood 1949) although some studies indicate that this system may be secondarily involved as a result of a disturbance which sensitizes it within the thyroid and not in other tissues (Paschkis Cantarow and Fallson 1947 Paschkis Cantarow and Peacock 1948) It seems quite likely that the antithyroid compounds exert their action by competing for oxidative enzyme systems ordinarily employed in the synthesis of thyroxin for the more easily oxidation of the antithyroid compounds of the thiocarbamide group takes place the greater is their inhibitory activity (Taurog Chaikoff and Tarplin 1945 Randall 1946)

Several enzyme systems have been identified in the thyroid by chemocytological procedures The more important of these concern oxidase peroxidase phosphatase and proteolytic processes and activities

Inasmuch as high redox potentials appear to be necessary for the oxidation of iodide with subsequent organic binding the most likely enzymes to be involved directly in the synthesis of thyroid hormone are the peroxidases They are capable of promoting the oxidation of iodide to iodine and could carry out the oxidative coupling by which thyroxin appears to be formed from diiodotyrosine (Westerfeld and Lowe 1942) Moreover such enzymes have been shown to be inhibited by thiourea and thiouracil evidence for which has been reviewed by Astwood (1949) Sulfonamides and para aminobenzoic acid may act by competing for rather than by inhibiting these same systems There is histological evidence for the presence of such enzymes in the thyroid (Dempsey 1944 1949 Dempsey and Singer 1946 Grasso and De Robertis 1946 De Robertis 1949) although Gloel (1944) was unable to extract them from thyroid tissue Astwood (1949) points out that the iron containing porphyrins may exert the peroxidase effect In any event a survey of the facts to date indicates that a peroxidase type of enzymic process is necessary for the successive oxidations through which thyroxin is eventually formed (Table III)

THE SECRETION OF THYROID HORMONE INTO THE FOLLICLE AND ITS SUBSEQUENT RELEASE

The thyroid is the only one of the endocrine glands that is known to synthesize its secretion and simultaneously store it outside the cells in the colloid spaces. During the secretory phase of follicular activity enzymic processes are accompanied by the formation of colloidal droplets within the cell particularly toward its apical portion. With proper technic these can be shown to bulge slowly into the follicular space carrying with them a small rim of cytoplasm which indicates the apocrine nature of the secretion.

From the present evidence the development of this secretion is a very orderly affair both chemically and histologically. The cell grows as the need for its hormone grows. Oxidative enzymes prepared by it or supplied to it proceed to convert iodide to nascent iodine, this in turn to diiodotyrosine and thence probably inside a protein molecular structure to thyroxin. This thyroxin remains bound to the protein thyroglobulin and with it is expressed into the follicular lumen (Leblond and Gross 1948b). In the next phase of activity of the thyroid the hormonal stream reverses itself and moves the stored material through the cell to the blood stream (Table III).

Apparently the orientation of activity that is whether to or from the follicular space depends upon the difference established in electrical potentials (*De Robertis and Gonçalves 1945 Grasso and De Robertis 1946 Keller 1947* De Robertis 1949). When demands for thyroid hormone are not great or are actually decreased or decreasing and the major activity is toward the colloid space the cells show a considerably higher potential than the colloid. Under the influence of cold emotions or other stimuli capable of increasing the production of thyrotrophic hormone by the pituitary or following the administration of such hormone the potential of the colloid is raised to the same level as that of the cells. When this occurs then a reversal of the hormonal stream takes place and droplets of diluted colloid appear at the base of the cell ready to enter the perifollicular capillaries. In actuality the processes of ingress and egress to and from the follicle may and do commonly occur simultaneously but under certain conditions the predominance of one trend over the other can be made clearly evident by cytohistochemical means. There seems now to be little doubt that proteolytic enzymes play a leading role in the actual mobilization of colloid preparatory to its extrusion from the thyroid gland (Table III).

Normally the processes by which colloid is formed stored and extruded remain in balance through the homeostatic interaction of inorganic iodide pituitary hormone thyroid hormone and environmental conditions (Fig. 4). Environmental conditions act by way of the lower brain centers particularly the hypothalamus to regulate the speed and intensity of secretory impulses to the pituitary. For example cold in

creases such impulses, heat reduces them Increased production of thyrotrophic hormone or thyrotrophin results in increased stimulation of the thyroid cell with an increase in the amount of hormone formed and extruded from the thyroid gland As the amount of thyroid hormone in the circulation and tissues thus increases it checks the pituitary activity and possibly also the action of preformed thyrotrophin Any marked increase in circulating iodide does the same thing (Fig 3 *A C*) (Wolff and Chaikoff 1948a b) and a deficiency of that material furthers the output of thyrotrophin and the activity of the thyroid cell

RATE OF SYNTHESIS AND RELEASE OF THYROID HORMONE

It has already been emphasized that the thyroid gland will pick up tracer doses of radioiodine with remarkable alacrity a maximum uptake sometimes being present within ten minutes Following such doses the highest titer of tagged thyroid hormone (thyroxin) may be found in the cell by the end of eight hours (Table III) (Lein 1943 Chagas et al 1945 Perlman et al 1941a b Leblond 1942 1943a b) while the maximum thyroid titer in colloid is noted in from 10 to 18 hours (Lein 1943 Leblond 1943a b)

Despite the amazing rapidity with which the thyroid collects and stores circulating iodine the gland is comparatively slow in releasing this material as thyroid hormone to other parts of the body (Perlman et al 1941a Hertz 1941 Morton et al 1942) Perlman and his associates (1941b) following the fate of tracer doses of radioiodine in white rats observed a maximum concentration at the end of 24 hours namely 65 per cent of the amount administered However at 96 hours 10 per cent was still present in the gland and at 192 hours over 20 per cent was still retained This does not preclude the fact that under certain conditions the thyroid gland is capable of rapidly synthesizing thyroid hormone and returning organically combined iodine quickly to the tissues as for instance under the influence of stimulation by the pituitary (Leblond 1941 Morton et al 1941 1942)

In spite of the availability of newer techniques particularly those employing radioiodine the amount of thyroid hormone formed in a given unit of time has not been accurately calculated for the human being although a satisfactory method is now available for the determination of thyroxin in tissue (Taurog and Chaikoff 1946) At present it is believed that for a 24 hour period thyroid hormone formation is in the neighborhood of 300 micrograms calculated as *l* thyroxin (Salter 1940 Stanley 1949) the isomer normally secreted by the body This isomer is probably 3 to 10 times as active as the dextrorotatory material (Rivers and Leiman 1948, Griesbach Kennedy and Purves 1949) and may represent the only normally active form (Reineke 1946) In rats the amount has been variously estimated from 2 25 micrograms (Griesbach and Purves 1945) to as high as 5 2 micrograms per 100 grams of body

weight daily (Dempsey and Astwood 1943) while the corresponding figure determined by Chaikoff and Taurog (1949) was 3.3 micrograms. This latter figure corresponds well with those found for dogs (Taurog, Chaikoff and Entenmann 1947) and goats (Schultze and Turner 1945) but is lower in relation to body weight than that obtained in rats by the majority of observers (Dempsey and Astwood 1943, Griesbach and Purves 1945, Schultze and Turner 1945, Monroe and Turner 1946, Hurst and Turner 1947, Taurog, Chaikoff and Entenmann 1947, Chaikoff and Taurog 1949).

Under normal conditions the percentage of iodine in the thyroid as thyroxin remains remarkably constant over a wide range of iodine intake and from species to species. Wolff and Chaikoff (1947) have briefly summarized the literature regarding this point and have set the average value for thyroxin at about 30 per cent of organically bound iodine. The ratio thus indicated between thyroxin and total iodine in the thyroid can be upset by a wide variety of factors, such as thyrotrophic hormone, antithyroid compounds, and so forth, under the influence of which the capacity of the thyroid to take up iodine and retain it in an inorganic form varies independently of its ability to synthesize the thyroid hormone. It must be emphasized, therefore, that thyroxin comprises a relatively constant proportion of thyroid iodine only so long as conditions are normal or ideal and varies widely when they are not.

The situation is different when we speak of the organically combined forms, diiodotyrosine and thyroxin, the chemical formulas of which are noted in Fig. 1. These are the only iodine containing amino acids which have been recovered from the thyroid gland. Under a wide variety of conditions the ratio existing between these two substances remains fairly constant, although the actual amount of each may vary considerably from time to time (Perlman et al. 1941b). In the normal gland slightly less than 70 per cent of the organically bound iodine is present as diiodotyrosine and a little more than 30 per cent as thyroxin. Indeed, the constancy of this relationship and the behavior of a tracer dose of iodine indicate that diiodotyrosine is the normal precursor of thyroxin and that a constant homeostatic balance is maintained at all times and under all conditions between the relative amounts of these two substances present (Taurog and Chaikoff 1947a, Rivers 1948, Chaikoff and Taurog 1949).

THE CHEMICAL STRUCTURE OF STORED AND CIRCULATING THYROID HORMONE

Inasmuch as diiodotyrosine alone exerts very little if any calorigenic action, some have assumed a priori that the physiologic potency of desiccated thyroid substance or of thyroid hormone could be measured by its thyroxin content. This, however, has not proved to be the

case (Means 1937, Leiman 1911 Salter 1910) Harington (1935) in an effort to explain these apparently contradictory facts has suggested that there is a special linkage in the thyroglobulin molecule between thyroxin and diiodotyrosine which is broken during the isolation of thyroxin from the thyroid hormone He postulated That the iodine which reaches the thyroid is first introduced into the molecule of tyrosine to form 3 5 diiodotyrosine The latter will then fulfill a duel role Part of it will be converted into thyroxin and another part will be linked with the thyroxin so formed together with other amino acids to form the true active principle of the gland

McClendon and his associates (1911) believe that the calorigenic effect of thyroid hormone depends upon the thyroxin content however one of the purest thyroglobulins which they have obtained from human thyroid glands contains less than 2 per cent of the thyroxin content normally found They conclude that although there might be other interpretations the existence of this thyroglobulin indicates that the thyroxin radicle may be synthesized within the thyroglobulin molecule and that one of the normal functions of thyroglobulin within the follicle is the formation of thyroxin from diiodotyrosine

Popoff's observation (1913) that old inspissated colloid contains thyroxin in a keto or insoluble form might well be interpreted as an end stage of thyroglobulin activity in which colloidal saturation with thyroxin has been attained Such colloid has a striking eosinophilic staining quality and despite its nonavailability is high in thyroxin and iodine content (Leblond 1911 Hewer 1927 Williamson Pearse and Cunningham 1928) Indeed it absorbs iodine rapidly (Leblond 1911)

Iodothyroglobulin and thyroxin possess calorigenic and myxedema relieving activities quantitatively dependent upon their total iodine content However thyroxin fails to raise the oxygen consumption of isolated thyroid tissue slices whereas iodothyroglobulin is capable of doing so (Table III) Thus would suggest therefore that thyroxin is not as has been proposed by many the entire or complete thyroid hormone Nevertheless the exact function of thyroglobulin is still not fully known (Leiman 1911) for in the release phase of thyroid follicular activity thyroxin leaves the gland but thyroglobulin as such is not found in the blood (Leiman 1910 1911) It has been suggested that thyroglobulin may be broken down into its component polypeptides peptones or amino acids by proteolytic enzymes and is thus extruded with thyroxin into the blood stream to be synthesized again by the tissues themselves (Leblond and Gross 1918a) Such an hypothesis has been neither proved nor disproved It is certainly unlikely that thyroglobulin with a molecular weight of about 700 000 (Heidelberger and Svedberg 1931 Heidelberger and Pedersen 1935) will diffuse through a cellular wall although it could readily migrate from the thyroid follicles by way of the intercellular canaliculi (Popoff 1913 Leiman 1910) Its absence

from the blood stream under normal conditions at all times is conclusive evidence that this does not occur (Leiman 1940)

In summary it is safe only to say that thyroid hormone is stored in follicular colloid as iodothyroglobulin and circulates as thyroxin probably loosely bound to some fraction of the protein of blood

THE FATE OF THYROXIN

While as aforesaid thyroxin comprises only about 30 per cent of the iodine of the thyroid gland it is the form of iodine preferentially discharged so that of the organically bound iodine of the blood it comprises from 90 to 95 per cent (Chaikoff and Taurog 1949) Study by means of tracer doses of iodine show that this thyroxin is loosely bound to a protein moiety within the plasma (Taurog and Chaikoff 1947b 1948 1949) the major portion being carried in the traditional albumin fraction of blood despite a higher concentration in one of the beta globulin fractions (Salter and Johnston 1948 Salter 1949)

Under normal conditions the turnover of plasma thyroxin appears to be rapid Eighty per cent of a tracer dose of radioiodine has been found in this fraction 24 hours after its administration (Chaikoff and Taurog 1949) Indeed in some animals the entire amount of plasma thyroxin may be replaced in as little as four hours (Taurog Chaikoff and Entenman 1947)

When calorigenically active materials such as desiccated thyroid substance iodothyroglobulin iodocasein and thyroxin are administered by mouth absorption rates vary with the thyroid status of the individual being more sluggish in the hypothyroid than in the euthyroid subject

For iodocasein the fecal loss is very high—reported by one group of workers as 60 per cent of the administered dose (Keating and Albert 1949) For the other materials mentioned the fecal excretion is still considerable being least with thyroxin (reported as 11 per cent in the experiments of the above mentioned workers)

If these hormonally active materials are tagged with radioactive iodine this labeled iodine can be identified in both the organic and inorganic iodine fractions of blood urine and tissue High concentrations of such radioactivity are observed over the liver for a considerable period of time when iodocasein thyroglobulin or desiccated thyroid substance has been administered Inasmuch as inorganic iodine is being released during this time it is presumed that deiodination has taken place either in the process of absorption or in the liver after absorption Thyroxin readily passes the gastrointestinal barrier and is not deiodinated until later This behavior seems again to make clear the fact that thyroxin is the most important single constituent of circulating thyroid hormone

A portion of each of the above mentioned calorigenic materials is excreted in the urine as thyroxin and a further fraction as diiodotyrosine However the *greatest portion of the iodine of each of the four* substances mentioned appears in the urine in an inorganic form It is reasonable to presume that the catabolism of hormone from the individual's own thyroid may pass through similar catabolic processes in *its circulation to and utilization by the various organs and tissues of* the body

Disappearance of Plasma Iodine Into the Liver, Gastrointestinal Tract, and Urine —If the blood stream is suddenly flooded with thyroxin a major portion of it is rapidly taken up by the liver some of which is promptly excreted in the bile Within two hours an average of 20 per cent is fixed in the liver 30 per cent is in the jejunum and ileum at *the end of 24 hours as much as 70 per cent can be found unchanged* in the feces During passage through the liver cells a certain percentage of the thyroxin has been destroyed (Monroe and Turner 1918 Elmer 1938 Leblond 1919 Keating and Albert 1919) yielding iodine *which may be reabsorbed and reused by the thyroid for the formation* of thyroid hormone

If physiological doses of tagged radioactive thyroxin (several micrograms) are injected intravenously the picture is quite different A smaller percentage is fixed by the liver amounting to 5 per cent in Leblond's experiments (1919 Gross and Leblond 1919) and a total of about 6 per cent is recoverable from analysis of the small and large bowels Normally only a small fraction of the thyroxin perhaps less than 1 per cent is excreted as unchanged thyroxin by the bowel (Monroe and Turner 1918 Leblond 1919) Ordinarily unchanged thyroxin is not excreted in the urine but considerable quantities may leave the body through this channel when an excessive amount is present (Leblond, 1919)

Detoxification and Excretion —From what has been said it appears that the detoxification and destruction of thyroid hormone occur in the liver thus *making available when necessary the raw materials, iodine* and tyrosine for the resynthesis of hormone by the thyroid In case of excessive formation of thyroid hormone much of the excess is promptly removed from the circulation by the liver some is detoxified or de*stroyed and the remainder often considerable in amount is excreted* unchanged in the bile and urine

Thyroid Hormone in the Blood —Two phases of iodine metabolism may be recognized in connection with the synthesis utilization and degradation of thyroid hormone anabolic and catabolic The anabolic phase begins with the absorption of iodide from the gastrointestinal tract and has to do with all the processes by which iodine is picked up concentrated organically bound and stored by the thyroid Iodothyroglobulin of the colloid and cells of the thyroid represent the end pro

duct of this phase The catabolic phase may be said to begin when iodothyroglobulin is split by proteolytic enzymes for its passage out of the thyroid into the blood and lymph streams and ends when it is released from the tissue cells for detoxification by the liver and excretion by way of the gastrointestinal tract and kidney The actual form in which it leaves the thyroid to enter the blood stream is not known It is clear however that thyroxin and possibly diiodotyrosine both of which appear in the blood when this release occurs are important constituents of the circulating hormone as they are of all substances which possess a thyroidal like action In the circulation thyroxin is associated with more than one protein fraction but the nature of the combination is not clear nor is it clear how and in what form this circulating hormone enters the tissues All that can be said is that the thyroxin moiety is present whenever and wherever a thyroid hormone action takes place

TISSUE DISTRIBUTION OF THYROID HORMONE

Apparently thyroid hormone is distributed to every tissue of the body with the exception of the thyroid itself Exogenously administered hormone does not enter this organ In the plasma the hormone travels loosely bound to protein and escapes from the blood stream into the various tissues in this form (Salter 1947 1949) Except for the endocrine organs its concentration within the various tissues is believed by Salter to vary with the percentage of protein present In regard to the amounts found within the pituitary and the ovaries there is considerable disagreement (Salter 1947 1949a Salter and Johnston 1948 Leblond 1949 Courrier Horeau Marois and Morel 1949) While muscles seem to be unusually well supplied (Salter 1947 1949a Gross and Leblond 1949) some of the tissue fluids with a low protein content show a concentration less than that of blood This preferential binding by some tissues in contrast to other Salter (1949) attributes to two factors protein concentration and enzyme systems acting specifically to hold the thyroid hormone Very little is known about the manner in which thyroid hormone finally reaches the individual cell and how when once arrived it brings about its remarkable metabolic effects Indeed there appears to be a considerable variation in the response of individual tissues if their oxygen consumption (QO) is any indication of thyroxin activity (Brophy and McEachern 1949)

PHYSIOLOGICALLY ACTIVE PRINCIPLES IN THE THYROID OTHER THAN IODOTHYROGLOBULIN AND ITS PRECURSORS

The possibility exists that thyroid hormone as above discussed represents only one albeit the most important active fraction of the secretions of the thyroid A thermolabile and a thermostabile material thermothyrine A and B respectively have been described which con

A portion of each of the above mentioned chlorigenic materials is excreted in the urine as thyroxin and a further fraction as diiodotyrosine However the greatest portion of the iodine of each of the four substances mentioned appears in the urine in an inorganic form It is reasonable to presume that the catabolism of hormone from the individual's own thyroid may pass through similar catabolic processes in its circulation to and utilization by the various organs and tissues of the body

Disappearance of Plasma Iodine Into the Liver, Gastrointestinal Tract, and Urine —If the blood stream is suddenly flooded with thyroxin a major portion of it is rapidly taken up by the liver some of which is promptly excreted in the bile Within two hours an average of 20 per cent is fixed in the liver 30 per cent is in the jejunum and ileum at the end of 24 hours as much as 70 per cent can be found unchanged in the feces During passage through the liver cells a certain percentage of the thyroxin has been destroyed (Monroe and Turner 1918 Lilmer 1938 Leblond 1919 Keating and Albert 1919) yielding iodine which may be reabsorbed and reused by the thyroid for the formation of thyroid hormone

If physiological doses of tagged radioactive thyroxin (several micrograms) are injected intravenously the picture is quite different A smaller percentage is fixed by the liver amounting to 5 per cent in Leblond's experiments (1949 Gross and Leblond 1949), and a total of about 6 per cent is recoverable from analysis of the small and large bowels Normally only a small fraction of the thyroxin perhaps less than 1 per cent is excreted as unchanged thyroxin by the bowel (Monroe and Turner 1918 Leblond 1949) Ordinarily unchanged thyroxin is not excreted in the urine but considerable quantities may leave the body through this channel when an excessive amount is present (Leblond 1949)

Detoxification and Excretion —From what has been said it appears that the detoxification and destruction of thyroid hormone occur in the liver thus making available when necessary the raw materials iodine and tyrosine for the resynthesis of hormone by the thyroid In case of excessive formation of thyroid hormone much of the excess is promptly removed from the circulation by the liver some is detoxified or destroyed and the remainder often considerable in amount is excreted unchanged in the bile and urine

Thyroid Hormone in the Blood —Two phases of iodine metabolism may be recognized in connection with the synthesis utilization and degradation of thyroid hormone anabolic and catabolic The anabolic phase begins with the absorption of iodide from the gastrointestinal tract and has to do with all the processes by which iodine is picked up concentrated organically bound and stored by the thyroid Iodothyroglobulin of the colloid and cells of the thyroid represent the end pro

Chapter X

THE EXTRATHYROIDAL PRODUCTION OF HORMONALLY ACTIVE IODINATED PROTEINS

Shortly after the true nature of the thyroid hormone was recognized the artificial iodination of hormonally active protein was successfully carried out independently by Blum and Vaubel (1898) and by Hofmeister (1897) At first it was thought necessary to utilize natural thyroglobulin or its split products to obtain a truly chemical linkage Further tests however showed that the nature of the protein material was not particularly important as all of a long series of iodinated proteins showed some activity (Rogoff and Marine 1917) It was necessary only that reactive tyrosine molecules be present in the protein selected The most highly active iodinated proteins have been prepared from casein egg albumin and soybean proteins by Reineke and Turner (1942) The complete relief of human myxedema by the use of iodinated serum protein was first reported by Salter and his associates (Salter and Lerman 1936 1938 Lerman and Salter 1939) However in terms of natural iodothyroglobulin the effectiveness of this artificially developed iodoprotein was as one to four thousand At the present time it has been possible to make artificially iodinated proteins with several times the potency of desiccated thyroid substance (Reineke and Turner 1943a b 1946) Excellent reviews of the whole subject of hormonally active iodinated proteins have recently been completed by Reineke (1946 1949)

In comparing the potency of artificially iodinated proteins with that of thyroid hormone it must be emphasized that our present methods of labeling the potency of thyroidally active materials by the acid insoluble content that is by the organically combined iodine content do not necessarily indicate the actual hormonal content (Dennesly and Parkes 1945) It seems much better to use the assay method originally described by Means (1937) in which the rate of increase of the basal metabolism of patients with fully developed myxedema from their lowest level is taken as an index of activity The nomogram of Salter (1947) can be employed for testing new preparations and for indicating therapy (Fig 12)

That such artificially iodinated proteins closely resemble the natural thyroid hormone iodothyroglobulin was first shown by Ludwig

tain no thyroxin but nevertheless possess pharmacologic activity simulating that of thyroid hormone (Berde 1915 1917a b Mansfield 1916)

There has also been described an entirely protein free fraction of desiccated thyroid substance which produces physiologic effects (Meyer and McEwen 1917) (See Chapters XIII and XXXV under paragraphs relating to the heart)

SUMMARY OF DATA REGARDING THE NATURE AND SYNTHESIS OF THYROID HORMONE (*Table III and Fig 1*)

Iodine in the form of the iodide is taken up and concentrated from thirty to several hundred times by the thyroid gland following which *by a series of oxidative reactions this iodide is converted to an* organically bound form Of the oxidative enzyme systems involved in this process the peroxidases probably play a leading role Iodide possibly through the intermediate formation of hypoiodous acid or hypoiodite is first converted to nascent iodine which is fixed to the 3 and 5 positions of the tyrosine molecule to form diiodotyrosine Through further enzymic activity within the cell and perhaps within a protein molecule (thyroglobulin) two molecules of diiodotyrosine are oxidatively coupled to form the diphenyl ether thyroxin with the subsequent splitting off of one aminopropionic acid side chain This thyroxin protein combination apparently represents the completed thyroid hormone and is thus stored in the colloid of the follicle

The speed with which the formation of thyroid hormone takes place depends upon such factors as the availability of raw materials (iodine and tyrosine) environment with its altering effect upon bodily needs the rate of production of thyrotrophin the amount of circulating iodine and thyroid hormone and so forth

Two major factors controlling the extrusion of thyroid hormone from the follicle are the levels of blood and thyroid iodine and the thyrotrophic hormone of the pituitary This release of thyroid hormone from the acini is accomplished through the cell by the aid of the proteolytic enzymes of *both colloid and cells so that it reaches the blood* stream as thyroxin some of which may be then loosely bound to the protein of the serum In the tissues a still closer association with protein probably occurs but the exact manner in which thyroid hormone produces its metabolic effects within the cells of the body is still unknown However while the precise nature of the thyroid hormone as it exists in the tissues is not fully established all the facts are consistent with the view that it represents thyroxin in firm combination within the protein molecule

Thyroxin is altered and at least in part destroyed by the liver and kidneys In the former instance a major number of both the iodine and the tyrosine molecules becomes available for re use in the metabolic pool of the body

natural thyroid hormone in every particular save for the fact that the cardioaccelerative effects are not seen (Reineke and Turner 1943a) However no carefully controlled work has been carried out in regard to this moot question (Reineke and Turner 1943a) There is in fact no good reason to believe that any qualitative difference should exist between the effects of these artificially iodinated proteins and the natural thyroid hormone Nevertheless by the goiter prevention method it has been shown that natural thyroid proteins parenterally administered to rats have consistently demonstrated more thyroxin like activity than could result from the *l* thyroxin contained in them whereas artificially iodinated protein when parenterally given showed only one half the activity which was to have been anticipated from the *l* thyroxin available in them (Frieden and Winzler 1948a b) It should be emphasized that the effects observed could not be accounted for on the basis of racemization as this factor was fully accounted for and discounted in the estimations of activity From what we have already said about the absorption of radioactively tagged synthetic and natural thyroidally active hormonal materials it seems more likely that these differences may be accounted for on the basis of the respective rates of absorption of the different materials (Frieden Tuckich and Winzler 1949) as well as the percentage lost in the feces Other reasons for variations in potency despite a similar content of *l* thyroxin are not apparent

The relative ease with which iodinated proteins with properties similar to iodothyroglobulin can be produced has given rise to the question as to whether or not the completely thyroidless animal is capable of manufacturing thyroxin or thyroxin like substances in his own tissues It was shown long ago that thyroidectomized animals were capable of a partial response to iodine resembling that to be seen after the administration of thyroid substance (Coindet 1820 Hoskins and Hoskins 1920 Allen 1919) With these facts in mind Chapman (1941b 1942) observed the effects of low and high iodine intake upon intact and thyroidectomized animals It was his conclusion from the data presented that iodine may play a role in body metabolism in the absence of thyroid tissue possibly by the production of a thyroxin like substance in the tissues Subsequently Morton Chaikoff Reinhardt and Anderson (1943) have shown that radioactive iodine injected intraperitoneally into rats deprived of all thyroid tissue was recoverable in appreciable proportion from the liver and intestines as diiodotyrosine and thyroxin Their experiments indicated that the thyroidless animal is capable of producing thyroid hormone (thyroxin) More recently Purves and Griesbach (1946a) have further confirmed the extrathyroidal production of hormonally active material as a result of histological studies of the pituitaries of thyroidless animals treated by iodine injections Such producton of hormonal activity falls far short of that necessary to maintain the animal in optimum condition even with the highest iodine

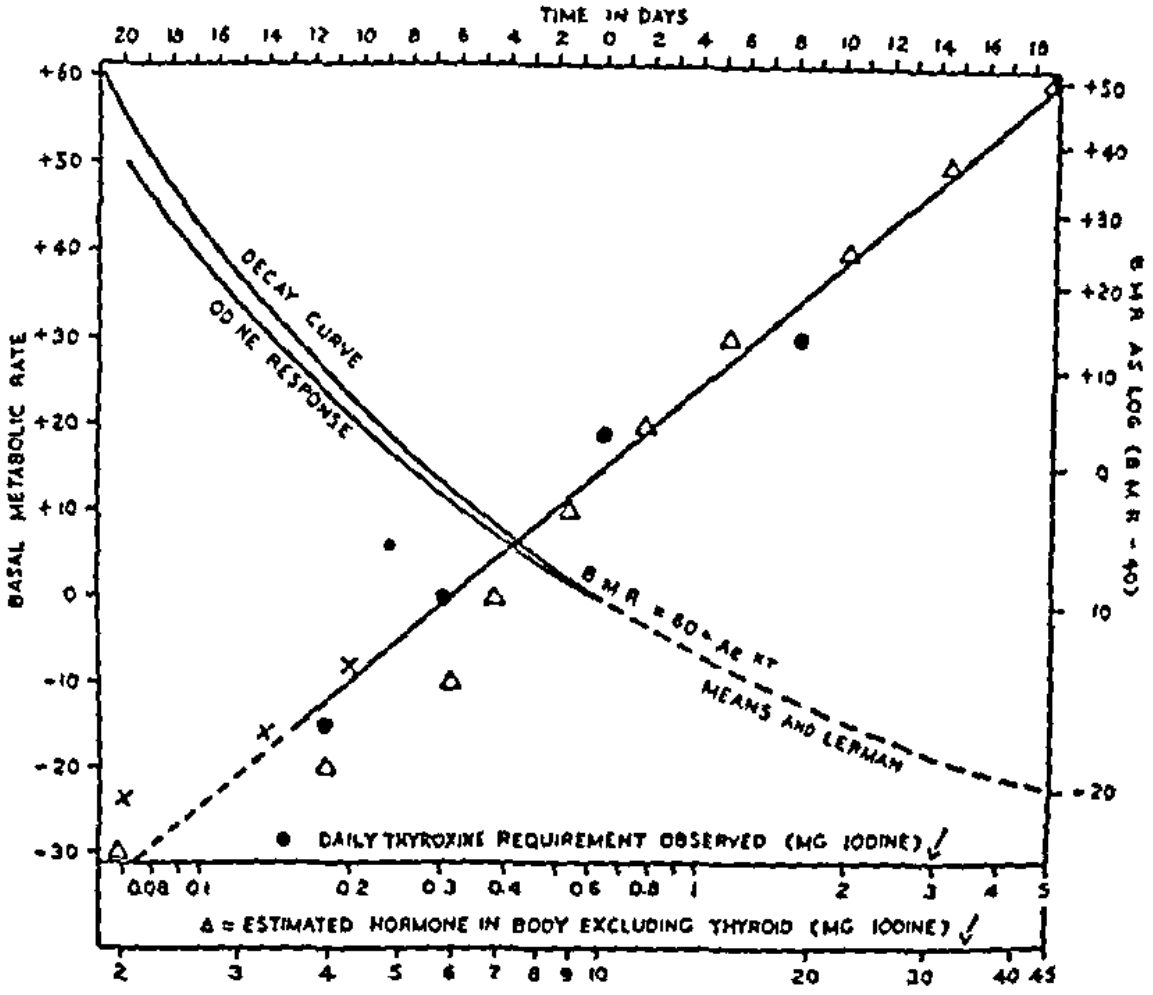


Fig. 12.—The daily requirement of thyroid hormone in relation to various metabolic levels and to the total amount of hormone in the tissues. The thyroid and iodine decay curves of Means and Lerman (1938) relating basal metabolic rate to the required amount for thyroid activity may be read directly. The straight line which has been constructed serves three purposes provided the appropriate scale value of each is used: *a* with the right hand ordinate and the top scale of abscissae gives the curve of Means and Lerman's illustrative logarithmic function; *b* with the left hand ordinate and the lowest abscissa (top scale missing) shows the hormone stored in extrathyroid tissues as estimated by integration of the decay curve against time; and with the left hand ordinate and the intermediate abscissa (oldest scale) are shown actual observations of the requirement of thyroxine like effect at various levels of thyroid activity. (After Salter 1940b.)

and von Mutzenbecher in 1939 when he isolated thyroxin from synthetically prepared thyroprotein. Other workers have confirmed this close relationship by the iodination of serum albumin in which physiologic activity first occurred when two atoms of iodine per molecule of tyrosine were added. Later a maximum of activity was obtained with the addition of from four to five atoms of iodine per molecule of tyrosine (Muus et al. 1941, Reineke et al. 1943) but most recently with improved conditions an even greater yield has been obtained when seven atoms of iodine have been added per molecule of tyrosine in casein (Reineke and Turner 1946). There are those who believe that such artificially manufactured thyroid active preparations resemble

Chapter VI

EXTRATHYROIDAL FACTORS KNOWN TO INFLUENCE THE FOLLICLE AND ITS CYCLIC ACTIVITY

The key position of the thyroid in metabolic processes and the enzymic nature of its activity rightly indicate the multiplicity of influences which even under physiological conditions are brought to bear upon the individual follicle Reference may be made to the nature and quantity of food the emotional state of the individual the character and degree of physical and mental activity environmental influences particularly temperature and so forth The picture becomes even more complex if one attempts to apply data gathered in various species of animals to conditions observed in the human being For instance iodine administration may produce suppression of thyroid function in dogs whereas in guinea pigs a corresponding dose may produce only stimulation Herbivorous animals withstand thyroidectomy better than carnivorous ones (DuBois 1941) and monkeys better than human beings (Jailer et al 1941) Even the age of the animal at the time of extirpation is important as animals are least susceptible to thyroidectomy during the stage of active sexual life It is obvious therefore that a complete interpretation of all the facts is not possible despite which however it seems important to discuss somewhat at length several of the more important factors which intimately influence metabolic processes within the individual thyroid follicle

1 IODINE

In view of its important role in the manufacture of the thyroid hormone it is a fair assumption that variations in available iodine may be of primary importance in the regulation of the activities of the thyroid follicle We have previously said that it is a primary function of the thyroid follicle to produce thyroid hormone Fundamentally the production of this hormone is an oxidative process accomplished by a series of enzymic reactions Because of their enzymic nature these processes are reversible It is not surprising therefore that phasic variations in thyroid activity have been observed following the use of varying doses of iodine Some of these effects are shown graphically in Table IV Particular attention is called to the phasic influence of administered iodine upon the ability of the thyroid to fix iodine to form

intake Moreover such subjects are deprived completely of the regulatory and storage facilities of the thyroid through which are maintained a normally adjusted activity with other glands and with the metabolic functions of the body in general From the above it would appear therefore that the thyroid is a specialized unit for doing quickly what every tissue may be capable of accomplishing very much more slowly and less efficiently

In acting as a specialized organ for the rapid production ready storage and quick delivery of so fundamental a hormone as iodothyroglobulin the thyroid and its primary functioning unit the follicle must at all times be sensitive to bodily needs and to a wide variety of extrinsic factors which may quickly and forcefully alter the requirements for growth and thermoregulation Without such influences some of which are dealt with in the next chapter no satisfactory control over thyroid activity would exist within the confines of the body

a clear factually correct but by no means all inclusive statement of the better known facts

If there is an iodine deficiency then both the previously normal and the previously hyperplastic glands develop an increased capacity for the fixation of iodine and its conversion into an organic form (Chapman 1941a Heitz 1941 Leblond 1941 Chagas et al 1943 Leblond 1943a Morton et al 1941 Hinton Eckerson and Bruger 1942) In response to this iodine deficiency the follicular cells of the normal thyroid hypertrophy and those of the formerly hyperplastic gland still further increase in size and activity

In the case of the previously normal gland the follicular colloid is low in iodine content and decreased in amount with concomitant diminution in the protein bound iodine of the blood The height of the individual follicular cell rises nodular formations occur lymphocytic infiltration becomes more noticeable and degenerative changes follow (King 1940) In such a gland if the condition continues for a long time then a large amount of abnormal colloid with a low thyroxin content is formed resulting eventually in a so called simple colloid or cystic goiter

In the case of the previously hyperplastic gland the same sequence of events takes place except that the protein bound iodine of the blood may remain at an elevated level for some time after the iodine deficiency is established moreover cystic formation is rarely seen Under the above conditions associated with iodine want vascularization of the thyroid is also increased (Chapman 1941a Dempsey and Singer 1946) It is probable that these effects are mediated by way of the pituitary gland for a deficiency of iodine invariably results in an increased release of thyrotrophic factor of that tissue (Leblond and Mann 1942) This statement does not ignore the fact that even in the hypophysectomized animal iodine deficiency results in an hypertrophy of the thyroid follicular cell In the latter instance however the change occurs at a much slower rate and is of lesser magnitude (Lerman 1941)

When iodine is fed to patients with simple deficiency goiter an increased metabolism results On the other hand no change in metabolism takes place in normal subjects who have had similar or even larger doses of iodine If however the metabolism is already increased as in hyperthyroid subjects a decrease in metabolism occurs from moderate doses of iodine (2 to 75 mg daily) (Houssay and Deulofeu 1943)

When an excess of iodine (it is rarely necessary to use more than 12 mg daily—Thompson et al 1932) is present there is a decrease in the capacity of the thyroid gland to convert iodide into an organic form (Wolff and Chaikoff 1948 a b c d Rawson 1949) Simultaneously

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In very early experiments Loeb and Thompson (1934) found that potassium iodide had no effect upon the thyroid of the hypophysectomized rat which not thyrotrophic hormone simultaneously diminished but differentiated and in the produces may a untf the negative characteristic of these results

and store organic iodine to influence the size and height of the individual cell to alter the amount and character of the colloid and to change the levels for iodine in the blood

TABLE IV

BASIC ACTION OF IODINE UPON THE THYROID GLAND

	INFLUENCE UPON					
	CAPACITY FOR		CELL SIZE AND ACTIVITY	COLLOID		BLOOD I I_2
	I_2 FIXATION	ORG. I_2 FORMATION		MANUFACTURE	STORAGE	
I_2 DEFICIENCY						
(a) in normal subjects	+	+	+	+	−	−
(b) in subjects with thyroid hyperplasia		−	−			
I_2 EXCESS						
A—in deficiency states						
Prophylactic doses (0.2—1.0 mg. daily)	+	+	+	+	+	+
B—in toxic hyperplasia						
(a) Moderate to large doses (2.0—7.0 mg. daily)						
Short periods of administration	−	−	−	−	−	−
(b) Large doses on prolonged administration	+	+	+	+	−	+

Plus sign (+) indicates an augmented influence and minus sign (−) a diminished effect of iodine upon the indicated function

Clear cut statements about the influence of iodine upon the thyroid gland are difficult to make despite a wealth of clinical and experimental data from which to draw conclusions. The condition of the thyroid at the time iodine is administered, the activity of the pituitary and of its thyrotrophic hormone, and the amount of iodine given all play leading roles in the effects to be observed. Variations in these and other factors in the hands of different observers have resulted in some of the conflicting statements now appearing in the literature. It is therefore possible to challenge almost any one of the following statements and the somewhat oversimplified Table IV. The effort here has been to develop

from the suppressive effects a statement for which experimental confirmation now exists (Stanley 1948) In other words the activity of the cell and its capacity for the fixation of iodine and the formation of organic iodine compounds again increase (Table IV) The manufacture of a colloid rich in thyroid hormone is augmented and its rapid release from the thyroid furthered thus returning the blood protein bound iodine to its previously high levels

The phasic reaction of the thyroid to iodine administration not only emphasizes the enzymic nature of the processes going on within the gland but also rationalizes the use of iodine in the management of thyrotoxicosis

In summary it may be said with some qualifications that the smallest doses of iodine exert a furthering effect upon thyroid follicular activity whereas moderate to large doses possess an inhibiting action These variations are currently explained by the now well recognized enzymic nature of the processes concerned in the elaboration storage and distribution of the thyroid hormone

2 THYROTROPHIC HORMONE ACTIVITY

The term thyrotrophic hormone is used here to represent one or several substances secreted by the pituitary gland which are capable of stimulating the thyroid gland The identity of such secretions was earlier discussed by Collip and Anderson (1935) Van Dyke (1936) and Collip (1940) Albert (1949) has critically reviewed the whole subject calling attention to the impurities present in all extracts and the possible influence of these upon the effects which have been described Thus far a chemically pure material has not been isolated but the physiological activity of thyroid stimulating extracts of the pituitary (TSH) is reasonably well delineated Albert has defined thyrotrophin as a substance obtained from pituitary tissue which when given parenterally in proper dosage to various vertebrates induces specific effects on the thyroid consisting of secretory alterations of the cytologic components of the follicular cells hypertrophy and hyperplasia of the epithelium vacuolization and resorption of colloid loss of hormonal iodine and increase of vascularity and of the size of the gland Some of its extrathyroidal effects will be discussed in connection with ophthalmopathic Graves disease (Chapter XXXIX) (q v)

Experimental evidence for a close relationship between the thyroid and the pituitary was first presented in 1888 when hypertrophy of all elements in the pituitary of the rabbit was produced by thyroidectomy (Rogowitsch 1888) Marine (1939) states that the enlargement of the pituitary gland in patients with decreased activity of the thyroid has been recognized for more than a century One observer found that the pituitaries of goitrous cretins weighed as much as 2 4 Gm as contrasted with a range in normal persons of from 0 5 to 0 7 Gm The striking

both the hypertrophy and the hyperplasia of the formerly overactive gland are decreased There is an interference with the manufacture of thyroid hormone However the capacity of the follicle to store the hormonally deficient colloid formed is definitely increased At the same time the high blood level of protein bound iodine decreases toward the normal As a result of in vitro work with thyroid tissue slices Morton Chaikoff and Rosenfeld (1941) and Lu (1942) have shown that inorganic iodine in sufficient amounts inhibits the formation of diiodotyrosine and thyroxin at the expense of the inorganic iodide of the medium More recently Chaikoff and his co workers (Wolff and Chaikoff 1948a b c d Chaikoff and Taurog 1949) have confirmed this work in vivo in the normal rat Their evidence is convincing proof that the effect is due to the inactivation of the enzyme or enzymes concerned in the conversion of iodine to its organic forms diiodotyrosine and thyroxin Certainly such a conception explains well the relief afforded to patients with toxic hyperplasia to whom iodine is administered Others (Silberberg 1929 1930 Elmer 1933 Krogh and Lindberg 1932 Okkels and Krogh 1933 Loeser and Thompson 1931 Blum and Sporri 1947) feel that these beneficial effects are produced through the influence of iodine directly upon the secretory activity of the pars glandularis of the pituitary Thus they claim that the action upon the thyroid is an indirect rather than a direct one

From the work of Morton Chaikoff and Rosenfeld (1941) Lu (1942) Hertz and Roberts (1941) Vanderlaan et al (1941) and Astwood (1949) it is suggested that the salutary action of iodine upon the toxic hyperplasia of the thyroid is the result of a direct action upon that gland and an indirect influence by way of the pituitary Furthermore iodine suppresses the action of thyrotrophin directly (Figs 7 and 9) (Friedgood 1935 Anderson and Evans 1937 Cutting and Robson 1939 Trikojus 1939 Vanderlaan et al 1941 McGinty and Sharp 1946 Rawson et al 1946 Albert et al 1947a b c Wolff and Chaikoff 1948a b d Astwood 1949 Chaikoff and Taurog 1949 McGinty 1949) Thus suppression is probably brought about by the ability of nascent iodine to oxidize and thus inactivate the thyrotrophin presented to the thyroid tissue (Rawson et al 1946 Albert et al 1947) Astwood (1949) suggests that a decreased quantity of iodide ion in the thyroid cell is a direct stimulus to that cell's activity Thus he explains not only cabbage goiters but also Graves disease and the beneficial action of iodine administration in the latter He properly emphasizes the speculative nature of his assumptions regarding the action of iodine upon thyroid function Nevertheless such thinking may not only prove therapeutically useful but may also lead the way to a complete understanding of the action of iodine upon the thyroid cell and colloid

As a rule in cases of toxic hyperplasia if large doses of iodine are continued for prolonged periods of time there appears to be an escape

hormone from the follicle (Fig 5) (Berg 1911 Durog Chalkoff and Bennett 1916 Rawson 1919) If large amounts of the hormone are used experimentally for sufficiently long periods of time then the gland can be brought to a stage of exhaustion with almost complete disappearance of intrafollicular proteolytic enzymes (Popoff 1913) However under normal conditions pituitary activity is curbed as soon as thyroid hormone is released from the follicle in any quantity (Aron et al 1931 Kuschinsky 1933 Crotti 1938 Uotila 1940) and the action of preformed thyrotrophin is probably blocked by thyroxin within the thyroid cell (Rawson and McArthur 1917 Rawson 1919)

When the depressant action of the thyroid hormone upon the anterior pituitary is sufficiently great then the thyroid enters a collapse phase or stage three This phase may be looked upon as a resting or exhaustion phase of the follicular activity During this time the follicle is not readily susceptible to pituitary influence This refractoriness is short lived and perhaps within a matter of hours the follicle is again responding to thyroid stimulating hormone of the pituitary gland with characteristic hypertrophy and hyperplasia which mark the recuperative state or stage four of thyroid activity (Hinton Eckerson and Bruger 1942 VanderLaan VanderLaan and Logan 1941)

The balanced action of the pituitary and the thyroid displayed in the above changes has been well named by Galli Mainini (1941 1942) Salter (1940) and others the pituitary thyroid axis (Fig 1) It must be emphasized however that the pituitary probably plays an accelerating rather than an essential role in the changes to be seen in the thyroid cycle In other words the thyroid is capable of a certain degree of autonomous activity totally independent of the hypophysis This is clinically evidenced by the fact that in Simmonds cachexia with its associated destruction of the anterior hypophysis the basal metabolic rate never falls to levels as low as those seen in complete thyroidectomy Moreover experimentally a complete atrophy of the thyroid does not occur following hypophysectomy Such autonomy does not detract from the important regulatory role of the pituitary upon the activity of the thyroid

The importance of the relationship between the pituitary and the thyroid has been further stressed by a number of observations of which the following are characteristic Under the influence of TSH there is a definite decrease in the inactive or acidophilic follicles of the thyroid associated with an increased uptake of iodine (Leblond 1944 Keating et al 1943 Morton et al 1941 1942) Simultaneously there is an increase in the number of basophilic or active follicles (Leblond 1944) Conversely hypophysectomy decreases the number of active follicles and the rate of the absorption of iodine by the thyroid (Leblond 1944)

An increase in the formation of organically bound iodine compounds having a thyroid function is the most important result of thyrotrophic hormonal activity TSH furthers the rate at which ingested

features of such hypertrophy are an increase in the number of the neutrophilic or reserve cells with vacuolization and a reduction in the number of the acidophilic cells with a tendency to degranulation (Purves and Griesbach 1946a) In all phases of severe experimental thyroid deficiency an hypertrophy of the pituitary gland occurs which is associated with an increase in the production of thyrotrophic hormone (Means 1939 1943)

If we reverse the conditions and remove the pituitary rather than the thyroid then involution and atrophy of the latter promptly ensue P E Smith in 1916 was the first to show this conclusively His demonstration of the retardation of the growth of the tadpole to as little as 7 per cent of normal emphasized the importance of hypophyseal secretion for the satisfactory performance of the thyroid gland (Smith 1916 Smith and Smith 1922a b) After partial thyroidectomy, the remaining cells and follicles of the thyroid of the otherwise intact animal rapidly increase in size and number Following hypophysectomy this compensatory hypertrophy is not observed

As a result of the above and other related studies it is now quite clear that some portion of the secretion of the anterior pituitary gland is essential for the proper functioning of the thyroid and conversely that the presence of the thyroid secretion has a profound influence upon the anterior pituitary It appears that this relationship between the two glands and their secretion is a balanced one in which the pituitary thyrotrophic factor acts to stimulate the growth of the thyroid cell to promote its secretory function to further the production of colloid and to increase the amount of thyroid hormone released (Fig 1) (Taurog Chaikoff and Bennett 1946 Astwood 1949) In turn the thyroid hormone thus poured into the circulation while stimulating all of the tissues and cells of the body except those of the thyroid and the pituitary actually depresses the latter in such a way as to decrease the further release of thyroid stimulating hormone (Aron et al 1931 Kuschinsky 1933 Crotti 1938 Lotili 1940) and to inhibit that already formed (Fig 1)

When we refer the influence of these two hormones to the cyclic changes occurring in the individual thyroid follicle it will be seen that the stimulating effect of thyrotrophin is to be noted predominantly in stages four one and two of the cycle as previously outlined In phase one the cells are shown to increase in height and activity while the follicular fluid increases in amount During stage two under the influence of thyroid stimulating hormone there is a marked increase in the activity of the individual cell and in the movement of colloid into and out of the follicle Indeed the gland can be kept in this stage of activity for rather long periods of time through the use of thyroid stimulating hormone (TSH) (Bassett Coons and Salter *1941*) A major action of TSH on the colloid itself is to aid in the release of thyroid

hormone from the follicle (Fig 5) (Berg 1911 Famulener Chalkoff and Bennett 1946 Rawson 1949) If large amounts of the hormone are used experimentally for sufficiently long periods of time then the gland can be brought to a stage of exhaustion with almost complete disappearance of intrafollicular proteolytic enzymes (Popoff 1915) However under normal conditions pituitary activity is curbed as soon as thyroid hormone is released from the follicle in any quantity (Aron et al 1931 Kuschinsky 1933 Crotti 1938 Uohlig 1940) and the action of preformed thyrotrophin is probably blocked by thyroxin within the thyroid cell (Rawson and McArthur 1947 Rawson 1949)

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An increase in the formation of organically bound iodine compounds having a thyroid function is the most important result of thyrotrophic hormonal activity TSH furthers the rate at which ingested

iodine enters the follicular colloid (Chagas et al 1915 Leblond and Sue 1941) and increases the amount of organically bound iodine in the thyroid and in the plasma (Morton et al 1941 Taurog et al 1946 Chaikoff and Taurog 1949) In connection with these changes the conversion of inorganic iodine to thyroglobulin is strikingly augmented as shown by a greater loss of iodine from the gland in an organic or protein bound form (Keating et al 1945 Leblond 1941 Morton et al 1941 Leblond and Sue 1941 VanderLaan et al 1941 Taurog et al 1946 Chaikoff and Taurog 1949 Stanley and Astwood 1949) The *administration* of potassium iodide in moderate quantities favorably influences the retention of iodine by the thyroid stimulated with thyrotrophic hormone (Table IV) (*Friedgood 1936, Talbot et al 1945*) *However this action* can be reversed if the amounts of iodide trapped by the thyroid are too great (Raben 1949) The action of TSH can be further augmented *at least in acute experiments by the use of adrenalin* (*Friedgood and* Cannon 1939 Gellhorn and Feldman 1941) or pilocarpine (Lolley and White 1936)

In vitro the temporary increase in the respiration of thyroid tissue obtained by the administration of thyrotrophic hormone can be abolished by the simultaneous use of iodine (VanderLaan et al 1941) Moreover prolonged treatments with TSH and iodine provoke involution and functional depression of the gland with a decreased ability to take up iodine (Keating et al 1945 Friedgood 1936 Hertz and Roberts 1941) Iodine prevents the metabolic action of thyrotrophic extracts probably by inhibiting the oxidative enzymic reactions within the thyroid which lead to the formation of thyroxin (Anderson and Evans 1937 Li 1942 McGinty and Sharp 1946 Astwood 1949 Chaikoff and Taurog 1949) This action is quite specific and reversible (Albert and Rawson 1946 Albert Rawson Merrill Lennon and Riddell 1946) Following the administration of sodium iodide Anderson and Evans (1937) noted a remission of the symptoms of hyperthyroidism in guinea pigs receiving thyrotrophic extracts These facts afford a logical clue to the favorable action obtained in patients with thyrotoxicosis as a result of the use of iodine (q v)

The direct influence of thyrotrophic hormone upon the liver and upon cholesterol metabolism is of importance in connection with thyroid function Of several purified hormones of the anterior pituitary tested *only the thyrotrophic hormone increased the absolute* and relative weight of the liver (Fraenkel Conrat et al 1942 Houssay and Deulofeu 1943) The thyrotrophic factor has produced a fall in the blood cholesterol *of hypercholesterolemic rabbits regardless* of the presence or absence of the thyroid gland (Turner and DeLamater 1942) However when the use of the hormone is continued for a long time in the intact animal *a prolonged maintained rise* in the cholesterol level is observed These observations suggest the fact that the thyrotrophic factor of the

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iodine enters the follicular colloid (Chagas et al 1915 Leblond and Sue 1941) and increases the amount of organically bound iodine in the thyroid and in the plasma (Morton et al 1941 Taurog et al 1946, Charkoff and Taurog 1949) In connection with these changes the conversion of inorganic iodine to thyroglobulin is strikingly augmented as shown by a greater loss of iodine from the gland in an organic or protein bound form (Keating et al 1945 Leblond 1941, Morton et al 1941 Leblond and Sue 1941, Vanderlaan et al 1941 Taurog et al 1946 Charkoff and Taurog 1949 *Stanley and Astwood 1949) The administration* of potassium iodide in moderate quantities favorably influences the retention of iodine by the thyroid stimulated with thyrotrophic hormone (Table IV) (Friedgood 1936 Talbot et al 1945) However this action can be reversed if the amounts of iodide trapped by the thyroid are too great (Raben 1949) The action of TSH can be further augmented at least in acute experiments by the use of adrenalin (Friedgood and Cannon 1939 Gellhorn and Feldman 1941) or pilocarpine (Folley and White 1936)

In vitro the temporary increase in the respiration of thyroid tissue obtained by the administration of thyrotrophic hormone can be abolished by the simultaneous use of iodine (Vanderlaan et al 1941) Moreover prolonged treatments with TSH and iodine provoke involution and functional depression of the gland with a decreased ability to take up iodine (Keating et al 1945 Friedgood 1936 Hertz and Roberts 1941) Iodine prevents the metabolic action of thyrotrophic extracts probably by inhibiting the oxidative enzymic reactions within the thyroid which lead to the formation of thyroxin (Anderson and Evans 1937 Li 1942 *McGinty and Sharp 1946 Astwood 1949 Charkoff* and Taurog 1949) This action is quite specific and reversible (Albert and Rawson 1946 Albert Rawson Merrill Lennon and Riddell 1946) Following the administration of sodium iodide Anderson and Evans (1937) noted a remission of the symptoms of hyperthyroidism in guinea pigs receiving thyrotrophic extracts These facts afford a logical clue to the favorable action obtained in patients with thyrotoxicosis as a result of *the use of iodine* (q v)

The direct influence of thyrotrophic hormone upon the liver and *upon cholesterol metabolism is of importance in connection* with thyroid function Of several purified hormones of the anterior pituitary tested only the thyrotrophic hormone increased the absolute and relative weight of the liver (Fraenkel Conrat et al 1942 Houssay and Deulofeu 1943) The thyrotrophic factor has produced a fall in the blood cholesterol of hypercholesterolemic rabbits regardless of the presence or absence of the thyroid gland (Turner and DeFanater 1942) However when the use of *the hormone is continued for a* long time in the intact animal a prolonged maintained rise in the cholesterol level is observed These observations suggest the fact that the thyrotrophic factor of the

(25° C.) an average of 5.2 micrograms of thyroxin was produced daily whereas at 1° C. there was a marked increase in the fixation of iodine by the thyroid (Leblond, Gross et al. 1944) and 9.5 micrograms of thyroxin were formed in the same length of time (Dempsey and Astwood 1943). Conversely, if the animals were maintained at a temperature of 35° C. the production of thyroid hormone decreased to 1.7 micrograms daily. It may therefore be stated as a general principle that secretory changes in the thyroid follicle and the rate of formation and discharge of iodothyroglobulin vary inversely as the surrounding temperature. These activities appear to be mediated through the anterior pituitary, as they do not occur in hypophysectomized animals or after transection of the pituitary stalk (Uotila 1939a; Purves and Griesbach 1946b).

6 ATMOSPHERIC PRESSURE

When rats are subjected to atmospheric pressures corresponding to altitudes of from 25,000 to 27,000 feet for from 14 to 20 day periods there occurs a reduction in the height of the acinar cell and a retention of colloid within the follicle (Gordon et al. 1943). Under these conditions the secretion of thyrotrophin by the pituitary is decreased. Hence this sparing action upon body metabolism at high altitude is probably mediated by way of the pituitary (Adams 1946, literature quoted).

7 AGE

The thyroid begins to function between the fourteenth and sixteenth weeks in the human embryo (Chapman et al. 1948) when synthesis, storage, and discharge of hormonally active material occur.

Puberty is commonly the time for a rapid increase in the size and activity of the thyroid, particularly in the female, at which time hypertrophy and hyperplasia are usually in evidence. These changes will be discussed in some detail under subacute goiter (q.v.).

The thyroid gland appears to attain its maximum normal size and possibly its maximum normal function between the ages of 15 and 20 years.

In the elderly (between 60 and 80 years of age) the thyroid is reduced in size, the follicles atrophy, the cells become smaller, and mitoses decrease. Colloid may be absent from many follicles and in others, when present, has lost its normal staining quality. The center of the follicle usually becomes acidophilic in reaction and shows little tendency to resorption. This change in the colloid, however, is not associated with an appreciable diminution in the amount of thyroxin present (Orr and Leitch 1929; Popoff 1943). Changes in the iodine content of the thyroid gland with increasing age have been both confirmed and denied (Curtis and Fertman 1943; Lerman 1941). The blood supply is markedly reduced and there is an enormous increase in the fibrous con-

attains its maximum in late estrus and declines throughout the rest of the cycle (Hunt 1911)

When estrogenic hormone is fed to small laboratory animals such as guinea pigs and rats the results seem to be equally conflicting (Herman 1911) However it has been suggested by Pincus and Werthessen (1933) that these discrepancies may be explained by their observations Injections of estrogen into animals over short periods of time namely five to ten days led to thyroid enlargement and increased activity whereas injections over longer periods of time that is for 20 days or more caused thyroid involution The first or stimulating effect was thought to be a direct one upon the thyroid gland while the second was ascribed to a suppression of the thyrotrophic activity of the anterior pituitary (See also thyroid gonadal relationship Chapter XIV)

4 SEASON OF YEAR

That seasonal variations do occur in the over all activity of the thyroid follicle seems to be generally admitted (King 1910 Starr and Roskelley 1910) but the nature degree and physiological explanation for such changes is by no means settled (Elmer 1938) In winter the amount of thyroxin necessary to prevent the hypertrophy and hyperplasia produced by thiouracil is twice that necessary in summer (Rabkin 1947) suggesting increased pituitary activity in the cold season of the year

5 TEMPERATURE

The secretory or second phase of follicular activity is furthered by low temperatures (Cramer 1928 Starr and Roskelley 1910 Ring 1942 Dempsey 1944 and 1949 Turner and Turner 1945 Schachner Gierlach and Krebs 1949) in effect which can be partially reversed by the administration of iodine (Fesser Winzler and Michaelson 1949) Under the influence of cold the individual follicular cells enlarge concomitantly the Golgi apparatus and mitochondria become increasingly active The mineral concentration of the cells decreases but the total amount of mineral per cell apparently remains constant (Dempsey 1944) A discharge of colloid is simultaneously induced (Cramer 1928) Conversely high temperatures (38 and 40 C respectively) have been associated with the collection of colloid and a decrease in the height and activity of the acinar cell of thyroid tissue slices despite a high oxygen consumption

The increase in follicular cell activity caused by cold occurs rapidly (Schachner Gierlach and Krebs 1949) and results in a heightened production and release to the circulation of thyroid hormone while the converse is true when the environmental temperature is high (Dempsey and Astwood 1943 Dempsey 1949) In rats kept at room temperature

8 CHEMICALS

This subject particularly as related to potassium thiocyanate thiouracil thiourea and closely related compounds will be considered in the chapter dealing with Antithyroid Compounds (Chapter XVI)

While every factor above mentioned in addition to others less well known exerts a regulatory action upon the thyroid cell and follicle it is evident that the *immediate* control depends upon an interplay of the available iodine thyrotrophin and thyroid hormone the so called iodo pituito thyroid axis

nective tissues between the follicles (Cooper 1925 Andrew and Andrew 1942 Blumenthal 1915) Changes of a senile type probably begin shortly after the age of 40 and differ only in degree from those just described in subjects of more advanced years (Doglioth and Nizzi Nuti 1935) Along with the rarely perfect involution of the gland which accompanies the waning activity of senescence go the formation of nodules and small colloidal cysts (King 1910 Martin 1915)

Premature aging may occur in patients who are subject to cystic degeneration of the thyroid especially when the cyst replaces an existing fetal adenoma (McGregor 1910 Hogg 1912) Both Hogg and McGregor have described effects from such cystic tumors that are similar to the symptoms and signs of aging The former substantiates his claim that the cystic material of these tumors induces senile changes by injecting some of the cystic material intraperitoneally into mice eight weeks old At the end of six weeks two thirds of the animals showed thinning of the hair with brittleness and a total thymic involution both of which phenomena were accepted as evidences of premature aging

The artificial aging produced experimentally by gonadectomy in small laboratory animals can be arrested by plurihormonal treatment with thyroid hormone progesterone estradiol and androsterone Moreover such therapy not only restores the *status ante quo* but may be so employed as to return the organ weights structure and function to that of an age below the chronological one (Kroenchevsky and Jones 1918) Obviously it would be foolhardy to anticipate that we can prevent the effects of age or that we can completely remake the tissues by altering their hormonal control However it does appear from such experiments and from clinical observations that much can be done to improve the nutritional status and the mental outlook in the later years of life

Citric acid appears in the thyroid in many times the concentration seen in the blood and is apparently held within the colloid in a complex form bound to calcium and magnesium (Brohm and Thunberg 1947) In the presence of phosphoric acid under properly adjusted conditions this material plays a part in the precipitation of calcium Increasing age is associated with a secondary rise in the citric acid values which together with other senescent changes may be significant in relation to the development of calcium concrements within the glands of the aged

It is believed that thyroid feeding will favorably influence reproductive activity as a mild degree of hyperthyroidism has tended to maintain egg production in chickens in the face of senescence (Turner and Kempster 1947)

In summary Under normal conditions the thyroid begins its activity early in uterine life reaches full development at puberty and undergoes a series of gradually increasing involutional changes from the climacterium to old age Thyroid feeding may retard some of the aging effects which are consequent upon the waning activity of the senescent gland

1948) enhancing its capacity for the uptake concentration and organic binding of iodine (Stanley and Astwood 1949) the digestion of stored or hormonally active colloid protein (De Robertis 1949) and the extrusion of hormone into the blood stream (Junqueira 1947 Rawson 1949) Most dramatic is its *ability to discharge stored hormone quickly* cause hypertrophy and hyperplasia of the acinar cells and enlarge their iodide trapping and concentrating capacity (evidence summarized by Rawson 1949 Rawson and Money 1949)

While the hypothalamicopituitary nervous pathways are continuously stimulating the pituitary cell to form TSH the activity of TSH within the thyroid is thought to set in motion its own self limiting homeostatic mechanism The increased concentration of iodine within the thyroid cell brought about by thyrotrophin decreases the further effectiveness of the latter Furthermore the additional thyroid hormone extruded under its influence while stimulating the majority of cells and tissues of the body exerts an inhibitory effect upon the formation and discharge of thyrotrophin by the anterior pituitary (Fig 1) Thus is completed the normal hormonal balance schematically represented in Fig 4 In such balance the thyroid cells and follicles vary within a reasonable range contain moderate amounts of colloid and extrude just that amount of hormone which the body needs for the maintenance of health Nervous impulses maintain the secretory activity of the pituitary on the one hand while blood and thyroid levels of iodine and thyroid hormone combine to block the effect of its thyrotrophic secretion within the thyroid to whatever extent may be necessary for homeostatic balance

A discussion of the blood levels for thyrotrophin may be omitted since our present methods of determination which are dependent in greater or less degree upon bioassay are too inaccurate to justify inclusion at this point and time However in passing it should be noted that the method recently proposed by D Angelo and Gordon (1950) may eventually solve this problem

C Role of Thyroid Hormone —Thyroid hormone aids in maintaining the homeostatic mechanism by which thyroid function is kept in balance by inhibiting the release of thyroid hormone from the anterior pituitary (Loeser 1934) and by diminishing the action of preformed thyrotrophin (Rawson et al 1946 Rawson and McArthur 1947 McQuillan et al 1948 Rawson 1949) (Figs 4 11) the latter effect possibly taking place only in the thyroid cell (Rawson 1949 Rawson and Money 1949) When thyroid hormone is administered in sufficient dosage over an adequate period of time the result is a disuse atrophy of the thyroid gland (McQuillan et al 1948) (see section on action of thyroid hormone Chapter XIII) as the preformed exogenous hormone has replaced the need for thyroid activity Simultaneously the mechanism is blocked through which stimulation of the thyroid is normally produced

Chapter XII

THE THYROTROPHIN-THYROID HORMONE-IODIDE BALANCE (IODOPITUITOTHYROID AXIS)

While there are many factors which influence the activity of the thyroid cell and follicle the immediate normal control of the thyroid appears to be closely held and delicately balanced amidst the action of ingested iodine pituitary thyrotrophin and thyroid hormone Under normal conditions it is to this trinity that the thyroid cell and follicle must give continuous account for their activity in the uptake and concentration of iodine (McGinty and Sharp 1916 Stanley and Astwood 1918 1919 Astwood 1919 Chinkoff and Lamog 1919) the binding of iodine to protein (Stanley and Astwood 1918 1919) the secretion of thyroid hormone into the follicle within the structure of the protein molecule (Leblond and Gross 1948b Remeke, 1949) the digestion of stored hormone in readiness for use (De Robertis 1941 1949 Dempsey and Singer 1946 Dempsey 1949) and its extrusion into the blood stream (De Robertis 1949 Dempsey 1949 Rawson 1949) Indeed the very configuration of the individual cell and the over all size of the follicle and the amount of stored colloid are dependent upon the interplay of these three materials In turn the action of each of these as well as that of the thyroid cell is conditioned to a greater or lesser extent by other influences such as emotional states nervous changes meteorological variants ingested nutriments goitrogenic drugs age other hormonal secretions and so forth Nevertheless in the interests of simplicity and the solution of the thyroid problems which the clinician must meet daily a schematic representation under postulated normal and abnormal conditions of the interlocking effects of the three factors first mentioned has been attempted (Figs 1 11)

A **Role of the Hypothalamus** —From Fig 1 it will be observed that the pituitary is believed to remain normally under the influence of an outflow of rhythmic nervous impulses from the hypothalamus the regular and tonal character of which predetermines the level of activity of the pituitary in the production of thyrotrophin (TSH)

B **Role of Thyrotrophin** —Thyrotrophin characteristically acts by increasing the size and secretory activity of the thyroid cell (hypertrophy and hyperplasia) (van Eck 1942 Dempsey and Singer 1946 Dvoskin

1948) enhancing its capacity for the uptake concentration and organic binding of iodine (Stanley and Astwood 1949) the digestion of stored or hormonally active colloid protein (De Robertis 1949) and the extrusion of hormone into the blood stream (Junqueira 1947 Rawson 1949) Most dramatic is its ability to discharge stored hormone quickly cause hypertrophy and hyperplasia of the acinar cells and enlarge their iodide trapping and concentrating capacity (evidence summarized by Rawson 1949 Rawson and Money 1949)

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D Role of Iodine—Iodine has a dual role in the work of the thyroid It is one of the raw materials needed for elaboration of thyroid hormone It exerts a controlling action upon the very processes by which it is combined organically to form the hormone When average amounts of iodine are ingested as food that is amounts between 50 and 200 micrograms daily then the uptake of iodide by the thyroid its oxidation to nascent iodine its binding by amino acids to form first the precursor diiodotyrosine and then probably within the protein molecule tetraiodothyronine or thyroxin proceed in orderly fashion Under such circumstances there follows normal storage of the finished product in the follicular colloid until such time as bodily demand may necessitate its mobilization and delivery into the blood stream

Aside from serving as a raw material for the completion of these processes the iodine of the thyroid regulates the speed with which they proceed (McGinty and Sharp 1916 Wolff and Chaikoff 1918a b d Stanley and Astwood 1918 1919) Under normal conditions levels for iodine within the gland vary directly with those in the blood (Chaikoff and Taurog 1949) although many times as great These levels regulate the activity of thyrotrophin When the level is high the action of thyrotrophin is suppressed (Albert et al 1917c) and the size and activity of cell and follicle are decreased When the level is low and there is iodine want thyrotrophic activity is enhanced and the cellular structure becomes columnar in type with evidence of increased function (Dempsey and Singer 1946 Dempsey 1949)

Thyrotrophin inactivation occurs by oxidation and within the thyroid the oxidizing agent is believed to be nascent iodine Within the thyroid trapped iodide is oxidatively converted into elemental iodine Therefore when large amounts of iodide are being so transformed thyrotrophin activity is inhibited thus removing the stimulus by which the work of the thyroid cell and its production of thyroid hormone are furthered (Fig 7 and Table IV) When iodine is scarce the reverse occurs thyrotrophin is not readily inactivated and exerts an unopposed effect by which hypertrophy and hyperplasia of the cell prepare it for the organic binding of available iodine at a higher level of efficiency Thus iodine an all important raw material in the manufacture of thyroid hormone exerts a regulatory homeostatic influence upon the rate of production of an internal secretion of which it is an integral part

E Production of the Thyrotoxic State—What happens when this homeostatic mechanism goes out of bounds? First let us consider *Graves disease* or *thyrotoxicosis* in which there is almost invariably an emotional or mental upset that markedly increases the number and intensity of the outflow of impulses from the lower brain centers thus giving rise to a marked increase in the amount of thyrotrophin formed (Fig 5) The consequent extrusion of large quantities of thyroid hormone from the follicle initiates secondary metabolic disturbances

throughout the body generally which account for many if not all of the manifestations of Graves disease However this excess of circulating hormone is not sufficient in amount to cope with and inhibit the markedly overstimulated anterior pituitary Unchecked this organ continues to form excessive amounts of thyrotrophin which acting upon the thyroid gland necessitates the establishment of a new balance therein at a much higher than normal level of activity Hypertrophy and hyperplasia of the cells occur hormone is extruded rapidly so that the storage space within the follicle is decreased The need for iodine rises and the capacities for absorbing concentrating and binding it to protein are simultaneously enhanced A relative iodine want may occur which still further increases the work of the cell and therefore further adds to the hyperplasia and hypertrophy Furthermore the necessary conservation of iodine and the relative deficiency of it clearly show that it is not sufficiently available to exert its regulatory inhibition of the action of thyrotrophin upon the thyroid cell and follicle The net result of these changes is a vicious circle of overactivity in which the hypothalamicopituitary influence is a primary causative factor

F The Influence of Antithyroid Compounds on Homeostasis —In what way do antithyroid compounds influence the normal gland as well as that already under the influence of thyrotoxicosis? This subject will be dealt with at more length in the section devoted to Antithyroid Compounds (Chapter XVI) but certain points are well illustrated in Figs 1 11 Under normal conditions the amount and concentration of circulating thyroxin is a major regulator of the speed with which further thyroid hormone is formed In addition high levels for blood *iodine* curb thyroidal activity (Wolff and Chaikoff 1948a b c d) (Fig 3 *A C*) Iodine accomplishes this by its ability to inactivate TSH inside the thyroid and probably also outside that organ (Rawson et al 1945 Danowski Man and Winkler 1945 Rawson and McArthur 1947 Wolff and Chaikoff 1948b Stanley and Astwood 1948 1949 Stanley 1949) This could readily account for the salutary action of large doses in Graves disease *Thiocyanate* acts by preventing the uptake of iodine by the thyroid gland (Fig 6) (Franklin Chaikoff and Lerner 1944 VanderLaan and Bissell 1946 Wolff Chaikoff Taurog and Rubin 1946 VanderLaan and VanderLaan 1947 Stanley and Astwood 1948 1949 and Stanley 1948) Therefore it interferes with the formation of thyroid hormone by depriving the gland of one of its raw materials but it does not prevent on the contrary it furthers the hypertrophic and hyperplastic action of TSH Moreover by decreasing the amount of circulating thyroid hormone it removes this normal check upon pituitary activity thus probably increasing the actual amount of thyrotrophin available to stimulate the cell which is already overactive as a result of the relative or absolute iodine want It is obvious that real danger of a thyrotoxic state is present under these conditions and has occurred when

sufficient iodine is supplied to break the thiocyanate block (Fig 7) This is probably the mechanism by which severe hyperthyroidism is produced when iodine is administered to certain European peoples who live in areas deficient in iodine and who in addition use a dietary in which cabbage and other *goiter producing foods are prominently featured* However if very large doses of iodine are used this danger is minimized as very high levels for blood and thyroid iodine are thus attained which promptly aid in the inactivation of thyrotrophin (Fig 7)

The block to the formation of thyroid hormone in association with the production of goiter is produced by *thiouracil* and its closely allied derivatives in yet another way Here iodine may be taken up and concentrated by the thyroid (Figs 8 and 9) indeed the capacity for so doing may be increased under certain conditions However these compounds are powerful reducing agents and are believed to exert much (Miller Robbins and Astwood 1945 Astwood 1949) if not all their action by reducing nascent iodine back to iodide as fast as it is formed by the thyroid cell under the influence of its all important oxidizing enzyme system (Fig 13) Simultaneously however the thyroid undergoes hypertrophy and hyperplasia because the thiouracil also reduces and therefore reactivates the thyrotrophic hormone present (Albert et al 1947a b c Albert 1949) thus enhancing its normal stimulatory effect upon the *thyroid cell*

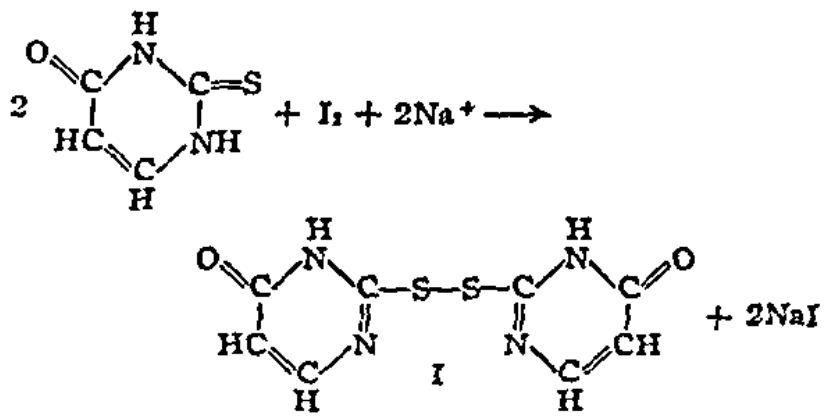


Fig 13—Illustration of nascent iodine (I) to iodide (I) by thiouracil There are many substances which will react as rapidly with nascent iodine as thiourea derivatives However none of these will disturb thyroid function The reason for this fact is also indicated in the reduction to iodide ought not by the ratio of this to all It has been suggested that the iodide to iodine oxidation has a very high potential that is higher than that of many common oxidations with the foods and the *thiouracil* compounds is high potent and be effective (After Astwood 1949)

Inasmuch as such a gland can take up concentrate and oxidize considerable amounts of iodine it is presumed that the favorable effects of large doses of iodine in such instances are brought about by its inactivation of thyrotrophin to which it yields oxygen as readily if not more easily than it does to the antithyroid compound The net result

is a considerable decrease in the hypertrophy hyperplasia and vascularity of the gland and the collection within the follicle of colloid which is partially or completely deficient in thyroid hormone (Figs 8 and 9) In other words the antithyrotrophic action of iodine can be exerted in the face of the thiouracil block (Fig 11) hence the justification for iodine therapy preoperatively in conjunction with the use of the thiouracil derivatives

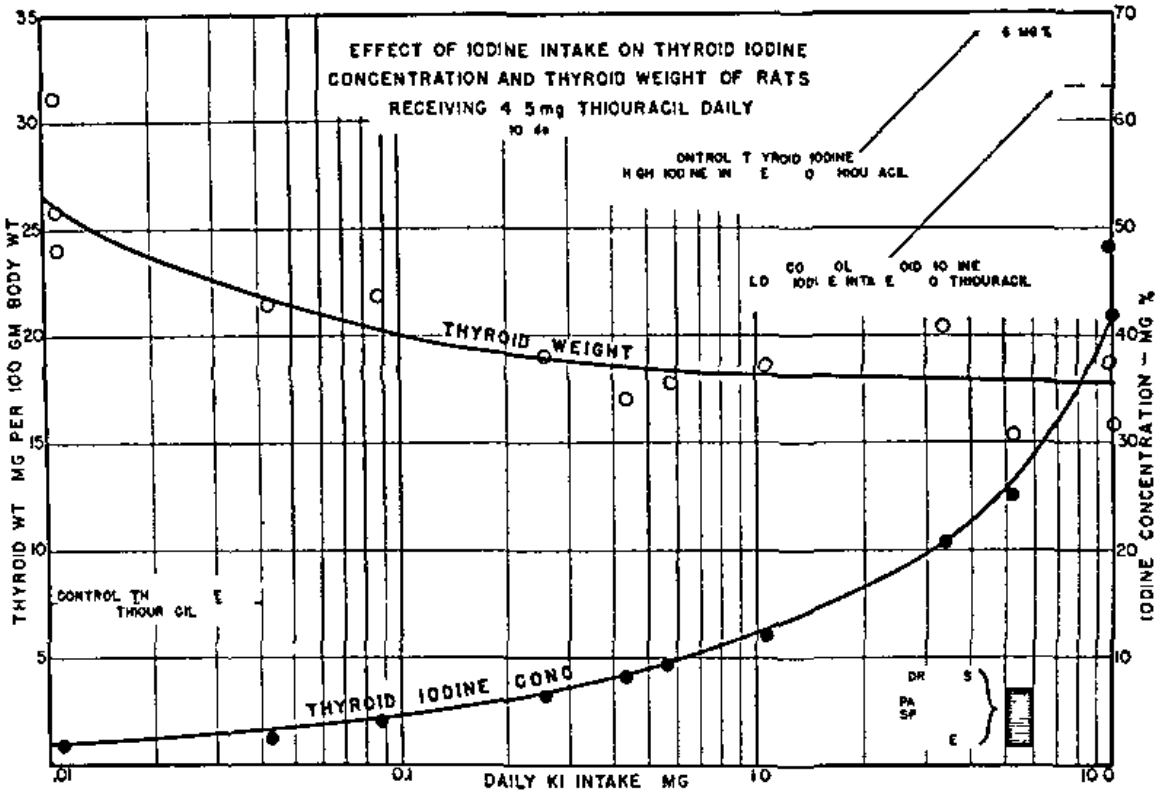


Fig 14—The influence of varied intake of iodine upon the weight of the thyroid and its concentration of iodine Rats were fed for 10 days with thiouracil sufficient gradually and progressively increased over a wide range of dosage The abscissae represent the daily intake of potassium iodide in micrograms The left ordinate *right ordinate represent the thyroid weight in milligrams per 100 grams of body weight and the concentration of iodine in the thyroid in micrograms per 100* respectively The curves illustrate the failure of thiouracil to inhibit iodine concentration in the face of blocking of thiouracil to inhibit organic iodine formation by an increase in the concentrating capacity of the thyroid gland for iodine that depends upon the physiological law of mass and diffusion also the effect of the weight of the thyroid but not the weight on the concentration of iodine which approaches normal values in the deficient (After McCarrison 1949)

The action of the *sulfa drugs* as antithyroid compounds is not so clear as that of the thiouracil derivatives In the present state of our knowledge it is not possible to explain fully the furthering effect of iodine upon the hypertrophy and hyperplasia produced by *sulfaguanidine* when the latter is used in submaximal amounts and iodine is administered in large doses (Mackenzie and Mackenzie 1943 Mackenzie 1947) (Figs 10 and 11) The present hypothesis postulates a difference

in the oxidative enzyme systems which convert iodide to nascent iodine and those which organically bind this nascent iodine to produce diiodotyrosine and thyroxine It is claimed that sulfaguanidine inhibits the latter but not the former although the evidence for this is inconclusive Therefore nascent iodine may be formed in the presence of a sulfa block but since the enzyme system concerned with organic binding is blocked the reaction can go no further Then it should be possible for the nascent iodine to oxidize and thus inactivate the thyrotrophin present Here again the reaction fails to take place if we postulate that the same enzymic systems are normally concerned with such oxidations as are employed for synthesis of hormonally active thyroxin Thus the TSH is unopposed in its normal activity hyperplasia is further increased and colloid fails to collect even in the presence of the excess of iodine This explanation is not very satisfactory as the phenomenon is best produced when the amounts of sulfa used are not maximal (Mackenzie 1917) In any event Mackenzie has reported that under suitable conditions iodine tends to increase the hypertrophy and hyperplasia caused by sulfaguanidine and does not favor the collection of colloid by the acini A point of practical importance is concerned with the fact that sulfa drugs should not be used during the preparation of a patient for surgery at least not during the time that iodine administration is necessary

Up to this point we have been concerned with the elaboration by the thyroid of thyroid hormone from the raw materials—iodine tyrosine and thyroglobulin—and the variety of influences which regulate its delivery to the blood for use throughout the body Let us proceed to follow it into the various organs and tissues for the normal functioning of which it is so essential

Chapter XIII

KNOWN PHYSIOLOGICAL ACTIONS OF THYROID HORMONE

The essential role of the thyroid in the economy of the body may be demonstrated by observing the phenomena which follow (a) destruction of the gland (b) feeding of thyroid substance to subjects deprived thereof (c) the presence of an excess of thyroid hormone within the organism and (d) the removal of other glands or the administration of the active principles of other glands The conclusions obtained from each of these methods will be briefly summarized under several headings somewhat in the order of their apparent importance

1 CALORIGENIC ACTION

The fundamental function of the thyroid hormone is the regulation of the rate of energy exchange or metabolism Such energy exchange is usually estimated by determining the consumption of oxygen over a given period of time This is readily altered by the feeding of thyroid hormone or thyroxin The rate of increase in metabolism and the final level attained will vary directly as the dosage used and inversely as the initial metabolic rate If the thyroid gland is completely removed then the basal metabolic rate will drop to approximately —45 in a period of from 40 to 70 days By application of the iodine decay curve of Means and Lerman (1938) it is possible to predict the rate of decline in the basal metabolic rate of the athyreotic individual

Thyroid hormone is not alone in its ability to accelerate oxidative process Proteins have been artificially iodinated which show a potency weight for weight greater than that of thyroglobulin (Reineke and Turner 1943a) Furthermore while the thyroid gland is especially adapted for the rapid and adequate production of thyroid hormone it has been shown that other tissues particularly the liver and the intestines are also capable of producing both diiodotyrosine and thyroxin (Morton et al 1943)

Under certain conditions the prolonged administration of thyroid hormone to euthyroid individuals will have a depressant rather than a stimulatory effect upon metabolism This has been seen in individuals who have employed thyroid hormone for the purposes of reducing Voldgoff and Stampfer (1950) in a group of women between the ages of 17

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and 30 observed a fall of the basal metabolic rate from normal to −30 or −40 within six to nine months after the beginning of treatment with doses of desiccated thyroid substance ranging from 6 to 18 grains They have carefully reviewed the literature regarding this subject and suggest that a compensatory mechanism against exogenous hormone is activated in such individuals It appears likely to us that the ingested hormone serves as a severe depressant to pituitary activity thus favoring atrophy or at least suppressed activity of the thyroid cells

2 ACTION UPON GROWTH

While growth may continue apparently undisturbed in some species of animals thyroidectomized early in life (Dye and Maughan 1929 Binswanger 1936) and in those the thyroid function of which is blocked by a thiourea preparation (Mayer 1917) the influence upon somatic differentiation and development in most animals is too well known to need very much elaboration In 1912 Gudernatsch observed that the feeding of thyroid to tadpoles caused metamorphosis in from two to five days The nature of this change was so quantitatively dependent upon thyroid hormone that it still remains a most delicate test for the bioassay of thyroid material This influence upon growth is a specific action (*Burns 1911 Silberberg and Silberberg 1942*) not shared by other substances such as dinitrophenol or adrenalin which are known to possess a definite chorigenic effect

When congenital athyreosis occurs in the human subject there is a stunting of mental physical and sexual development resulting in the clinical syndrome cretinism The somatic changes associated with the condition include a retardation in bony development and typical changes in the skin and its accessory structures Conversely the feeding of thyroid hormones causes an accelerated development of the organism In rats the complete removal of the thyroid at birth does not prevent a specific response to the growth hormone of the pituitary in large doses (20 to 30 hypophysectomized rat units daily) (Scow and Marx 1945) Small doses are completely ineffective (Salmon 1941) It would appear that the thyroid is not capable of exerting its beneficial influence upon growth in the absence of the anterior pituitary growth factor The converse is not true for the pituitary growth hormone is capable of producing characteristic effects in completely thyroidectomized animals although the degree of growth is materially augmented in such instances

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The fundamental question of how the thyroid brings about its characteristic changes in metabolism is still not clear Cordon and Henning (1944) have recently shown that with oxygen consumption of various rat tissue following the feeding of thyroid An increase was noted in the liver kidney diaphragm and heart muscle but not in the pieces brain tested A decrease in the respiratory quotient of the liver and diaphragm of hypothyroid rats was observed even though both glucose and glycogen are available for the energy requirement of the tissues The respiratory quotient of the kidneys was increased This study would seem to indicate clearly that thyroid hormone does not enter directly into the oxidative enzyme systems as a true prosthetic group

by the simultaneous feeding of thyroid hormone The growth promoting effect of thyroid hormone appears to be a nonspecific regulatory action upon each cell of the body whereas the growth hormone of the pituitary acts by stimulating the proliferation of certain cells in a specific fashion and in relationship to highly differentiated growth areas such as the epiphyses of the long bones This view has been challenged by the work of Laqueur and his associates (1941) Nevertheless it is clear from similar conditions observed in human beings that the thyroid hormone cannot in any way supply the need for anterior pituitary growth hormone For complete differentiation and development of the organism the combined action of the two appears to be essential

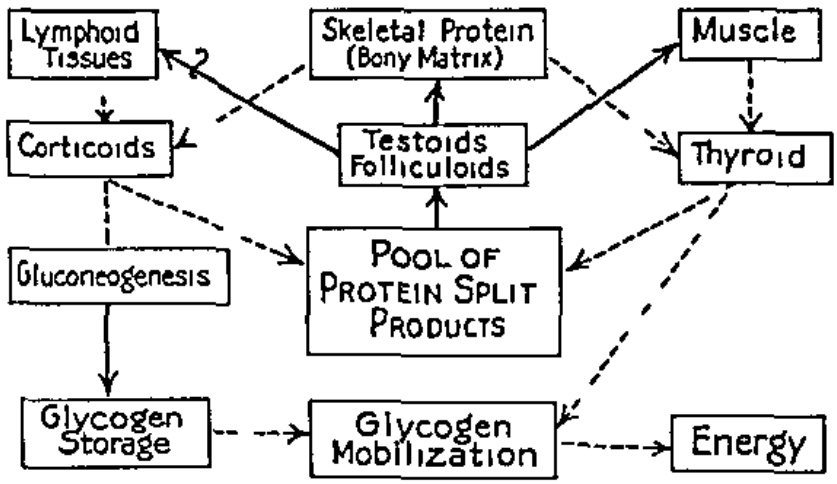


Fig 1 —Schematic presentation of some of the relationship of the endocrine glands to nitrogenous protein metabolism Solid lines indicate apparent activity with storage of protein and interrupted lines indicate catabolic activity with the breaking down of protein

The influences of the thyroid the pituitary the adrenals and the testes upon growth is undoubtedly a delicately balanced mechanism in which the regulation of protein metabolism may be a common denominator (Fig 15) The pituitary and the testis (or testoid hormones) build up tissue reserves of protein while the thyroid and adrenals make these available for the growing process As applied to the growth of bones Vergara Soto (1948) believes that both the pituitary chondrotrophic factor and the thyroid exert their fundamental action upon the protein matrix of the bone The former together with hormones of the adrenal cortex contributes to the formation of the connective tissue ground substance and thus to the development of the matrix of the bones Thyroid hormone by mobilizing the ground substance favors the change of preosseous to osseous matrix The alterations in calcium and phosphorus metabolism within the growing part follow rather than precede these effects

The action of thyroid hormone upon growth seems to be peculiarly related to testicular or testoid hormone function Both thyroidectomy

(Persike 1918a b) and a block in the formation of thyroid hormone by a thiouracil derivative (Mayer 1947) produce changes which may be ascribed to a simultaneous diminution of testicular activity In puppies treated with thiouracil Mayer (1947) observed a retardation in the maturation of the testes which was later spontaneously compensated In thyroidectomized rats Persike (1918a b) found a negative nitrogen balance accompanied by a decrease in organ weight sufficient to account for the increased urinary nitrogen It seems likely that the loss of thyroid hormone temporarily at least decreases the formation of testosterone and thus deprives the body of its anabolistic influence upon tissue protein The relationship is still further emphasized by the fact that the inhibition of the growth and development of the epiphyseal cartilages seen following castration can be counteracted at least in part by the administration of thyroxin Moreover the aging and closure of epiphyseodiaphyseal unions are encouraged by such treatment (Silberberg and Silberberg 1947) Finkler's (1946) failure to obtain epiphyseal union in several eunuchoid boys may have been due to a need for further thyroid hormone at such periods of growth and development

In summary thyroid hormone plays a very important role in somatic differentiation and development which is dependent upon an intact anterior pituitary gland and is furthered at least in the male by normal production of testosterone

3 ACTION ON THE PITUITARY

a **Functional Changes** It has been said previously that the major function of thyroid hormone is to stimulate every cell and tissue of the body except the pituitary gland It now seems to be well proved that thyroid hormone actually decreases the output of thyrotrophic hormone by the anterior pituitary (Adams and Jensen 1941 Chapman and Higgins 1944 Loeb 1932 Loeser and Thompson 1931 Aron Van Caulaert and Stahl, 1931 Loeb Bassett and Friedman 1930) Indeed if sufficient thyroid hormone is furnished the characteristic hyperplasia and increased metabolism produced by administration of thyrotrophic hormone to intact guinea pigs can be completely abolished (Loeb 1932 Loeb Bassett and Friedman 1930)

While some contradictory evidence exists it would nevertheless seem to be a fair generalization that the concentration of thyrotrophic hormone in the anterior pituitary varies inversely with the amount of thyroid secretion (Kuschinsky 1933, Grasso and De Robertis 1946) Consequently, when the concentration of thyroid hormone in circulating blood falls that of the thyrotrophic hormone in the pituitary probably rises In such an event thyroidectomy should produce very high titers of thyrotrophic hormone in the blood stream

In other words after the removal of an endocrine gland which is normally under the influence of a pituitary trophic hormone the pitui

tary becomes hyperactive for a time at least and produces an excess of the trophic secretion in question (*ablation phenomenon*) While Van Dyke (1936) feels that the evidence does not fully support this contention for the removal of the thyroid gland there has been demonstrated nevertheless a marked increase in thyrotrophic activity of the urine of patients and animals from which most of the thyroid tissue has been removed (Aron and Klein 1930) Moreover the same thing has been observed in cases of myxedema (Cope 1938 Hertz and Ornstein 1936)

The feeding of thyroxin and thyroglobulin suppresses the thyrotrophic activity of the anterior pituitary (McQuillan et al 1948) in mice it has been depressed to as little as 8 per cent of normal (Adams and Jansen 1944) In keeping with this alteration of physiologic activity certain changes take place in the histologic appearance of the gland some of which have already been described (Chapter XI) (Chapman and Higgins 1944) We may conclude that thyroxin tends to lessen the activity of the anterior pituitary and is associated with a marked decrease in thyrotrophic hormone production and activity (Adams and Jensen 1944 Cortell and Rawson 1944)

b **Histologic Changes** —In small laboratory animals thyroidectomy produces hypertrophy of the anterior pituitary (Marine 1939 Warkany and Nelson 1939 Penn 1940) Destruction of the thyroid by radioiodine (Goldberg and Chaikoff 1950 literature cited) suppression of its function by antithyroid compound (Griesbach Kennedy and Purves 1941 Mertes and Turner 1947 Goddard 1948) and severe clinical thyroid insufficiency in man (Marine 1939) evoke similar responses Conversely in Graves disease the pituitary is usually normal or low normal in size However the histologic elements seem to undergo an hypertrophy similar to that seen in severe thyroid insufficiency and the most striking single characteristic histologic difference between the two is a degranulation of the eosinophilic cells (Marine 1939 Purves and Griesbach 1946a) The entire hypertrophic picture in Graves disease may be promptly restored to normal by the administration of large doses of thyroxin or desiccated thyroid substance (Marine 1939)

4 ACTION ON THE THYROID GLAND

In general it has been shown that the giving of thyroxin or thyroglobulin depresses the responses of the intact animal s thyroid gland to the administration of exogenous thyrotrophic hormone This again illustrates the antagonistic action to be seen between the thyroid and the anterior pituitary The administration of thyroxin to the immature female guinea pig has been shown to depress the responses of this animal s thyroid gland to exogenous thyrotrophic hormone as determined by the mean cell height of the thyroid epithelium (Cortell and Rawson 1944) When thyroid hormone is fed to or injected into animals or

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and development in utero The result will be abnormal hyperplasia and hypertrophy of the fetal thyroid with the added possibility of generalized somatic retardation

In summary it can be said that the thyroid gland responds by disuse atrophy to the influence of the hormone it produces

5 ACTION ON THE MAMMARY GLAND

Thyroid by mouth or thyroxin by injection has produced large increases in the volume and in the fat content of cows milk (Graham 1931 Folley and White 1936 Mixner and Turner 1942 Harington 1944 McQuillan et al 1948) These same factors are decreased following thyroidectomy (Mixner and Turner 1942) The effect of thyroxin upon the mammary gland is probably a nonspecific sensitizing action due to its ability to augment the growth of any and all tissues in the body (Mixner and Turner 1942 McQuillan et al 1948) Thyroidectomy in immature male rats produces a small compact type of mammary gland with thickened ducts but with a rather marked development of the lobular alveolar system (Karnofsky 1942 Smithcors and Leonard 1942) Adrenalectomy materially alters this picture (Johnston and Smithcors 1948) However if thyroidectomy is performed just before conception or during gestation there is no inhibition in the evolution of the mammary gland to the lactating stage (Karnofsky 1942) It is logical to conclude that a pituitary mediation in the effects of thyroidectomy undoubtedly exists (Karnofsky 1942) (See Interrelationship of the Thyroid and Mammary Glands Chapter XIV)

6 ACTION ON THE PANCREAS

Prolonged thyroid feeding will produce diabetes mellitus in a subject the pancreas of which has been previously damaged by partial ablation or by the feeding of pituitary extracts (Houssay 1944a b 1946 1948) or alloxan (Molander and Kirschbaum 1949) However thyroid feeding will not cause diabetes mellitus in the animal with an intact pancreas The diabetes produced by thyroid feeding may last only so long as the thyroid feeding is continued (thyroid diabetes) or it may continue afterward (metathyroid diabetes) The damage to the beta cells of the pancreas may be temporary or permanent and irreversible The presence of the gonads the adrenal medulla and the thyroid are not necessary for the production of such permanent diabetes The influence of the simultaneous removal of the hypophysis and the adrenal cortex has not been observed because all groups of animals thus treated died in hypoglycemia when thyroid was fed (Houssay 1944a b) Thyroid feeding decreases the sensitivity to insulin whereas ablation of the thyroid or spontaneous hypothyroidism is associated with an increase in

human beings with goiter, the histological picture of a hypofunctioning gland is obtained (Gray and Rabinovitch 1929 Kuschinsky 1931 Uotila 1940 Rienhoff 1940 1941 Belisco and Martin 1941) There is a drop in the number of mitoses to a quarter normal (Gray and Loeb 1928 Limer 1938) *The overgrowth of the thyroid gland which follows the use of thyrotrophic hormone does not occur on the contrary a depression of growth is observed* Moreover the oxygen consumption *in vitro of thyroid* gland tissue is decreased by the addition of thyroid hormone *In* other words thyroid hormone is capable of suppressing the activity of the follicular cell indirectly by way of an inhibiting influence upon the anterior pituitary and of thyrotrophin as well as directly (Galli Mainini 1941 Beforzo Membrives 1938) Rienhoff's (1940) observations indicate that colloid goiter may arise as a result of a thyroid pituitary imbalance of the type just described

The administration of thyroid hormone has invariably produced atrophy of the thyroid gland and the degree as well as the permanence of this atrophy has depended upon the size of the dose of thyroid hormone used and the length of time it was continued (Rienhoff 1940) Rienhoff believes that this atrophy is due to a gradual diminution of secretion of the patient's own thyroid as a result of disuse In support of this claim he mentions the necessity for continuously increasing the amount of thyroid hormone required to produce or maintain a given level of metabolism This contention is further supported by the fact that thyroxin decreases the uptake of iodine by the thyroid (Johlot et al 1945 Astwood 1949 Rawson 1949) such lowering of thyroid function is secondary in whole or in part to an inhibitory effect of thyroid hormone upon thyrotrophin (Rawson 1949)

Artificially iodinated proteins are capable of producing the same hypofunctioning of the thyroid as is the naturally occurring material they are capable of suppressing the thyroid gland of the hen to such an extent that little or none of her thyroid hormone is deposited in the egg to aid in the development and maturation of the chick The result is a prolonged hatching period and a marked hypertrophy and hyperplasia of the chick's thyroid (Wheeler and Hoffmann 1948a b) Should artificially iodinated proteins become popularly applied in clinical medicine a point of practical importance may emerge from these observations It is believed that they demonstrate a failure of iodinated protein to pass membrane barriers from mother to offspring Should this hold true for the placental barrier then artificially iodinated proteins should never be used in human beings during pregnancy as they will inhibit normal formation of thyroid hormone by the mother's own thyroid and be unable themselves to augment the inadequate fetal supply for growth

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On the other hand our workers have seen little change in the cellular activity of the thyroid following the administration of thyroxin to the glands (Elliott Fekerson and Bragg 1941)

7 ACTION ON THE LIVER

Both storage (Abelin 1939 Abelin and Wehren 1940 Javadovsky and Azimov 1927) and destruction (Abelin 1930 Elmer 1938 Salter 1940 McIver 1942 Kellaway Hoff and Leblond 1945 Gross and Leblond 1947) of thyroid hormone are believed to occur in the liver Thyroid hormone which has performed a normal endocrine function is partially destroyed by the liver and secreted in the bile

When the blood levels of thyroid hormone are increased by ingestion a marked decrease in liver glycogen is one of the most constant effects observed Since Cramer and Krause first reported this effect in 1913 it has been proved that the action is due to an increased mobilization of glycogen rather than to an inhibition of its formation Even with a diet rich in carbohydrate it is difficult to prevent this effect in the experimental animal or in the patient suffering from thyrotoxicosis In fact we share the belief of many observers that all the histological changes occurring in the liver and the entire range of hepatic disturbances noted in thyrotoxicosis are related directly or indirectly to this effect upon the glycogenolytic function of the liver Conversely thyroidectomy is followed by a rise in hepatic glycogen (De Minjer 1918)

The influence of thyroid hormone upon cholesterol metabolism is not clear It is known that as thyroid gland activity increases there is a decrease in the concentration of cholesterol in the blood and that conversely as hypothyroidism supervenes the value for cholesterol rises However efforts to show that these disturbances in the blood level of cholesterol are reflected in the cholesterol of the bile have been unsuccessful (Johnson and Riegel 1939) partly because of rather large normal variations (McMaster 1924)

A decrease in the fat content of the liver occurs when thyroid hormone is fed (Elmer 1938 Abelin 1941) This is dependent in part at least upon the presence of adequate amounts of choline (Forbes 1944) Conversely thyroidectomy produces an increase in blood lipids (Handler 1947 1948) which is not altered by hypophysectomy (Entenman Chaikoff and Reichert 1942b) but is markedly accentuated when both hypophysectomy and thyroidectomy are performed (Entenman Chaikoff and Reichert 1948 Entenman et al 1948 Chaikoff et al 1948) Indeed the high levels for blood lipids produced by extirpation of the thyroid appear to be dependent upon the nutritional state and do not occur if the animal is fasted or if its caloric intake is restricted to the point of chronic undernutrition (Entenman Chaikoff and Reichert 1942a) Apparently the thyroid hormone causes a shift of cholesterol to and from the blood plasma without disturbing its production function or excretion (Fleischmann and Shumacker 1942) In other words the changes in concentration of cholesterol in the serum following the feeding of thyroxin or following thyroidectomy do not parallel changes in

response Coexisting hyperthyroidism and diabetes mellitus mutually aggravate each other

Diabetes is more common among patients with hyperthyroidism than it is in the population at large perhaps two to three times as frequently observed The converse of this statement is not true as diabetes does not per se predispose to hyperthyroidism In fact involution of the thyroid has been reported following illness in diabetes (Koneff Bennett and Wolff 1918 Deschamps Soulairac and Brocheriou 1918) With an increase in thyroid function there is uniformly a diminished tolerance for glucose (Wilder and Simsum 1917) and the liver is more responsive to glycogenolytic stimuli (Burn and Marks 1925) When thyroxin is fed at physiological levels there is a decrease in the insulin content of the pancreas of hypophysectomized rats This effect is probably due to the withdrawal of insulin from the pancreas in response to thyroxin (Frenkel Conrat et al 1942) it is in keeping with the observation that the insulin of the blood is increased after thyroid stimulation In normal rats the production and pancreatic concentration of insulin are both increased in response to thyroxin (Houssay 1946)

Following thyroidectomy the diabetogenic hormone of the anterior pituitary gland drops to extremely low values (Reineke Bergman and Turner 1941) Within physiological limits it would seem likely that thyroid hormone stimulates formation of the diabetogenic hormone in the pituitary gland (Reineke Bergman and Turner 1941)

In summary it would appear that the thyroid exerts a regulatory action upon blood and tissue sugar through its ability to mobilize rapidly available glycogen from the liver The slow drop of blood sugar in myxedema and its equally slow return to normal can be best explained by the fact that all metabolic processes are retarded because of the deficiency in thyroid hormone

The sequence of events which brings about a diabetic state in hyperthyroidism begins with the extrapancreatic disturbances which the heightened thyroid state favors increased rapidity of absorption of glucose from the intestinal tract hyperglycemia due to the rapid absorption a lowering of hepatic and muscle glycogen increased energy requirements of the organism and increased usage of fats for energy with a tendency to ketonemia and ketonuria All of these call upon the pancreas to increase its activity by supplying greater quantities of insulin which may eventually result in a breakdown of the normal islet cell mechanism particularly if it has been previously subjected to damage or if a constitutional or hereditary tendency to diabetes previously existed If we are made aware of the abnormal carbohydrate metabolism sufficiently early in our management of the thyrotoxic state it may often be possible to prevent permanent damage to the pancreas by the early use of insulin and antithyroid compounds

Feeding of liver to hyperthyroid rats counteracted the inhibition of growth and ovarian development which is characteristically seen in the animal fed excessive doses of thyroid hormone but did not influence the other manifestations of the toxic state (Irsholl 1917) This suggests some fraction in liver capable of protecting the growing animal from the stunting caused by induced hyperthyroidism

In connection with the regulatory role of the thyroid hormone upon certain phases of hepatic activity it is not surprising that it influences certain enzyme systems within that organ Both alkaline and acid phosphatases decrease as the glycogen stores are depleted by thyroxin (Kochakian and Bartlett 1948) The activity of both succinoxidase and cytochrome oxidase are furthered by the presence of thyroid hormone an action which can be diminished by adrenalectomy (Tipton et al 1946) Thyroid hormone like adrenalin activates the glycogenase of the liver but unlike adrenalin simultaneously increases its activity above the normal levels (Kotlyarov 1946) These and other changes in enzymic reactions are part of the metabolic changes in the liver over which thyroid hormone exerts a regulatory control

A logical relationship between the thyroid and the liver is justified by the position each occupies in body metabolism The liver is an important organ in the assimilation storage intermediary metabolism and mobilization of carbohydrate protein and fat It is clear therefore that its functions in these regards must alter in direct proportion to the metabolic needs Since the one essential function of the thyroid is to regulate the *speed* with which metabolic processes evolve it is obvious that an increase in the amount of this hormone will place greater demands upon the liver while a decrease will be attended by a slowing down of its several essential functions

In other words within physiologic limits the response of the liver to thyroid hormones will be exhibited by a mobilization of hepatic glycogen and an increase in blood and tissue sugar a drain upon the blood and tissue lipids with a decrease in hepatic phospholipid and cholesterol an increase in the catabolism of protein with an increase in the deamination processes within the liver a true work hypertrophy of the hepatic cell and an over all increase in the weight of the liver and in the number of cells and lobules present

However should the strain placed upon the liver be increased beyond the physiologic limits as for instance in clinical thyrotoxicosis or in experimental hyperthyroidism a disturbed physiology will result in which the glycogen stores of the liver will be exhausted the blood sugar will be decreased instead of increased provided the pancreatic islets remain competent the utilization of fat will be disturbed and fatty infiltration will occur side by side with destruction of liver cells amination and deamination of protein will cease to occur normally

the concentration of cholesterol in the tissues of the body (Fleischmann and Shumacker 1912)

Fatty and cirrhotic livers occur in thyroidectomized dogs despite the use of a high protein (lean meat) diet adequate in all respects and particularly as regards its content of lipotropic factors (Entenman Charnoff and Reichert 1918) Although hypophysectomy alone does not cause fatty or cirrhotic changes in the liver it intensifies the effects of thyroidectomy possibly due to the more complete inactivation of aberrant thyroid rests missed at the time of thyroidectomy (Entenman Charnoff and Reichert 1918) When *free* choline is added to an already well balanced high protein diet all fatty and cirrhotic changes in the liver of the hypophysectomized thyroidectomized animal are prevented (Entenman Charnoff Gillman and Reichert 1918) It is concluded from these experiments that the thyroid secretion contains a factor probably thyroid hormone, which is necessary to make the *bound* lipotropic substances of a normal diet available to the liver in the carrying on of normal fat metabolism

The actions of the thyroid hormone upon carbohydrate and fat metabolism respectively must be looked upon as interrelated In association with the increased metabolic needs attendant upon the presence of *increased amounts of thyroid hormone in the blood and tissues* there is an increased mobilization of sugar from the glycogen stores in the liver So long as such stores are available this results in a hyperglycemia and in an increased utilization of sugar If considered from a teleologic point of view it is probable that the variations in blood lipids represent a similar drain upon the fat stores of the body in an effort to keep pace with the increased metabolic needs

That the liver has increased work to do when the thyroid is overactive has been known for a long time (Hoskins 1916) Due to this work hypertrophy the livers of thyroid fed animals are considerably heavier than those of a control series This increase in the size of the liver occurs despite the fact that thyroid hormone withdraws stored glycogen Moreover it has been shown (Higgins 1933) that when a portion of the liver is destroyed regeneration occurs more rapidly in animals that received thyroid hormone than in those that served as controls It has been suggested that this hypertrophy of the liver is caused by the augmented flow of blood through this organ like that observed in the kidney and heart under similar conditions

In thyroidectomized animals and in those with a suppression of thyroid function caused by thiouracil there is an increase in total plasma proteins due chiefly to an increase in globulin (Leathem and Seely 1917 1948) Concentrations of proteins *in the liver were the same as* for control animals but the livers of thiouracil treated animals were heavier than those of the thyroidectomized subjects so that total hepatic protein was increased as a result of the thiouracil administration

lobular hepatitis The condition described by Weller predominantly involves the peripheral portion of the lobule and is characterized by chronic fibrosis and lymphatic infiltration rather than by proliferation of the bile ducts

In 60 per cent of the patients examined by Beaver and Pemberton (1933) a cirrhotic condition of the liver was found This was believed to represent a late stage of the acute and atrophic changes above described

In summary it would appear that the physiologic response of the liver to an increase in the amount of thyroid hormone is a work hypertrophy If however too much hormone is used or its administration is too long continued this physiologic response gives way to a complete breakdown in function associated early with acute fatty metamorphosis and degeneration and later with chronic atrophy and cirrhosis

8 ACTION ON THE STOMACH AND INTESTINES

Thyroid hormone exerts a furthering action upon the absorption of carbohydrate and fat This action is dependent at least in part upon stimulation of the preferential intestinal absorption of substances susceptible to obligate phosphorylation in the intestinal mucosa (Althausen 1939 1949) The increased fecal excretion of calcium during hyperthyroidism or following the feeding of thyroid hormone experimentally is believed by some workers to be due to hyperperistalsis and overeating (Althausen 1939) However no completely satisfactory correlation between the gastrointestinal symptoms and the status of the thyroid has been clinically possible to date Both experimental and clinical data may be variously interpreted (Scarf 1936 Althausen 1939 Portis 1941 Brown Pendergrass and Burdick 1941 Oppenheimer and Glver 1941 Fink 1941 Pelner 1944)

Variations from individual to individual are in part dependent upon the constitutional diathesis particularly upon the previously existing balance between the sympathetic and parasympathetic divisions of the autonomic nervous system In both animals and human beings where the sympathetic nervous system predominates one usually finds achlorhydria a prominence of the gastric rugae an increased rapidity with which the stomach starts to empty but a delay in complete evacuation and a decrease in both small and large intestinal motility and tone On the other hand if there is vagal preponderance then hyperchlorhydria rapid emptying of the stomach and an increase in tone irritability and motility of the small and large intestines will occur Undoubtedly the altered responses within the autonomic nervous system are closely associated with the disturbances in calcium metabolism For instance while calcium stores are still readily available one may expect a sympathomimetic effect of the thyroid upon the gastrointestinal tract later with depletion of calcium a vagal response

functional tests for liver damage will become positive and diffuse histologic changes will appear throughout the liver

Galactose and bromsulfalein tolerance tests are usually among the first laboratory procedures to yield abnormal results in the face of hepatic damage due to thyrotoxicosis Glucose and levulose tolerance tests may similarly be altered and in the more severe forms of liver damage disturbances in hippuric acid synthesis and an increase in the bilirubin of the blood are common

Hepatic lesions in thyrotoxicosis have been described by a number of workers (Beaver and Pemberton 1933 Kerr and Rusk 1922 Raab and Terplan 1923 Weller 1933 Marine and Lenhart 1911 Goodpasture 1921 Hiban 1933 Cameron and Karunaratne 1935 Boyce and McFetridge 1938 Shaffer 1910 Lord and Andrus 1911) It is possible to trace these changes in the experimental animal In early stages a fatty degeneration or infiltration occurs which is most marked around the central vein As the intoxication proceeds all stages appear from relatively simple fatty degeneration to actual necrosis These changes at first involve the central portions of the lobules and later spread toward the periphery until the entire liver may be involved The nature of the early alterations indicates that anoxemia is a prominent feature in the development of the hepatic damage In line with such a thought recent experimental work (McIver and Winter 1913) has shown that when hyperthyroid animals are exposed to artificial atmospheres containing *low percentages of oxygen degeneration lesions occur in the liver* which cannot be produced in the livers of normal animals similarly treated

The actual changes to be observed in any individual patient dying of hyperthyroidism depend upon the severity of the intoxication its duration and such variable and complex features as the general state of nutrition the presence or absence of avitaminosis and so forth On the basis of postmortem findings Beaver and Pemberton (1933) divide the hepatic lesions seen in hyperthyroidism into acute and chronic Since the descriptions of other workers would fall into the categories devised by them and since their classification is an extremely simple one it will be detailed Fatty metamorphosis and central or focal necrosis are changes observed in the acute types the lesions at times becoming so pronounced as to warrant the diagnosis of moderately severe acute yellow atrophy These workers observed chronic atrophy and cirrhosis as the two common lesions of protracted cases In 67 per cent of the cases of chronic atrophy the liver was much decreased in weight Not infrequently this was associated with the acute degenerative changes above described and occasionally with some degree of cirrhosis Usually the liver cells were small and at times there was some increase in connective tissue occasionally limited to the hepatic tissue near Glisson's capsule This latter lesion is suggestive of that mentioned by Weller (1933) under the name patchy chronic parenchymatous inter

leading to severe decalcification of the skeleton In children small doses of thyroid hormone cause a retention of calcium while larger doses produce a decrease (Johnston 1911) On the other hand the rates of calcium and phosphorus exchange are quite strikingly increased when excessive doses of thyroid hormone are administered (Puppel Klassen and Curtis 1939 Althausen 1939 Logan Christensen and Kirklin 1942) There is a marked increase in the fecal secretion of calcium by the lower bowel and a less apparent loss through the urinary tract Althausen (1939) believes that the loss is primarily due to the hypermotility of the intestinal tract but the majority of investigators would probably not favor this view (Robertson 1911 Calcium and the thyroid gland (Edit) 1942) Robertson and other investigators (Puppel Klassen and Curtis 1939) have shown that if sufficient calcium is given a positive balance can be established even though excessive doses of thyroid hormone are administered to the experimental subjects Moreover in thyrotoxicosis previously negative calcium balances can be abolished by calcium feeding

Conversely a decreased utilization of calcium occurs in hyperthyroidism Moreover when therapeutic doses of thyroid hormone are given to cretins a calcium retention may occur which aids in osseous development and is accompanied by a retention of nitrogen (Maroney and Johnston 1938)

Not only may thyroid hormone influence calcium exchange but conversely calcium metabolism may influence the status of the thyroid gland (Goitrogenic action of calcium salts 1943 Puppel Klassen and Curtis 1939 Sharpless et al 1943 Sharpless and Anthony 1943) Hyperplastic goiters have been produced experimentally by calcium only when it was administered as the chloride However this effect was uncertain unless viosterol was given simultaneously Under the combined treatment a goiter was routinely produced in which the iodine content of the thyroid gland was low Despite the fact that these effects can be produced whether the iodine content of the diet is low or high they are presumed to be associated with the substitution of chloride for iodine within the thyroid gland In thyrotoxicosis therefore it would seem to be wise to supply calcium in some other form than the chloride and to limit the intake of vitamin D

In hyperthyroidism the turnover of phosphorus is more rapid than normal and its increased uptake by muscular tissue indicates not only an increase in energy exchanges but also an effect of thyroid hormone upon the transfer of phosphorus across cellular membranes (Greenberg Fraenkel Conrat and Glendenning 1947)

10 ACTION ON THE KIDNEY

Both thyroxin and desiccated thyroid substance produce a definite increase in the creatinine clearance the maximum rate of transfer of

In hyperthyroidism appetite is a complex of many factors but it is usually good as long as the patient's metabolic needs can be met Contrary to common conception diarrhea occurs in not more than 20 per cent of all cases of thyrotoxicosis Usually hypermotility of the intestinal tract can be demonstrated by x ray in such individuals Constipation is a more common complaint appearing in 30 to 40 per cent of all patients and has been known to go on to obstipation It is probably due to a combination of sympathetic stimulation plus the sympathomimetic action of calcium The kinetic ulcer of Crile is rarely seen but abdominal pain nausea and vomiting occur in 10 to 20 per cent of hyperthyroid subjects probably secondary to the altered activity of the autonomic nervous system

9 ACTION ON ELECTROLYTE AND WATER BALANCE

A storage of water salt and protein occurs when the individual is lacking in thyroid hormone This so called deposit of protein along with electrolytes and water is retained in the body fluid and not stored or deposited in the cell protoplasm Conversely under the influence of thyroid hormone this extra deposit protein (Leiman 1941) is rapidly metabolized and eliminated in the urine along with the water and salt which is held in combination Indeed thyroxin is a powerful diuretic agent capable of increasing the output of water even in diabetes insipidus (Grant Cordsen and Liling 1941) The diuretic action of thyroid hormone may also be observed in normal persons There is however a distinct difference between the diuresis occurring in myxedema and that occurring in the normal individual as the former is accompanied by a loss chiefly of the sodium salts while with the latter potassium is excreted suggesting that fluids are being derived in the main from intracellular sources Indeed the thyroid is believed by some observers to have considerable effect upon the potassium content of body cells (Boekelman 1918)

Animals made hyperthyroid by the administration of thyroid hormone show a marked resistance to water intoxication (Grant Cordsen and Liling 1941) This resistance is due in part to the fact that hyperthyroid animals lose less chloride than normal ones during diuresis The chloride retention is probably due to the well known adrenal hypertrophy and associated increase in adrenocortical secretion that is seen in hyperthyroidism Conversely the reduction in plasma volume and the increased concentration of plasma protein observed in myxedema are associated with an adrenocortical hypoplasia These statements are in keeping with the fact that the blood volume in thyrotoxicosis tends to be above normal (Gibson and Harris 1939)

Calcium and phosphorus metabolism are also influenced by the administration of thyroid hormone It has been known for many years that an increase in calcium excretion occurs in thyrotoxicosis often

The increase in urinary creatine when thyroid hormone is fed has been attributed to a loss of muscle creatine The concomitant decrease in creatinine has been ascribed to a diminution in the conversion of creatine to creatinine (Williams and Fleischmann 1916) Conversely the individual deprived of thyroid hormone retains more creatine than the normal or hyperthyroid subject All these changes are intimately associated with variations in the phosphorylating mechanism in connection with the creatine phosphocreatine cycle within the muscle

In hyperthyroidism functional changes in the muscle are associated with a degeneration of the fibers Where a deficiency of thyroid hormone exists an interstitial edema develops

12 ACTION ON FAT

The consumption of glycogen in adipose tissue is enhanced in thyrotoxic rats an influence presumably due to the generally accelerated metabolism (Tuerkischer and Wertheimer 1942) Stores of body fat are reduced both in hyper and hypothyroid states (Mackay and Sherrill 1943)

The administration of thyroid hormone has been shown to decrease the spontaneous atherosclerosis normally seen in chickens but the dosages must be comparatively large (Dauber Horlick and Katz 1947 Horlick Dauber and Katz 1948) In human thyrotoxicosis a lowering of blood lipoids particularly cholesterol is characteristic of the effects of thyroxin However the physiological strain upon the cardiovascular system is more liable to increase rather than to decrease the incidence of vascular damage and atherosclerosis

13 ACTION ON THE HEART AND CIRCULATION

In the subject with a fully compensated heart excessive amounts of thyroid hormone produce significant increases in the cardiac output the blood volume the pulse pressure the pulse rate and the peripheral blood flow If only the mechanical factors concerned in these changes are considered it is quite clear that thyrotoxicosis places an increased burden upon the heart It would seem unnecessary therefore to recognize a specific cardiotoxic principle in thyrotoxic goiter (Neter 1934 Rihl Oestreicher and Reiss 1936 Means 1937 Tochowicz 1938 Fishburne and Cunningham 1938) although there are those who still seem to favor the existence of such a substance (Meyer and Wertz 1939 Meyer and Yost 1939 Meyer and Danow 1940 1941 Meyer and Marine 1942 Schmidt and Hertzler 1942 Leblond and Hoff 1944 Meyer 1946) Meyer (1946) thinks that inositol may be such a material

The suggestions of Raab (1944a b) and of Gross and Greenberg (1944) that a synergistic action between epinephrine and thyroxin occurs in thyrotoxicosis seem to be a likely explanation for the untoward

glucose and the maximum clearance of diodrast (Eiler Althausen and Stockholm 1941) Confirmatory observations have been made on patients suffering from thyrotoxicosis and those suffering from hypo functioning of the thyroid gland In the former urea clearance is increased and in the latter it is decreased (Mackay and Sherrill 1943) These workers conclude that a direct relationship between urea ratios and basal metabolic rates can be established Selye and his associates (1945) call attention to the potentiating effect of thyroxin upon kidney function and structure through its influence upon the adrenotrophic activity of the anterior pituitary This is apparently a specific synergism as they failed to find any similar potentiating action of thyroxin administered in conjunction with methyltestosterone

Aging is accompanied by a fall in urea clearance inulin clearance diodrast clearance and diodrast functional tubular mass (Tm) (Lewis and Alving 1938 Shock 1946)

When employed alone thyroid hormone increases the filtration rate and blood flow through the kidney and also causes an hypertrophy of the tubular cells When used in conjunction with estradiol hyperplasia of the tubular epithelium with a definite increase in mitotic figures is observed (Jones and Korenchevsky 1946)

In the present state of our knowledge it is fair to conclude that thyroid hormone exerts a positive effect upon the kidney altering it both structurally and functionally Hypertrophy and hyperplasia go hand in hand with an increase in tubular capacity

11 ACTION ON MUSCLE

In clinical states where an excess of thyroid hormone exists changes occur in muscular activity varying from slight weakness to marked atrophy The capacity for muscular work is lessened in both hypo thyroid and hyperthyroid conditions (Cox 1918)

The behavior of creatine and creatinine in the presence of excesses and deficiencies of thyroid hormone respectively is presumed to give some indication of muscular activity in the two states although the essential nature of the changes which thyroid hormone evokes in muscular tissue is far from clear *Creatine output is increased in hyperthyroidism* and decreased in hypothyroidism with a reduction in tolerance for exogenous creatine in the former state (See each of these subjects for further effects on muscle—Chapters XXX XXXIV and XXXV) conditions are exactly reversed in the case of creatinine (Wilkins and Fleishmann 1946) *Therefore the total of creatinine* plus creatine remains practically a constant as we pass in any given instance from overfunction to underfunction of the thyroid or vice versa

In rats muscle creatine and phosphocreatine are decreased in hyperthyroidism and increased in hypothyroidism

thyroid hormone and the reverse in those to which it was fed They believed that their results indicated a protective action of thyroid hormone on erythrocytes preventing their rapid destruction

It has been suggested that the administration of thyroid hormone affords some protection against certain infections (Zimanyi 1948) There are times when one feels justified in corroborating this statement on the basis of clinical observations

Variations in the sensitivity of the individual to different drugs can be correlated with the level of thyroid activity For example in myxedema and other conditions associated with a low basal metabolic rate morphine and other sedatives are poorly tolerated whereas in thyrotoxicosis it is difficult to elicit their characteristic effects even with massive doses Apparently the effects of certain barbiturates as measured by the duration of anesthesia obtained by sodium pentobarbital are little if at all influenced by thyroid feeding or deprivation (Ederstrom 1947)

Thyroidectomy decreases the severity of anaphylactic and histaminic reactions while thyroid feeding has the reverse effect (Leger and Masson 1948) the reasons for these actions have been variously explained but no single theory has been adequately substantiated

Hyperthyroidism appears to increase and thyroidectomy to decrease the sensitivity of the skin to ultraviolet and roentgen radiations (Ellinger 1945)

Levels for blood amino acids vary directly with the status of thyroid function that is thyroid feeding increases and thyroid deprivation decreases them (Friedberg and Greenberg 1947) In recent investigation it has been shown in thyroidectomized rats that doses of thyroid hormone within the physiological range produce anabolic effects *only* whereas they have no apparent influence on the intact subject (Rupp Paschkis and Cantarow 1949a b) Following large doses of hormone these same workers demonstrated a catabolic action in both intact and operated animals which could be abolished if the pituitary was removed It seems likely that glands such as the adrenal and the gonad are secondarily concerned in these various reactions the control of which is vested in the pituitary Not only these but many other effects of thyroid secretion are influenced by the level of activity of associated incretory structures and the availability of nutrient materials such as vitamins and minerals To the analysis of a few of these interrelationships the immediately succeeding chapters are devoted

cardiac effects often seen In the heart of an obese woman who died suddenly with cystic thyroid disease Rabb (1911a) observed tremendous accumulations of epinephrine He has furthermore shown (1911b 1917) that the lethal myocardial concentrations of epinephrine in rats can be distinctly lowered by pretreatment by thyroxin and distinctly elevated by pretreatment with thiouracil Other workers (Gross and Greenberg 1911) were able to show a marked accentuation of the cardiac hypertrophy myocardial fibrosis and infiltrative lesions produced by adrenalin when thyroid was administered simultaneously Increased cardiac irritability and tone go hand in hand with thyrotoxicosis and are probably due to the direct action of the thyroid hormone upon the cardiac musculature

When thyroid hormone is wanting as in myxedema cardiac engorgement occurs the tone of cardiac musculature is decreased and proper irrigation of the myocardium with blood is hindered by the infiltration and deposit of cholesterol and its salts in the coronary blood vessels Some increase in pericardial fluid probably always exists Disturbances in the muscle bundles themselves have also been described

14 OTHER ACTIONS

It is obvious that the thyroid hormone affects every organ and tissue of the body It would therefore be impossible to discuss in detail both clinical and experimental observations connecting its action with each cell and function For instance the hyperthyroid patient is subject to disturbances of the nervous system which commonly manifest themselves through an increased irritability emotional instability and psychotic tendency Conversely the hypothyroid subject reacts slowly at a low emotional level while he may cerebrate correctly he does so very sluggishly

Changes in the blood forming organs are common where there is either an excess or a deficiency of thyroid hormone (Burns 1914 Wilson 1914 You Kwang and Chu 1941) Pernicious anemia like pictures have been seen in both (Lerman and Means 1932 Means 1937 Boenheim Schwimmer and McGavack 1945) The commonest findings are an increase of mononuclear cells in the blood stream of patients with hyperthyroidism and a moderate anemia in hypothyroidism It is believed by some that these effects may be mediated by way of the pituitary the activity of which has been shown to have an influence upon erythropoiesis (Van Dyke 1936)

Wilson (1911) recognized the presence of anemia in both hyperthyroidism and hypothyroidism and attributed the increased cellularity of the bone marrow in the former and the decreased cellularity in the latter to a nonspecific control of thyroid hormone over the metabolism of the erythropoietic elements You Kwang and Chu (1914) found reticulocytosis and increased red cell fragility in animals deprived of

reproductive tract (Evans and Simpson 1930 Hohlweg and Junkmann 1933 Van Horn 1933 Collins 1941 Drill Overman and Leathem 1943 Chu 1944 Chu and You 1945) Larger doses or too protracted a period of treatment may reverse the effect (Schilling and Laqueur 1941 Warner and Meyer 1949)

Indeed any form of menstrual irregularity may be seen either in hyperthyroidism or in hypothyroidism The force of this statement is difficult to appreciate fully but rests firmly upon the synergistic and antagonistic actions to be observed between the thyroid the ovary and the pituitary when varying levels of the activity of each are encountered For instance a moderate increase in the thyroid hormone will increase the gonadotrophic hormone content of the pituitary and will simultaneously increase the action of the ovary through a direct influence upon its cells If however the dosage of thyroid hormone be large or too long continued there is a direct antagonism between its effect and that of the ovarian hormone (Hoffman 1944 McDonald Riddle and Smith 1945) Under other circumstances the effect may be indirect as it is known that the feeding of thyroid substance may decrease the gonadal response to a given quantity of gonadotrophic extract (Smelser 1939 Hoffman 1944)

A Thyroid Influence on the Gonad —*The feeding of thyroxin or desiccated thyroid* gland to male rats has resulted in interference with the activity of the testis The weight of the testis the production of spermatozoa and the secretion of testosterone are all decreased an effect which Smelser (1939) explains at least in part by a depression of the ability of the testis to respond to pituitary hormones On the contrary in short term experiments on vasligated rats Richter and Winter (1947) found that relatively large doses of thyroid hormone increased spermatogenesis and raised the functional level of the mechanisms for transporting germinal products through the efferent genital tract By varying the experimental conditions it has been possible to show that thyroxin or thyroid hormone will suppress testicular function (Da Costa and Carlson 1933 Smelser 1937 1939) or improve it (Crew 1925 Kunde Carlson and Proud 1929 Richter and Winter 1947) which is really another way of emphasizing the point that the net result of hormonal activity depends upon the interplay of several or many factors

Each such factor can only be appraised in terms of all the rest For instance whether the gonadotrophins of the pituitary are stimulated or suppressed by thyroid hormone depends among other things upon the size of the dose its frequency the duration of the treatment the functional capacity of the pituitary the responding capacity of the gonad at the time and so forth Some of these conditioning factors have now been studied but it is not possible at present to offer conclusions of unerring value at the bedside

Chapter XIV

INTERRELATIONSHIP BETWEEN THE THYROID AND OTHER GLANDS OF INTERNAL SECRETION

It is impossible to understand the functioning of the thyroid or of any other gland of internal secretion without in some measure relating its activity to that of its fellows. Important thyropituitary relationships have been discussed previously. In considering the mutual influence existing between the thyroid and each of the other endocrine glands no attempt will be made to follow the secondary ramifications of such interaction upon other glands or structures of the body. Oversimplification may lead to some misinterpretation but without it the *mass of accumulated data is for the most part incomprehensible*. It seems best to approach the whole subject of interglandular relations by dwelling upon the better known facts in the following way. Any known direct influence of the thyroid upon the gland in question will be mentioned first, then any indirect influence by way of some other glands as for instance the pituitary will be discussed. In similar fashion the direct and indirect effects of the second gland upon the thyroid will be summarized.

THE THYROID GONADAL RELATIONSHIP

The similarity in the appearance of the pituitary gland following thyroidectomy and gonadectomy implies an important connection between these two structures. Clinical evidence for such a relationship goes back to the medicine of the ancients who accurately described *the enlargement of the thyroid gland which may occur during puberty* menstruation pregnancy and the menopause.

Cyclic variations in the basal metabolic rate with various phases of the menstrual cycle alone serve to emphasize the close association between the thyroid and the ovary. The nonspecific stimulative action of thyroid hormone upon all tissues is responsible for at least a part of the improved function of the gonad in animals previously completely or partially deprived thereof. In addition to this direct action however thyroid feeding may increase the gonadotrophic content of the anterior pituitary thus explaining the favorable results obtained with small doses of thyroid in the treatment of some of the disorders affecting the

Therefore the ovaries of such subjects are much more responsive than those of intact animals to potent hypophyseal gonadotrophic extracts (Evans and Simpson 1930 Hohlweg and Junkmann 1933 Drill Overman and Leathem 1943 Chu 1944 Thyroid and sex function (Edit), 1945 Chu and You 1945) Increased follicular activity has also been seen following the use of an antithyroid compound (*Roszkowski 1948*) Furthermore the uterine fibroids frequently observed in colloid types of goiter are similarly ascribed to hyperfolliculism (Perrault Vignalou and Castillon 1949) However, hypophyseal extracts from thyroidectomized animals do not produce characteristic effects in the genital sphere for in such subjects the gonadotrophic potency of the pituitary is decreased (Collip and Anderson 1935 Stein and Lisle 1942) In other words thyroid hormone may either suppress or stimulate the production of gonadotrophic hormone by the anterior pituitary depending upon the dose employed Therefore when there is a deficiency and not a complete absence of thyroid hormone it seems clear that varying degrees of ovarian activity can be observed in which almost any type of menstrual irregularity may occur That is the amenorrhea and oligomenorrhea of severe hypothyroidism or myxedema may actually give way to menorrhagia and metorrhagia and the menorrhagia of hyperthyroidism to amenorrhea

Indeed it appears to take relatively little thyroid hormone to maintain a reasonably satisfactory balance between the pituitary and the gonad so that only at the extremes of thyroid hormone production do we see clinically recognizable disturbances in the function of the ovary or of the testis In hyperthyroidism libido may be increased in myxedema diminished However it is not clear that such disturbances represent an endocrine imbalance as much as they do a variation in nervous stability or irritability While gonadal function is always low in myxedema it is never lost and decreased reproductive function may accompany both hyperthyroidism and hypothyroidism

From all the data several facts stand out clearly (1) complete thyroidectomy decreases but does not completely suppress the production of gonadotrophic hormone by the anterior pituitary (2) complete thyroidectomy increases the sensitivity of the gonad to potent gonadotrophic extract (Evans and Simpson 1930 Hohlweg and Junkmann 1933 Peterson et al 1941 Reineke Bergman and Turner 1941 Chu 1944 Chu and You 1945) (3) small doses of thyroid hormone show a predominantly stimulative effect upon the gonadotrophic output of the anterior pituitary as well as upon gonadal tissue Such doses tend to re establish a normal gonadal activity and a balanced pituitary gonadal relationship in previously thyreoprivic animals (4) a definite antagonism to estrone is observed as the dose of thyroid hormone is increased but within the physiological range of dosage the stimulative action upon gonadal tissue and upon the pituitary continues to outweigh

It has long been known that high environmental temperatures depress spermatogenesis. This effect can be offset by the feeding of thyroxin (Bogart and Mayer, 1916) and can be simulated by the administration of thiourea (*Bogart and Mayer, 1916; Davis and Fugo, 1917*). Again in growing animals it has been demonstrated that estrogen inhibits long bone growth by interfering with the orderly progression of cartilaginous hypertrophy and extension followed by osteoblastic proliferation, bone deposition, and finally absorption of excess cartilage and bone just proximal to the growing center. This inhibition is partly counteracted by thyroid hormone (Silberberg and Silberberg, 1946), but the net result will vary with the relative amounts of the two hormones used, the duration of the therapy, the age of the animal, and so forth.

The administration of thyroid hormone diminishes the response of the vaginal mucosa to estrone, whereas thyroidectomy and thiourea act to increase the estrogenic effect (Langham and Gustavson, 1947).

Uterine myomata are more often associated with hyper- than with hypothyroidism (Rouhunkoski, 1948).

Dosage often has much to do with the effects observed from the use of thyroid hormone. On the basis of experiments in which large doses of thyroxin or thyroid gland grafts were brought into direct contact with the ovary, Stein, Quimby, and Moeller (1947) concluded that large doses of thyroid hormone have a direct suppressive effect upon the germinal epithelium, whereas smaller doses may be stimulating. Many other factors undoubtedly influence the reaction, such as the condition of the tissue, e.g., maturity, the amount of estrogen present, and so forth. As Schneider (1939) expressed it, "Dosage is the factor which determines the predominant phase of metabolism in isolated tissue. In the case of accelerated cell division the dosage or concentration of thyroid is undoubtedly of a nature conducive to a predominance of anabolic over katabolic metabolism. In cases where cell division is retarded there is an increase in oxygen consumption, resulting from a predominance of katabolism."

Observations following suppression of thyroid function by an *antithyroid compound, thyroidectomy, or deprivation of thyroid hormone* present a picture equal in complexity to that which follows excessive thyroidal activity. In such instances there is a temporary increase in gonadotrophic activity of the anterior pituitary followed by a profound decrease. Therefore, while there is some authority to the contrary, a loss of thyroid hormone usually delays maturity and retards genital development in the *immature animal*. In the *fully grown*, a thyroid deficiency causes a lengthening or absence of estrous cycles associated with involutionary changes in the secondary sex organs, retardation of follicular maturation, and a marked depression of reproductive function (Engle, 1944; Mason, 1947). Obviously, thyroidectomy is followed by a loss of the directly suppresive effect of thyroid hormone upon estrone

Grassner and Gustavson 1915 Grassner Burrell and Gustavson 1918) and in the immature animal retards growth Moreover the estrogen alleviates the mild goiter which is produced by the slightly iodine deficient diet testosterone propionate has a like effect in the similarly treated male rat Under the above circumstances estrone markedly increased the pituitary weights of female rats fed the low iodine diet and invariably produced exophthalmos testosterone propionate in male rats caused no change in size of the pituitary nor any tendency to exophthalmos In other words thyroid responses to estrogen and androgen in animals insufficiently supplied with iodine are similar and in the direction of normal whereas estrogen produces gross changes in the pituitary and testosterone does not These experiments may have some bearing on the etiology of many symptoms of hyperthyroidism and its predilection for the female Furthermore they may indicate the important role that the pituitary plays in its production and course

THE THYROID ADRENAL RELATIONSHIP

The thyroid and adrenal cortex have in common an action upon somatic development calorigenesis protein metabolism and the balance for water and electrolytes The thyroid and adrenal medulla share an influence upon the vegetative nervous system which is reflected in their effects upon the cardiac rate vascular tone capillary bed intestinal musculature hepatic sugar and so forth

Probably under direction from the pituitary the hormonal control of the individual's response to acute and prolonged stress seems to be jointly vested in the thyroid and the adrenal which through a system of complementary and reciprocal activities mediated over glandular and nervous pathways balance the organism's adjustment to a wide range of environmental influences When properly stimulated it seems to be the major province of these two structures to regulate the *level* of activity of the whole individual Moreover in so doing the status of the one is rapidly reflected in the behavior of the other If these facts are kept in mind it is not difficult to clarify an extremely bulky often superficially contradictory literature on the subject

A The Influence of the Thyroid Upon the Adrenal Cortex —Since the repeated confirmation of Hoskins' observation made in 1910 it has now been generally conceded that the administration of thyroid hormone produces a true hypertrophy of the adrenal cortex (Ingle and Higgins 1938 Marine 1939 Trikojus and Ellis 1939 Uotila 1940 Interrelations of the thyroid gland (Edit) 1941 Lowenstein and Zwemer 1943) while atrophy of that structure occurs in myxedema These states of the adrenal represent a work hypertrophy and a disuse atrophy respectively and lay emphasis upon the close relationship which exists between the thyroid and the adrenal cortex in carrying on the metabolic func

any such effects (5) when the feeding of thyroid hormone is pushed to high levels then the action of estrone is inhibited and the gonadotrophic activity of the anterior pituitary is suppressed with the appearance of oligomenorrhea amenorrhea or other menstrual disorders (6) when the amount of thyroid hormone is below physiologic limits ovulation does not occur (Chu 1941) and intermenstrual bleeding or metropathia hemorrhagica may result

Variations in the amount of gonadotrophic principle in the urine have been more or less uninformative (Howell Drips and Fisher 1941) Lerman (1941) states and we have recently confirmed (McGavack 1949) that a low urinary excretion of 17 ketosteroids and of estrogens is observed in patients with myxedema and that the output of these substances is increased when thyroid hormone is administered

B Gonadal Influence on the Thyroid — The relationship between the thyroid gland and the gonad is apparently a reciprocal one While there is some experimental evidence to show that *castration* produces a slow involution of the thyroid and a slight reduction in total metabolism such a sequence of events has not been observed in human beings It seems likely that the experimental data from dogs rabbits and rats which support such a view represent a period of readjustment of thyroid activity following castration rather than the end result The uptake of iodine in tracer doses was not influenced in adult female rats by castration or estrogen administration (Paschkis Cantarow and Peacock 1948)

The effects of *estrogen* on thyroid function are related directly to dosage and the period over which administration is continued (Pincus and Werthessen 1933 Sherwood and Bowers 1936, Lerman 1941) Physiologic amounts of both estrogens and androgens are capable of stimulating the activity of the thyroid (Nathanson Brues, and Rawson 1940 Lerman 1941 Lewis and McCullagh 1942) When still larger doses of estrogen are used thyroid function is definitely depressed (Briglet Laprida 1933b Gardner 1949) and the basal metabolic rate is lowered (Kunde et al 1930 Sherwood Savage and Hall 1933) Such inhibitory effects are probably mediated through the pituitary as well as directly A similar depressant effect has been observed following the administration of chorionic gonadotrophin This is believed to be due to the production of estrogen by the stimulated ovary for it occurs only when functioning ovaries are present (Starr and Patton 1934) This suppressive effect of estrogens upon thyroid activity can be materially increased at least in the experimental animal if an iodine deficient diet is employed (Gustavson Koenig and Gassner 1941 Koenig Gassner and Gustavson 1945 Gassner Barrett and Gustavson 1948) The administration of estrone and stilbestrol under such conditions decreases the iodine content of the thyroid of the female rat to a level below that of similarly fed controls (Gustavson Koenig and Gassner 1941 Koenig

mal losses of carcass nitrogen were negligible whereas when both the adrenals and thyroid were removed the major loss of nitrogen percentage wise was from the liver The specificity with which direct control is exerted by the thyroid over carcass nitrogen is emphasized by these experiments However the loss of weight which occurs in hyperthyroidism clinically is undoubtedly due not only to the muscular wasting but also to the indirect effect upon the adrenal cortex which results in the mobilization and use of proteins from the lymphoid tissues and probably from the bony matrix Glucose decreases or inhibits these actions of the adrenal hormones but does not influence the ability of thyroid hormone to break down muscle protein (Bondy 1949)

iii Calorigenesis—It is logical to assume that at least a part of the increased oxygen consumption in hyperthyroidism results from the influence of thyroxin upon the adrenal cortex The resulting increase in gluconeogenesis makes readily oxidizable materials available from the tissue proteins (Wells and Kendall 1940a) and perhaps from other sources These assumptions are confirmed by the fact that adrenalectomy prevents the usual calorigenic response to the feeding of thyroid hormone (Brownell and Hartman 1941 Doetsch Verzar and Wirz 1945 Hoffmann Hoffmann and Talesnik 1948) There is under such circumstances a decreased ability of the tissues to carry on such normal metabolic processes as deamination (Jimenez Diaz 1936 Russell and Wilhelmi 1941)

Calorigenesis may be improved by the administration of corticoids (Hoffmann Hoffmann and Talesnik 1948) However that the thyroid is not wholly dependent upon the adrenal cortex for its ability to increase calorigenesis is evidenced by the fact that gluconeogenesis is more depressed in thyroidectomized adrenalectomized animals than in those subjected to adrenalectomy alone (Wells and Kendall 1940a Hoffmann Hoffmann and Talesnik 1948)

iv 17 Ketosteroid Excretion—Both hyperthyroidism (Callow Callow and Emmens 1939 1940 Baumann and Metzger 1940 Fraser et al 1941 Engstrom and Mason 1943 1944 McGavack 1949) and hypothyroidism (Lerman 1941 Fraser et al 1941 Talbot and Butler 1942 Engstrom and Mason 1943 1944 Benda and Birby 1947 McGavack 1949) are associated with a decrease in the excretion of 17 ketosteroids in female as well as in male patients This decrease is moderate in hyperthyroidism (values for women ranging from 3 0 to 10 0 mg in 24 hours) and very marked in myxedema (values for both sexes ranging from 1 0 to 2 0 mg in 24 hours) In myxedema there is a concomitant decrease in the excretion of 11 oxycorticoids (Talbot et al 1947 Daughaday Jaffe and Williams 1948)

The reason for the decrease in 17 ketosteroid excretion in hyperthyroidism is not clear It is always moderate in degree and may in

tions of the body Should the adrenal be unable to respond to thyroid hormone as in Addison's disease or dyspituitrous myxedema an adrenal crisis occurs in both animals (Kendall 1940) and men (Means Hertz and Lerman 1940)

In carrying out the metabolic processes of the organism, the requirements for adrenal cortical hormones (corticoids) vary directly with the amount of thyroid hormone present in the body In hyperthyroid states therefore the need for corticoids increases materially If the capacity of the adrenal to respond to this excessive stimulation is normal the bodily economy may be maintained at an efficient level the hyperthyroidism is of a *compensated type (see Hyperthyroidism Chapter XXXV)* If on the other hand the excess of thyroid hormone is too great or lasts too long the adrenal cells become exhausted a diminishing amount of corticoids are formed and the patient's clinical condition rapidly becomes serious, the hyperthyroidism is of a decompensated type

a Histological Changes—The hypertrophy of the adrenal in hyperthyroidism or following the administration of thyroid hormone affects chiefly if not solely the zona fasciculata However it is associated with an increased hormonal activity not only of that zone but also of the glomerulosa (Deane and Greep 1947) In hypothyroidism there is atrophy of the zona fasciculata while the zona glomerulosa apparently maintains a normal activity These disturbances appear to be associated with alterations in the adrenotrophin output of the anterior pituitary *this material being increased in hyperthyroidism and decreased in hypothyroidism* Furthermore the evidence developed by Deane and Greep (1947) points to the zona fasciculata as the chief source of the 11 oxycorticoids which exert a regulatory effect not only upon protein and carbohydrate metabolism but also in processes concerned with immunity

b Nitrogen Balance—By increasing the activity of the middle zone of the adrenal cortex and thus stimulating its production of 11 oxycorticoids, *hyperthyroidism exerts a profound albeit indirect effect upon* nitrogen balance and gluconeogenesis (Fig 14) Only through such an action upon the adrenal is the thyrotoxic subject enabled to mobilize sufficient energy reserves to maintain the glycogen stores of the liver against the heightened metabolism present In making these statements it must be emphasized however that the thyroid hormone can and does exert a direct effect upon nitrogen balance which has nothing whatever to do with its influence upon the adrenal (White and Dougherty 1947 Bondy, 1949) In the fasting mouse White and Dougherty (1947) found the percentage of the depletion of nitrogen in lymphoid hepatic and carcass tissues to be of importance in the order named In the fasting adrenalectomized animal little or no nitrogen was lost from the lymphoid tissues In the fasting thyroidectomized ani

disease then the condition may be still further aggravated by the feeding of thyroid hormone Indeed patients may be thrown into crisis by such a procedure (Means Hertz and Lerman 1940) In keeping with this thought several workers (Zondek 1935 Wells and Kendall 1940a b) have shown that thyroidectomized animals survive total adrenalectomy longer than those possessing thyroids Grollman (1936) considers this a nonspecific effect due to the increased metabolism thus produced

viii Depressed Thyroidal Function—As has already been stated thyroidectomy is followed by a disuse atrophy of the adrenal cortex De pression of thyroid function by thiouracil or one of its closely allied com pounds secondarily produces an involution of the adrenal cortex which is both morphological and physiological in nature (Zarrow and Money 1949) Lipids disappear especially from the fascicular zone (Li Voti 1949) The capacity to withstand low temperatures is diminished In young rats the relationship is quantitative as the size of the gland and the ability to withstand cold has been shown to vary directly and proportionately

B The Influence of the Adrenal Cortex Upon the Thyroid—That the adrenal gland influences the thyroid is shown by the fact that cortical extract will prevent the rise of basal metabolic rate which would ordinarily follow the administration of thyroid hormone or of the hypophyseal thyrotrophic principle in the animal with an intact thyroid (Oehme 1936 Hoen Langefeld and Oehme 1939) This action may be due to the ability of the cortical hormones to inhibit the mechanisms which are responsible for the activation of succinoxidase and cytochrome oxidase in hyperthyroidism (Tipton et al 1946) To accomplish this effect the dosages must be large With dosages more nearly in the physiological range there is an augmentation of the characteristic furthering action of thyroxin upon growth (Bock 1938 Vergara Soto 1948) and calorigenesis (Hoffmann Hoffmann and Talesnik 1948) and an antagonism to thiouracil action on growth (Parmer 1947) Adrenal cortical extract has been recommended for the treatment of Graves disease and has been shown to protect the heart from the deleterious action of thyroxin (Kinsell et al 1942) The major benefit derived from such therapy is probably due to the action of the adrenal cortex upon the formation storage mobilization and utilization of sugar Inasmuch as an increase in metabolic rate causes a loss of intracellular potassium with a consequent elevation of the potassium level of the plasma cortical hormones as well as cardiac glucosides will antagonize the action of thyroxin by restoring a normal balance between intracellular and extracellular potassium (Kinsell et al 1942) The therapeutic level necessary for this action was found to vary indirectly as the basal metabolic rate In connection with the above activities Reiss and Peter (1938) have observed that cortical hormone also lowers the blood iodine and causes involution of the thyroid when Graves disease is present

dicate (a) a preferential formation of 11 oxycorticoids so badly needed for maintaining the increased metabolic activities of the organism (b) an hypertrophy of the fascicular zone of the cortex crowding the reticular zone which is probably concerned with the formation of the adrenal precursors of the urinary 17 ketosteroids (Blackman 1916), or (c) a heightened capacity of the liver for detoxification fully in keeping with its increased activity in many other directions We prefer to think of the decrease in urinary 17 ketosteroids in hyperthyroidism as the result of a preferential formation of large amounts of 11 oxycorticoids and the still greater decrease in myxedema as a result of the adrenal cortical atrophy which characterizes that condition

v Ascorbic Acid Content Long (1917) and Sayers and Sayers (1918) have demonstrated that the concentrations of cholesterol and ascorbic acid in the adrenal cortex are a reliable index of its functional activity More recently in long term experiments Wallach and Reineke (1919) have described the phasic effect of thyroxin feeding upon the ascorbic acid content of the adrenal cortex In response to the injection of 20 micrograms of thyroxin daily adult male white rats showed a depletion of adrenal ascorbic acid during the first four days This was followed by a progressive increase which together with an increment in adrenal weight reached a maximum at the end of the fourth week and maintained it thereafter It was estimated that this dose of thyroxin had produced an increase in the over all activity of the adrenal cortex equivalent to from 10 to 20 dog units of watery extract daily

vi Other Actions—The diuretic action of thyroid hormone has long been known (see Thyroid Hormone Action on the Kidney Chapter XIII) Selye (1935) believes that this effect is mediated through the adrenotrophic hormone of the anterior pituitary acting upon the adrenal cortex Brausch (1919) emphasizes the coordinated participation of the pituitary the thyroid and the adrenal cortex in the protein metabolic response to trauma

Administration of thyroxin even for short periods of time reduces the cholesterol content of the adrenal cortex (Abelin 1911) and raises the resistance of small laboratory animals to the toxic action of potassium and its salts (Trikojus and Ellis 1939 Lowenstein and Zwemer 1943) After prolonged thyroid feeding or in long standing hyperthyroidism there is a marked increase in the size of the adrenals with an absolute increase in the amount of cholesterol but a relatively low concentration for it

vii Prolonged Thyroidal Overactivity—If hyperthyroidism is long continued and severe both experimental and clinical observations indicate that a reduction in the function of the adrenal cortex does occur (Abelin 1914 Hoffmann Hoffmann and Talesnik 1918) If the activity of the adrenal cortex is already decreased as for instance in Addison's

roidism there is an increased rate of liberation of epinephrine from the adrenal gland This finding is more or less in keeping with Crile's conception (1931) that overfunction of the adrenal medulla is present in exophthalmic goiter

Further synergism is seen between thyroid hormone and adrenalin in that each acts to increase creatinuria (Comsa 1946a) and to decrease blood cholesterol (Comsa 1946b) In the case of adrenalin these effects are abolished by thyroidectomy but reappear when thyroid hormone is fed to the thyroidless animal

From all the evidence it appears that thyroid hormone functions to sensitize the organism to the action of adrenal medullary secretion Thus too may be explained some of the reactions of the vegetative nervous system which occur in hyperthyroidism

The Thyroid Mammary Relationship

A study of the interaction of the thyroid and mammary glands upon each other is complicated by species differences in behavior by variations in technic from investigator to investigator by the age of the experimental subjects when observations were made and by our inability to appraise satisfactorily the many hormonal factors which may enter into the development and function of the mammae

Among the more comprehensive and critically analytical recent reviews of the subject is that of Folley and Malpress (1948a b) who conclude that from the present data no very clear cut conclusions can be drawn Both hyperthyroidism and hypothyroidism have been credited with increasing the development of the lobule alveolar system Thyroidectomy in the immature animal is usually followed by a stunting of the ductal system but seems to have variously affected the subsequent response of the alveoli to stimulation by estrogen and progesterone It seems quite likely that a major factor in the activity to be observed in the breast as a result of altering the function of the thyroid gland depends upon the age at which such changes are produced Increased activity of the thyroid or increased amounts of thyroid hormone will further the phase of growth occurring at the time of the augmented thyroid influence A thyroidal deficiency will cause stunting of the somatic structures which should be undergoing development at the time the thyroid lack is created Such a concept may be an oversimplification of the tremendous mass of accumulated facts but it is a trend suggested although not fully proved by exhaustive reviews

If any specificity of thyroid effects upon the mammae exists it may be analyzed as follows In the immature animal thyroid deficiency results in a stunting of the mammary duct system and an increase in the susceptibility of the lobule alveolar system to subsequent stimulation with estrogens (Chamorro 1949) and progesterone If a lack of thyroid function occurs after lactation has been established or the gland

If the adrenal cortex is removed there is a decrease in calorigenesis and a consequent lowering of the basal metabolic rate This reaction upon metabolism probably results from a lowering of the oxidizable reserves of the body as a result of the adrenalectomy (Doetsch Verzar and Wirz 1915 Hoffmann Hoffmann and Talesnik 1918) Confirmatory of such a conclusion are the facts that (1) thyroxin administration to the adrenalectomized animal rapidly increases the mortality rate resulting from the latter procedure and (2) adrenalectomized animals do not react to administered thyroxin by an increase in the basal metabolic rate Indeed there are those who suggest that the adrenal cortex is more essential than the thyroid gland for the maintenance of the metabolic level (Hoffmann Hoffmann and Talesnik 1918)

In Addison's disease atrophy of the thyroid gland occurs the incidence of such a change being so high that some years ago Schmidt (1926) suggested the existence of a bi glandular disease a thyroadrenal condition While Schmidt applied the term only to cases in which a cytotoxic adrenocortical atrophy existed, it is now known that the thyroid may undergo such changes in Addison's disease of any etiology The changes in the thyroid are of such degree that were the level of adrenal cortical activity not low clinical hypothyroidism would be commonly manifest although hypothyroidism with and without myxedema has been observed (Rowntree and Snell 1931 Sorkin 1949) Contrariwise the combination of Addison's disease and hyperthyroidism is not unknown a fact which indicates the mediation of the pituitary in the changes which take place in the thyroid in connection with underfunction of the adrenal cortex The decrease in thyroid function produced by Selye's alarm reaction (Paschkis Cantarow Eberhard and Boyle 1950) is further evidence indicating the role of the pituitary in thyroadrenal relationships

C Interaction of the Thyroid and the Adrenal Medulla—Marine (1939) called attention to the fact that some interrelationship between thyroxin and epinephrine should exist on the basis of their common derivation from tyrosine and as a result of their capacity for powerful activation of metabolism albeit through different mechanisms It is not surprising therefore that following thyroidectomy in animals the adrenal medulla hypertrophies (Marine, 1939)

Thyroidectomy has been shown to decrease and thyroid feeding to increase the response to epinephrine In other words patients with myxedema are clinically less sensitive to adrenalin than normal individuals whereas those with thyrotoxicosis show an increased sensitivity Long ago Goetsch's test (1918) for exophthalmic goiter was based upon these facts (see Hyperthyroidism Chapter XXXVI) Ferman (1941) believes that this exaggerated sensitivity to epinephrine on the part of patients with hyperthyroidism suggests an underfunction of the adrenal medulla but Rogoff and Cortell (1941) have shown that in hyperthy

The Thyroid Thymus Relationship

Despite our lack of knowledge of the fundamental nature of thymic function its status is materially altered by the function of the thyroid the adrenal and the gonad as well as by certain diseased states such as myasthenia gravis Addison's disease and long standing infections In relation to the thymus the action of the thyroid and the adrenal appears to be reciprocal as an increased activity of the former is associated with thymic hypertrophy while cortical hyperfunction causes rapid and profound atrophy The interactivity of the thyroid and thymus may be briefly summarized in relation to growth pituitary activity and adrenal influence

A Growth—In their influence upon the growth of the organism the thyroid and the thymus appear to be mutually antagonistic As early as 1912 Gudernatsch observed that thymus gland fed to tadpoles increased their rate of growth retarded their metamorphosis and decreased the effectiveness of fed thyroid Contrariwise thyroid hormone hastened metamorphosis while retarding the over all rate of growth

Thyroid feeding causes a compensatory hypertrophy (Speidel 1926) or overactivity of the thymus reciprocally the feeding of thymic extracts produces thyroid hyperplasia (Kjerulf Jensen 1947) It has indeed been claimed that a condition identical with or similar to *status thymicolymphaticus* can be produced by the feeding of thyroid hormone Functionally an enlarged thymus affords the organism some protection from thyroid hormone because immature animals that is those with normally large thymuses are less sensitive to thyroxin than are adults Conversely thymectomy heightens the sensitivity to thyroid secretion

B Thyrotrophic Hormone—The anterior pituitary produces thyrotrophic hormone in an active reduced state During the process of oxidation it exerts its stimulatory influence upon the thyroid gland Once oxidized it is no longer active and is excreted in the urine in this inactive form Of all the tissues in the body the thymus and lymph nodes alone share the ability of the thyroid to oxidize this material (Rawson 1949) Although their capacity weight for weight to inactivate thyrotrophin is far below that of the thyroid it is nevertheless considerable (Rawson Sterne and Aub 1942 Rawson 1949) Teleologically therefore one might say that thymic hypertrophy occurs in thyrotoxicosis to aid in the oxidation of thyrotrophin thus helping to relieve the existing overstimulation of the thyroid

C Adrenal Influence—Thymic atrophy follows overactivity of the adrenal cortex or the administration of its steroid hormones whether 11 oxycorticoids (Wells and Kendall 1940b White and Dougherty 1946) or mineralocorticoids (Selye 1940 Selye and Albert 1942 Don

has been prepared for lactation histological changes within it are negligible although its functional capacity can be increased by the feeding of thyroxin under such circumstances The influence of sex, adrenal pituitary and other hormones will have to be more fully studied however before the role of the thyroid in mammary development can be fully appraised

When the subject of lactation is discussed in relation to thyroid hormone the picture is much more sharply defined Lolley and Mal piess (1918b) summarize it admirably when they state The mechanism behind thyroid involvement in lactation is still believed primarily to be simply one expression of its general systemic influence on metabolic rate The production of a more quickly circulating blood stream a richer supply of milk precursors to the gland and a heightened metabolic activity of the alveolar cells themselves are the most likely properties we can assign this hormone in its relation to milk secretion The propensity of thyroxin to stimulate milk secretion could perhaps be most faithfully represented as a fevered whipping of the whole organism into hyperactivity in the cause of benefitting one of its parts an overall participation to produce a very local gain In this connection however it must be kept in mind that failure to establish lactation satisfactorily may point to a latent hypothyroidism for which thyroid hormone in proper doses will afford a satisfactory solution (Robinson 1917)

There is no evidence to suggest that the function of the mammary gland has a *direct effect* upon the thyroid nor that per se it *initiates* an action through any other gland which finally alters thyroidal activity

The Thyroid Posterior Pituitary Relationship

Thyroid feeding opposes the antidiuretic action of the posterior pituitary (Mahoney and Sheehan 1935 Radcliffe 1913 Swann 1913) It apparently produces this effect by way of the anterior lobe of the pituitary for no diuretic action can be observed unless a functional anterior lobe is present (Schweizer et al 1911) We (McGavack et al 1946) have observed a case of craniopharyngioma in which the posterior pituitary function was first affected at the onset of diabetes insipidus when the patient was 15 years old Two years later at the age of 17 the function of the interior lobe was destroyed with a complete disappearance of the syndrome of diabetes insipidus Radcliffe (1913) has shown that in cats with diabetes insipidus thyroid feeding produces an increase in the urinary output and a *further decrease in the chloride output* Conversely in these same animals thyroidectomy was associated with a decrease of 25 to 35 per cent in the polyuria but its complete disappearance did not occur Injecting solutions of the posterior pituitary will abolish the polyuria due to thyroid feeding

Chapter XV

INTERRELATIONSHIPS BETWEEN THYROID FUNCTION AND VITAMIN METABOLISM

It is difficult to appraise the vast number of experimentally possible conditions permutations and combinations which may arise when one attempts to interrelate the effects of two biologically reactive materials as for instance the thyroid and any one of the vitamins Undoubtedly many of the apparent contradictions in the literature represent merely differences in technic concentrations of the substances employed duration of the experiments variations in the time at which the biologically reactive substances were introduced and so forth Therefore mooted points will not be discussed further than is absolutely necessary to clarify the major relationships believed to exist between the action of any particular vitamin and the thyroid In general the requirements for certain vitamins will vary directly as the functional state of the thyroid In other words in hyperthyroidism there is a definite increase in the requirements for vitamins A B and C which if not met will result in a relative deficiency Indeed it is likely that some of the symptoms previously ascribed to hyperthyroidism may actually be secondary to a lack of these substances

VITAMIN A AND THE THYROID

A lack of vitamin A initially produces in experimental animals hypertrophy of the thyroid (Lipsett and Winzler 1947) which if sufficiently long continued gives way to an atrophy that is usually more marked in the male than in the female The entire effect seems to be enhanced if an iodine deficiency exists simultaneously The nature of the changes seen in simple vitamin A deficiency in no way suggests that it is etiologically related to the development of simple goiter (Remington Harris and Smith 1942) although many instances of distended degenerated follicles are seen throughout these glands (Lipsett and Winzler 1947) The iodine uptake and concentration have been found to be normal but the percentage of organically bound iodine is low which indicates that iodine metabolism is abnormal in the vitamin A deficient rat (Lipsett and Winzler 1947)

No constant influence upon the thyroid has been observed following the feeding of large amounts of vitamin A Moreover from the experi

tigny 1916) Adrenalectomy results in hypertrophy of the thymus and all other lymphoid structures a fact carefully noted and detailed by Addison in his initial description of the disease which bears his name In hyperthyroidism therefore during its compensated phases a balanced action of the thyroid and the adrenal is evidenced by which the thymus may not be materially influenced at least as to size and histological appearance

The role of the thymus together with other lymphoid structures in the nonspecific resistance to stress and in immunity now seems well established (White and Dougherty 1916 and literature therein cited) While the control of such processes seems to be vested mainly in the adrenal the thyroid acts also to cause thymic hypertrophy and increased function At least it is evident to the clinician that hypothyroid subjects are more prone to infection than euthyroid or hyperthroid individuals and less capable of withstanding stress than those in a euthyroid state

In summary the thyroid and the thymus act antagonistically upon growth and somatic differentiation but possibly act synergistically in the control of metabolic and immune processes

The Thyroid Parathyroid Relationship

The disturbances in calcium and phosphorus metabolism seen in *thyroid disease are separate and distinct from those produced by primary dysfunction of the parathyroid glands*

Both thyroid feeding and the administration of thyrotrophic hormone greatly increase calcium excretion by all routes Thyroidectomy decreases the loss of calcium and simultaneously causes an involution of the parathyroid gland The values for blood calcium are only slightly decreased in thyrotoxicosis (*Robertson 1911*) those for *blood phosphorus* are not altered While thyroidectomy in rabbits on diets with a normal calcium phosphorus ratio causes an involution of the parathyroid the increased thyroid activity of animals on a rachitogenic diet is usually associated with parathyroid hypertrophy

The increased excretion of calcium and phosphorus which attends *the administration of thyroid hormone is probably mediated through* an action upon the parathyroid as it does not occur in the absence of the parathyroid tissue (Logan Christensen and Kuklin *1912*) Therefore there seems to be some significant complementary action between the thyroid and the parathyroid despite the establishment of entirely independent functions for each of the two glands

(Wendt 1937a b) These may be still further lowered by large doses of estrogen an effect not obtained however in the euthyroid subject (Williamson 1917)

In hyperthyroidism there seems to be no difficulty in the conversion of provitamin A to vitamin A or in the storage of the latter in the liver In such instances the low blood serum values are explained on the basis of a failure to mobilize hepatic stores (Lufinger and Gottlieb 1933 Drill 1943 Interrelations between thyroid function and vitamin metabolism 1944) In fact Wolff (1932) and Moore (1937) both observed an increase in the hepatic stores of vitamin A in human cases of exophthalmic goiter It may be said therefore that thyrotoxicosis increases the stores but inhibits the mobilization of hepatic vitamin A However it is claimed that thyrotoxicosis depletes the tissue reserves an effect diminished by thiouracil (Johnson and Baumann 1948)

The well known ability of thyroxin to mobilize glycogen from within the liver can be modified or even checked completely by the use of vitamin A Wegelin (1939) believes that this is due to a storing effect of vitamin A Simultaneously vitamin A decreases the number of mitoses ordinarily seen in microscopic sections of liver which have been subjected to a thyroxin action

A vitamin A deficiency interferes with the use of nitrogen for growth Thyroxin has a similar effect in the normal animal but improves utilization when used in the presence of vitamin A deficiency (Brown and Morgan 1948)

This antagonistic action between vitamin A and thyroxin is by no means complete as the former does not prevent the removal of fat and glycogen from the kidney following the administration of thyroxin Nor will vitamin A have a direct effect upon the thyroid gland histologically Nevertheless it is capable of counteracting the influence of the thyrotrophic hormone upon the thyroid (Elmer Giedosz and Scheps 1935 Fellinger and Hochstadt 1936 Wegelin 1939 Drill 1943)

In summary it would seem that hypothyroidism and thyroidectomy interfere with the conversion of carotene to vitamin A decrease storage in the liver and reduce the requirements for this vitamin but do not interfere with its utilization On the other hand when there is an excess of thyroid hormone as in thyrotoxicosis the requirement for vitamin A is increased its formation from precursors is readily accomplished and where abundant it is satisfactorily stored in the liver In both hypo and hyperthyroidism there is a decrease in the blood serum values for vitamin A A mutual antagonism exists between vitamin A and thyroxin which is seen chiefly in their action upon glycogenolysis and cellular division in the liver In addition vitamin A is capable of lowering the basal metabolic rate in thyrotoxic animals and patients and aids in maintaining the body weight of the latter

mental evidence it would appear most unlikely that any human being has ever suffered from hypervitaminosis A In experimental or clinical conditions associated with an increase in the amount of thyroid hormone as for instance in thyrotoxicosis there is simultaneously an increased need for vitamin A (Sure and Buchanan 1937 Logaras and Drummond 1938 Wegelin 1939 Remington Harris and Smith 1942 Mandelbaum Candel and Millman 1942 Interrelations between thyroid function and vitamin metabolism 1941) Conversely thyroidectomized animals apparently *need less vitamin A than normal animals* (Remington Harris and Smith 1942 Drill 1943 Wiese Mehl and Deuel 1948)

In some respects the action of vitamin A and the thyroid hormone are mutually antagonistic If vitamin A and thyroid substance are administered simultaneously the ability of the thyroid hormone to raise the basal metabolic rate is markedly decreased If the subject is already hyperthyroid vitamin A in relatively large doses tends to diminish the size of the thyroid decrease the protein bound iodine of the thyroid and liver and cause a rather minor reduction in the basal metabolic rate (Logaras and Drummond 1938 Sadhu and Brody 1947 Truscott and Sadhu 1948 Sadhu and Truscott 1948) effects possibly due to its inhibition of thyrotrophin secretion by the anterior pituitary (Sadhu 1948)

Vitamin A has been of clinical value in enabling patients with thyrotoxicosis to gain weight Inasmuch as the respiratory quotient in such subjects is not changed it would appear that the effect is not directly attributable *to a change in the metabolism of any particular foodstuff* in the hyperthyroid subject

In hypothyroid states and in thyroidectomized animals the ability of the liver to convert carotene to vitamin A is decreased or lost (Drill and Truant 1947a b Kelley and Day 1948) and the capacity of the liver for the storage and mobilization of this vitamin is disturbed Thiouracil also produces this effect probably by inhibiting directly or indirectly the action of carotinase (Crandell and Garcia Valdecasas 1947 Kelley and Day 1948)

The increased creatine metabolism of hyperthyroid individuals has been lessened by the administration of carotene (Drill 1943 Interrelations between thyroid function and vitamin metabolism 1941 Mandelbaum Candel and Millman 1942 David 1938)

Low values for vitamin A in the serum have been described both in hypothyroidism and in thyrotoxicosis (Remington Harris and Smith 1942 Mandelbaum Candel and Millman 1942 Drill 1943 Interrelations between thyroid function and vitamin metabolism 1941) When there is a deficiency of the thyroid hormone it is believed that the liver shows a decreased ability to convert provitamin A that is carotene to vitamin A (Johnson and Bauman 1947 Drill and Truant 1947a b) Therefore in hypothyroidism or in thyroidectomized animals the vitamin A supplies of the liver are depleted and hence the low blood serum values

are partially or wholly brought to normal by the feeding of thiamine (Williams et al 1943) Simultaneously the use of thiamine prevents the fall in liver glycogen commonly seen in experimental animals during thyrotoxicosis This would suggest therefore that a relative deficiency of vitamin B and an increase in the activity of thyroid hormone combine to arrest intermediary carbohydrate metabolism at the pyruvic and lactic acid stages On the other hand thyroid hormone does not prevent the phosphorylation of thiamine (Williams et al 1943)

Thiamine also exerts an effect upon calcium and phosphorus metabolism in animals with hyperplastic goiters There is a marked increase in calcium excretion similar to that observed when iodine is fed

In instances of *riboflavin* (vitamin B) deficiency stimulation of the thyroid has been reported (Giedosz 1938) accompanied by a slightly less than 50 per cent increase in weight of the gland (Sure 1938) This increased activity of the gland indicates that thyrotrophic function of the anterior pituitary may be increased during riboflavin deficiency although this has been denied (Schulze and Hundhausen 1939a b) It has not been possible to suppress the production or effect of thyrotrophin by the use of this vitamin (Cutting and Robson 1939) nor indeed has the feeding of riboflavin been found to alter the histological picture of the normal gland or of that subjected to the influence of thyrotrophin (Wahl 1939) In hyperthyroidism there is a marked increase in the urinary excretion of riboflavin which is derived at least in great measure from the catabolism of tissue (Sure and Ford 1943) The need for additional amounts of riboflavin in hyperthyroidism goes hand in hand with the increased requirement for thiamine and nicotinic acid amide

Nicotinic acid amide deficiencies have been observed in thyroidectomized animals (Kunde 1926) and in myxedematous patients (Greene 1938) It appears therefore that underfunction of the thyroid probably interferes with the absorption or utilization of this material Hyperthyroidism may be accompanied by a relative deficiency as it also increases the requirement for this vitamin

When there is a deficiency of either *pantothenic* or *folic acids* the subject is more susceptible to the toxic action of thyroxin (Haque et al 1948) Apparently folic acid blocks or alters the action of thyroxin in some as yet unexplained way as it is able to prevent completely the characteristic effects of thyroxin on the feathering of chicks (Haque et al 1948) Feeding thyroxin increases the requirement for folic acid and if not met results in a characteristic leukopenia in the experimental animal (Martin 1947)

Pantothenic acid and *pyridoxine* (*vitamin B*) are necessary to prevent the loss of weight in hyperthyroid animals In such subjects thiamine improves the appetite and increases the food intake but will not enable the subject to regain weight until these two factors from the B

VITAMIN B AND THE THYROID

A deficiency of certain factors in the vitamin B complex, particularly thiamine riboflavin pantothenic acid folic acid and pyridoxine makes the liver more susceptible to the action of thyroxin and thyroid hormone The requirements for these several vitamins increase as hyperthyroidism grows worse No final statement should be made at this time about the effects of the deficiency of vitamin B upon the weight histology or function of the thyroid gland However Blatzot and his associates (1917) observed the following series of changes in chronically deprived animals The thyroid remained histologically normal for five weeks without thiamine except for a progressive increase in chromophilic colloid This was followed by one week of intensive transitory resorption of colloid, after which the acini became distended with inactive colloid surrounded by a flattened resting epithelial lining A steady loss of weight accompanied these changes

That a quantitative relationship exists between the caloric intake and amount of *vitamin B* required by the organism has been demonstrated many times In experimentally produced hyperthyroidism it was some time ago proved possible to prevent loss of weight and appetite in dogs by the feeding of vitamin B (Sure and Smith 1934, Sure and Buchanan, 1937 Drill and Sherwood 1938) Vitamin B appears to be equally effective and will often enable the animal to regain weight previously lost (Drill 1943) Pyridoxine and pantothenic acid (Drill and Overman 1942) may be similarly important in preventing some of the untoward effects due to excessive amounts of thyroid hormone such an influence in the case of the latter has been confirmed (Haque et al 1948 and denied (Ershoff and Hershberg 1945 Bethell et al 1947)

Experimental hyperthyroidism produces hepatic damage which is more pronounced where vitamin B_1 is deficient When vitamin B is fed in sufficiently large amounts there is a tendency to restoration of glycogen stores in the liver (Drill 1943) A further need for thiamine is seen in hyperthyroidism because this condition decreases the amount of that vitamin in various tissues and increases its excretion (Drill 1938 1943 Williams et al 1943 Interrelations between thyroid function and vitamin metabolism 1941) *On the other hand in thiamine deficiencies* at least in experimental animals the ability of thyroid hormone to raise the basal metabolic rate is decreased (Williams et al 1943 Williams and Kendall 1942 1943) Because of this fact it is believed that thyroid hormone functions primarily to mobilize metabolites for oxidation by enzyme systems and only indirectly does it function to increase oxidative processes (Williams and Kendall 1942, 1943)

The disturbances in thyrotoxicosis associated with thiamine activity are concerned primarily with the intermediary metabolism of carbohydrates There is a decrease of the thiamine level in the blood with a concomitant increase in both pyruvic and lactic acids These changes

VITAMIN D AND THE THYROID

There is no evidence that a deficiency of vitamin D has any effect upon the thyroid gland (Drill 1943) On the other hand the feeding of large amounts of vitamin D has been found to increase the basal metabolic rate (Reed et al 1933 Reed 1934) provided the thyroid gland is intact (Deutsch Reed and Struck 1936 Handovsky and Goormaghtigh 1937) The increased fecal excretion of calcium seen in hyperthyroidism has been counteracted by the administration of vitamin D with a restoration of the calcium balance to normal

VITAMIN E AND THE THYROID

Any interrelationship between vitamin E and the activity of the thyroid hormone appears to be mediated by way of the gonads However the experimental and clinical data are so conflicting that further studies seem necessary to ascertain the presence of a cause and effect relationship between alterations in the status of the thyroid and the metabolism of vitamin E (Drill 1943)

SUMMARY

It would appear that hyperthyroidism increases the need for and tends to deplete the bodily stores of vitamins particularly vitamins A B and C Moreover it appears that some of the symptoms formerly ascribed to hyperthyroidism are probably due to a relative deficiency in one of these Hence it is logical to believe that an increased vitamin intake will offer some protection against thyroxin administration or against some of the clinical manifestations of thyrotoxicosis Such activity does not necessarily indicate a true antithyrogenic action on the part of any one of these nutritional factors

complex are added (Drill and Overman 1942 Glanzmann and Meier 1945) A deficiency of pyridoxine is accompanied by a 30 per cent increase in thyroid weight (Sure 1938)

Other factors contained in the B complex such as *biotin inositol* and *para aminobenzoic acid* may play some as yet undetermined role in thyroid activity

In summary the needs for thiamine in thyroid disease vary directly with the caloric intake Riboflavin in addition to that of the diet is needed when the gland becomes overactive Pantothenic acid and pyridoxine when used in conjunction with thiamine are capable of returning the weight of hyperthyroid subjects to normal and seem to be the only two of the B complex fractions essential for this purpose *Deficiencies of pantothenic and folic acids sensitize the individual to* the action of thyroid hormone Both hypothyroidism and thyrotoxicosis increase the need for nicotine acid amide *In the present state of our* knowledge judicious use of the entire vitamin B complex in the management of hyperthyroidism seems justified Vitamins B_1 and B_2 are clearly indicated in all such cases Attempts to select certain other specific fractions of the B complex while ignoring still other additional ones are fraught with considerable danger of overlooking some hitherto unrecognized substance of importance for the proper functioning of the thyroid gland Liver and yeast remain our best sources of B complex as they contain life maintaining factors that have not yet been isolated and identified (Elsholf 1917 a b)

VITAMIN C AND THE THYROID

When there is a long standing vitamin C deficiency or chronic scurvy hemorrhagic infiltration and hyperplasia of the thyroid gland *may occur (Gabe and Parrot 1948) The administration of thyroxin* has been shown to hasten the development of scurvy in vitamin C deficient subjects (Marine 1939) Both experimental and clinical hyperthyroidism increase the requirements for vitamin C and reduce its concentration within the tissues of the body (Johnson Hansen and Lindy 1948) At the same time less vitamin C is excreted which suggests that the hyperthyroid individual destroys it Both the vitamin C and cholesterol content of the adrenal cortex may be markedly decreased in thyrotoxicosis

No positive effects upon liver glycogen have been demonstrated for *vitamin C but the creatinuria seen in hyperthyroid animals is always* reduced by its administration (Fischer and Oehme 1937) Simultaneously the basal metabolic rate may fall Whether any of these effects are produced through the influence of vitamin C upon the activities of the thyrotrophic hormone has not been demonstrated *It has been sug*gested that the closely related vitamin P an active flavone possesses positive antithyrotrophic activity (Gabe and Parrot 1948)

I FOODS

In his book on the thyroid gland McCarrison in 1917 summarized data pointing to the goitrogenic activity of foods particularly emphasizing the presence in beef and liver of a factor with such properties It remained however for Chesney Clawson and Webster in 1928 to reawaken interest in the subject by reporting the development of large goiters in an entire colony of rabbits fed a daily ration of cabbage Williams (1945) and Rawson Hertz and Means (1943) have quoted rather fully both the early and current literature concerning these cabbage goiters In these there is an extreme hyperplasia of the thyroid associated with a low basal metabolic rate very low levels for the protein bound iodine in plasma and all of the clinical symptoms and signs of hypothyroidism or myxedema Such goiters can be prevented or the attendant hypothyroidism mitigated by the use of either thyroid hormone or iodine Indeed with the administration of iodine a severe thyrotoxicosis has been known to develop

It is clear from the above and other work (Kennedy and Purves 1941 Griesbach 1941 Griesbach Kennedy and Purves 1941 Purves 1943 Greer and Astwood 1948 Greer Ettlinger and Astwood 1949) that members of the Brassica family prevent the formation of thyroid hormone thus producing a lowered basal metabolic rate which in turn favors the elaboration of thyroid stimulating hormone by the anterior pituitary

Using radioiodine as an investigative tool Greer and Astwood (1948) and Greer Ettlinger and Astwood (1949) have recently assayed more than 60 foods for their influence upon the uptake of iodine by the thyroid glands of 100 human subjects Some of these foods showed considerable antithyroid activity When judged in relation to the average serving their descending order of potency was somewhat as follows rutabaga carrots lettuce turnips peas peaches grapefruit baked beans pears and walnuts For instance two average servings of rutabaga or carrots ingested at a single sitting showed inhibitory effect while to obtain a definitive change with walnuts it was necessary to take ten times the amount one would ordinarily consume Still slighter degrees of goitrogenic activity were demonstrated in milk oysters beets spinach cabbage filberts string beans celery and grapes From these lists it will be seen that substances containing an antithyroid principle are rather widely distributed in nature for the three most active vegetables —rutabaga carrots and lettuce—represent as many families the Cruciferae the Compositae and the Umbelliferae respectively However members of the Cruciferae to which cabbage and other Brassicae belong were more consistently active than the other substances

The rather slight action of cabbage in these experiments of Greer and Astwood (1948) emphasizes the differences in the reactions of vari

Chapter XVI

ANTITHYROID COMPOUNDS

In the broadest sense the term antithyroid substance includes any agent capable of suppressing the formation of thyroid hormone by the thyroid gland of the intact animal Among such materials must be included

1 Certain foods
2 Thyroid hormone
3 Thyroxin analogues
4 Iodine
5 Thiocyanates and certain nitriles
6 Aniline derivatives
   (a) N Methylated anilines
   (b) Aminoheterocycles
7 *Mercapto and (or) thio compounds*
   (a) Mercapto and (or) thioheterocycles
      (i) Thiouracils
      (ii) Thiobarbituric acids
      (iii) Thiohydantoins
      (iv) 2 Thiazolethione derivatives
      (v) Other Mercaptoheterocycles
   (b) Thioureas

Already a vast literature has grown up about the antithyroid substances much of which has been summarized in four reviews which have respectively stressed their chemical classification in relation to activity (Anderson 1951) their comparative effects in different species (Charipper and Gordon 1947) a differentiation of the nature of their action (Astwood 1949) and the therapeutic efficiency of individual members of the aniline and mercapto series of compounds when applied to human beings (McGavack 1948) Much of the nature of these materials and their modus operandi is still unknown but sufficient is well proved to afford us an extended knowledge of thyroid function in health and disease

iodine is probably dependent upon the extensive usage of cabbage and similar foods as articles of diet

Other members of the Brassica group particularly rape seed may have a different mode of action as iodine does not completely overcome the goitrogenic effect (Purves 1943)

Can the dietary become an important determining factor in the appearance or incidence of simple sporadic or endemic goiter? It has long been recognized that a low intake of iodine is probably responsible for the endemic form of goiter but even this fact has not clearly indicated why some subjects and even families in such areas may escape while others develop thyroid masses of considerable size Not one factor but several probably combine to set the stage for the development of so called simple or sporadic goiter

1 **Goitrogenic Foods**—In order to inhibit the uptake of iodine by the thyroid Greer and Astwood (1948) found it necessary for their subjects to consume large quantities of the goitrogen It is not likely that the average subject will take any one of these materials in such amounts but a person of predominantly vegetarian habits may take several such foods at one meal with an additive effect sufficient to interfere with the synthesis of thyroxin In such instances it is probably also necessary that there exist either a deficiency of iodine or an individual susceptibility to the action of the thyroid depressing agent

2 **Iodine Deficiency**—The combination of a dietary containing goitrogens and a low intake of iodine undoubtedly plays a part in the production of goiter endemically and perhaps sporadically Indeed some of the observations of Greenwald (1945 1946) may be fully explained on this basis

3 **Individual Susceptibility**—The phenomenon of adaptation to environment is well known Through many generations a people may gradually acquire a capacity for compensation against an influence commonly unfavorable to the species as a whole For instance in certain parts of Poland where the daily ingestion of iodine is not above 15 micrograms as compared with an optimum of 200 micrograms there is little or no clinical evidence of disturbances in the function of the thyroid gland (Salter 1940) Similarly differences in susceptibility to goitrogenic stimuli may be expected from individual to individual a fact well proved by the widely divergent requirements for an antithyroid compound commonly observed from subject to subject in the management of hyperthyroidism While subjects A and B may consume identical amounts of goitrogen in their foods A may retain normal thyroid function while B develops a simple goiter The management of such goiters in the future may be logically directed not only to the administration of iodine but also to some critical review of the dietary and the elimination of foods known to depress the activity of the thyroid gland an approach which Astwood (1949a) has recently initiated

ous species to a single antithyroid agent and clearly illustrates how futile it is to judge the potency of any antithyroid compound in human beings by its behavior in blocking the formation of thyroid hormone in small laboratory animals or its capacity for producing goiter in them *under standard conditions of feeding*

Several facts indicate that the same compound or principle is not *responsible for the antithyroid activity of all goitrogenic foods* The species difference in response illustrated just above is one reason for such a conclusion Since the activity of some vegetables such as rutabaga and peas was destroyed by heating and that of others such as peanuts peas and beets was not so affected it is likely that the antithyroid material is not the same in all of them Considerable effort has been made to find the compound or compounds in foods which accounts for the depressing influence upon the formation of thyroid hormone Inasmuch as the Brassicae to which rutabaga cabbage and mustard belong have proved to be the most active of these compounds Marine and his associates (1931) postulated that isothiocyanates (mustard oils) might be the substances concerned These however, proved to be inactive Of other compounds then tried these same workers found organic cyanides goitrogenic, acetonitrile being the most potent Apparently specific conditions are necessary to bring out this effect of acetonitrile as it has not been widely confirmed Following the report that thiourea was goitrogenic (Mackenzie and Mackenzie 1942) Kennedy (1942) suggested that the isothiocyanates might be converted to thiourea or allyl thiourea in vivo and thus exert their thyroid depressing action Greer and Astwood (1948) made an ether extract of rutabaga which contained a water soluble potent material, the chemical formula of which has now been found to be 5 vinyl 2 thiooxazolidone one of the thio compounds (Astwood Greer and Ettinger 1949a b Greer Ettinger and Astwood 1949 Carroll 1949) To date this is the only active goitrogenic compound isolated from food in pure form

Since an excess of iodine will relieve the goitrous condition pro*duced by some of the Brassicae* such as rutabaga or cabbage it is likely that their major action is to prevent iodine from being taken up and utilized by the thyroid cell It is as though we have raised the threshold of the thyroid cell membrane to iodine and that the giving of iodine surmounts this heightened barrier Once enough iodine is given in such instances formation of thyroid hormone goes on without further interference Such a concept will account not only for the ability of iodine to destroy the effect but also for the thyrotoxicosis *sometimes observed* following its administration In other words the hyperplastic thyroid cell produced by the ingestion of certain of the Brassicae is capable of forming thyroid hormone at an accelerated rate provided sufficient iodine is present The 'Jodbasedowism' seen among some of the peoples of the Carpathian Mountains following the administration of

IV IODINE

The importance of iodine as a homeostatic regulator of thyroidal activity has already been emphasized (Wolff and Chaikoff 1948c d) (see extrathyroidal factors which influence the thyroid follicle Chapter XI) It will receive further attention in the present section only as it may influence the responses to be obtained by some of the other groups of antithyroid compounds

V, VI, AND VII THE THIOCYANATES ANILINE DERIVATIVES, AND MERCAPTO COMPOUNDS

The remaining three groups of antithyroid compounds — thiocyanates aniline derivatives and mercapto compounds have several actions which may be considered collectively in arriving at a basic understanding of their position in the management of thyroid conditions Some of these are suggested schematically in Figs 4 11 In grouping these effects much of the finer detail of action is necessarily lost and possibly some factors may be minimized The main object is to emphasize those features which will enable us to apply these drugs to better advantage in the management of thyroid disease Therefore in delineating the major trend of their action the influence of species age sex diet environmental temperature dosage and manner of administration will be for the most part neglected as it has been critically considered not too long ago (Charipper and Gordon 1947) and will be of little help for our present purposes

1 **Gross and Microscopic Changes in the Body Tissues** —With optimal doses of the effective members of these groups of compounds changes in the appearance of the thyroid rapidly take place Hyperemia heightening of the acinar cells and a loss of colloid appear within 24 to 48 hours Eventually usually between the tenth and the twentieth days the epithelium is high cuboidal or columnar little or no colloid is left and the hyperplasia and hypertrophy result in an increase in the number and size of the follicles with invagination of their epithelium and the formation of new follicles In many areas the reaction is so intense that cordlike masses of cells occur Later after prolonged administration for many months adenomata may be formed particularly if thyroid function is depressed to myxedematous levels

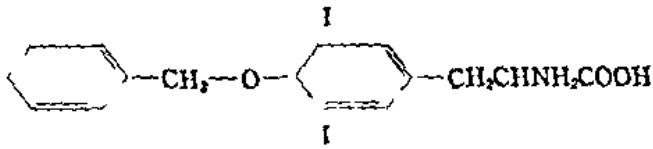
In other instances continuous treatment for long periods of time results in a diminution of the hyperplasia or an exhaustion atrophy This has been recorded both in animals (Griesbach 1941 Engle and Aranow 1946 Crasso 1946a b) and in human beings (Reveno 1945 Sexton 1947) although a permanent myxedematous state in the latter is rare even though treatment is continued for several years (McGavack 1949a)

II THYROID HORMONE

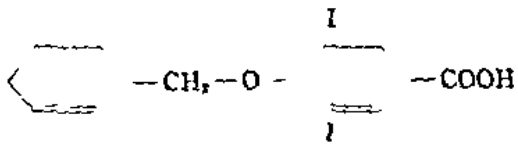
Thyroid hormone probably acts in a twofold way to moderate the activity of the thyroid gland by inhibiting the production of thyrotrophin by the anterior pituitary (Loeser 1931 Rawson and McArthur, 1947) and by suppressing the action of preformed thyrotrophin (van Dyke 1939, Cortell and Rawson 1941 Rawson and McArthur 1947) Its influence has already been detailed at some length (Chapter XIII)

III STRUCTURAL ANALOGUES OF THYROXIN

Many compounds related structurally in specific ways to metabolically important substances are capable of producing signs of insufficiency of the analogous metabolite (Woolley 1941) In line with this thought Woolley (1946 and 1947) has prepared several new ethers of N acetyldiiodotyrosine of which representative formulas appear below that are capable of preventing the metamorphosing and lethal effects of thyroxin in the tadpole



Benzyl ether of diiodotyrosine



Benzyl ether of diiodobenzoic acid

Structural analogues of thyroxin that possess an antithyroid effect through their inhibition of the action of thyroxin

Some closely related analogues may be inactive (Barker et al 1949 Cortell 1949) although one (2 6 diiodothyronine) was proved capable of suppressing the action of 1/150 of its weight of thyroxin (Cortell 1949)

The nature of the action of such compounds needs further clarification before any therapeutic application becomes apparent Theoretically they should be able to suppress the effects of thyroxin in a quantitative manner (Winzler and Frieden 1948 Frieden and Winzler 1948 1949) and one of them has already done so

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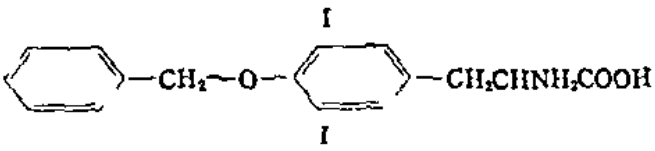
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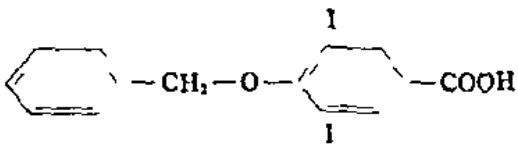
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It is difficult to produce alterations in the *peripheral blood* of small laboratory animals as a result of the administration of antithyroid compounds in any dose although moderate anemia and leucopenia have been recorded (Charipper and Gordon 1947—literature cited)

A decrease in the myeloid erythroid ratio of the *bone marrow* has been observed following the use of large doses of thiouracil in rats (Vogel and McGavack 1946) a phenomenon possibly related to the high concentration of drug occuring in this tissue (Williams Kay and Jandorff 1944 [Table V]) In patients with leucopenia and granulocytopenia there is demonstrable in the sternal marrow a failure in maturation of the granulocytic series of white cells (Gessler 1946 Sikkema Thewlis and Meyer 1946 Blackburn 1948) but serial studies both of marrow and peripheral blood have failed to reveal any regularly occuring changes during thiouracil therapy by which the advent of serious bone marrow depression can be predicted (Sikkema Thewlis and Meyer 1946)

Arteriosclerosis has been produced in dogs given large supplements of cholesterol (10 Gm daily) and very heavy doses of thiouracil (1 0 Gm daily) (Steiner Bevans and Kendall 1948 Steiner Davidson and Kendall 1948) Perhaps it is wise to ensure a low cholesterol diet to those under treatment with a thiouracil derivative although it hardly seems likely that correspondingly high doses of an antithyroid compound will ever be needed for the control of human thyrotoxicosis

In connection with the use of thiouracil and closely related compounds in the therapy of thyrotoxic states the question of the development of *cancer* is always raised Thyroid adenomata are readily produced in small laboratory animals and in patients whose treatment is pushed to the point of creating a negative basal metabolism They are much more rarely observed in the well controlled patient whose metabolism is kept between plus 5 and plus 15 per cent A relationship between adenomas and carcinomas is now widely accepted but the small multiple adenomata due to overtreatment with a thiocarbamyl derivative are not the type most likely to become cancerous Experimentally Bielschowsky (1944 1945) and Paschkis Cantarow and Stasney (1948) produced cancerous liver lesions by the combined use of allylthiourea or thiouracil respectively and the carcinogen 2 acetylaminofluorene In animals the development of hepatic lesions due to 2 acetylaminofluorene was hastened by estrogens and androgens This effect was partially abolished by thiouracil but simultaneously thyroid tumors appeared (Cantarow et al 1946)

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While there are *minor variations in the appearance of the pituitary* from species to species and under different conditions of experimentation the over all picture is similar in most respects to that which follows thyroidectomy and which has already been described in relation to the discussion of the pituitary thyroid axis (Chapter XII)

The influence of the antithyroid substances upon *other organs* and *tissues* has not been fully delineated nor has a sharp distinction been made between the action of the drug per se and that of the ensuing hypothyroid state Nor indeed has the possibility that thiourea derivatives can influence the action of *thyroxin* in the tissues been given any consideration at all (Andik Balogh and Donhoffer 1919)

The *adrenal* has been reported as hypertrophied (Kennedy and Purves 1941 Reveno 1915) and decreased in size (Leblond and Hoff 1941b Williams Weinglass Bissell and Peters 1941 Leathem 1915) If used in toxic amounts both aniline and thiocarbamyl derivatives have *caused necrosis and hemorrhage in the adrenal cortex* (Endicott Kornberg and Daft 1941 McGavack and Vogel 1945, Glock 1945 McCloskey Lillie and Smith 1947) Alterations in function of the adrenal cortex when present probably depend upon the associated alteration in the functional status of the thyroid gland (Florentin Martin and Sadoul 1947)

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usage The amazing concentrations reached in the bone marrow are probably related to the appearance of granulocytopenia and also suggest the true toxic nature of this reaction Of the tissues not shown on this table a late increase in concentration may occur in the pancreas testis ovary kidney liver spleen and brain Skeletal muscles and prostate rarely show a concentration much above that of the blood

TABLE V

DISTRIBUTION OF THIOURACIL IN HUMAN TISSUES

TISSUE	DURATION OF DRUG ADMINISTRATION			
	LESS THAN 3 DAYS		MORE THAN 5 DAYS	
	MG /100 GM DRY WEIGHT	TISSUE/BLOOD RATIO	MG /100 GM DRY WEIGHT	TISSUE/BLOOD RATIO
Pituitary	14	7	58	29
Adrenal	12	6	44	22
Thyroid	3	1 5	92	46
Bone marrow	24	12	170	85
Blood	2		2	

Arranged from the data of William Kay and Jandorf 1944

Further light is thrown upon the variations to be observed in the potency of very closely related thiouracils in the human being by the recent work of McGinty Sharp Dill and Rawson (1948) For instance in standard tests for potency in the rat 6-propylthiouracil proved to be 11 times as active as thiouracil but in man it is only slightly more effective The above workers found that much more of the latter drug appeared in the urine in a free form while most of the former was excreted in conjugated form They have concluded therefore that a differential conjugation of these substances by the organism plays a considerable role in altering their effectiveness as antithyroid compounds

3 The Influence of Antithyroid Compounds Upon the Thyroid and Its Behavior Toward Iodine —The manner in which the thyroid behaves toward administered iodine sharply distinguishes the action of the thiocyanates from other goitrogens and aids in differentiating the actions of certain of the mercapto compounds from those of the aniline series (Figs 6 11) In discussing the synthesis of thyroid hormone (Chapter IX) it was emphasized that the thyroid successively picks up concentrates organically binds stores and discharges iodine (Fig 4 and Table III)

Price (1917) have reported the appearance of carcinoma of the thyroid in a patient while receiving treatment with thiouracil In the present state of our knowledge it is difficult either to incriminate or wholly to exonerate thiocarbamyl derivatives in the genesis of thyroid cancer However it is fair to say that the tumors which have been described are not due to a direct carcinogenic action of this group of drugs but may result from excessive and prolonged stimulation which under certain circumstances they afford the follicular epithelium of the thyroid gland It is our personal belief that therapeutic doses of these compounds may be used for very long periods of time (several years) without causing such overstimulation provided sufficient thyroid function is retained to keep the basal metabolism of the individual on the high normal side (between +5 and +15)

2 **Tissue Distribution** —Most of the studies of absorption excretion and tissue distribution of antithyroid compounds have been carried out with thiouracil (Williams R H 1941b Williams Kay and Jandorff 1944 Williams and Kay 1947)

While no statement can apply equally to all the mercapto or aniline derivatives or to each of them in a quantitatively equivalent manner the summary of Williams and Kay (1947) in regard to the behavior of thiouracil affords a satisfactory idea of the general manner in which the body may be expected to metabolize the thiourea and thiouracil derivatives

1 Accurate estimations can be made of its concentrations in all the tissues and fluids of the body

2 It is rapidly absorbed from the gastrointestinal tract significant concentrations in the blood developing within fifteen minutes but about 15 per cent of the drug is destroyed in the gastrointestinal tract The secretions of the stomach duodenum and jejunum but not the contents of the ileum possess the capacity to break down the drug

3 *Most of the thiouracil in the blood is in the cells and nearly* all of it is bound to protein It can be freed from the protein by digestion with trypsin it has been released from serum by ultrafiltration at a low pH The concentration of thiouracil in the blood rarely exceeds 6 mg per hundred cubic centimeters regardless of dosage damage to the kidney or hepatic damage

4 It has been found in essentially all the tissues and fluids of the body but the concentrations have been different

5 Approximately one half of the total amount of thiouracil ingested is broken down in the body essentially all tissues possessing this capacity to varying degrees

6 About one third of the drug ingested is excreted unchanged in the urine The products of disintegration of thiouracil have not been established but following its administration there is an increased excretion in the urine of neutral sulfur

7 Thiouracil is transported through the placenta in biologically active *quantities*

The accompanying table (Table V) arranged from the data of Williams Kay and Jandorff (1944) shows the major areas of distribution of thiouracil after a short period of time and following more prolonged

and Gordon 1917 literature cited Astwood 1919 literature cited) These substances interfere with the enzymic processes by which nascent iodine is bound to the amino acid tyrosine to form thyroxin and thyroid hormone (Figs 8-11) (Charipper and Gordon 1917 Astwood 1919)

Aniline compounds such as the sulfa drugs and thiocarbamyl derivatives such as thiouracil and its substitution alkyls decrease the amount and the speed of the pickup and concentration of iodine by the thyroid gland when the amount of iodine available is not great Beyond a certain critical point of blood concentration however there is an actual increase in such absorption and concentration (McGinty and Bywater 1915a Salter Cortell and McKay 1915 McGinty 1919) Under such circumstances the capacity of the thyroid for iodine has been increased the action thus contrasting quite sharply with that of the thiocyanate ion However the organic binding of this iodine is prevented by the aniline or thiocarbamyl preparation and its return to the circulation in an inorganic form continues as long as a block is maintained by the antithyroid compound (Figs 8-11) Since under these conditions thyroid hormone cannot be synthesized thyrotrophic hormone of the pituitary exerts an unopposed influence upon the follicle producing marked hypertrophy and hyperplasia of the cells and the extrusion of the hormone from the thyroid rich colloid which has been previously stored

How and at what point in the process of thyroid hormone manufacture is the action of these compounds exerted? Present knowledge of this subject has been ably reviewed recently by Anderson (1919) Certain points may be brought out here As we have previously seen (Chapter IV) the processes by which thyroid hormone is synthesized are oxidative in nature and involve first the oxidation of iodide to nascent iodine second its combination with tyrosine to form diiodotyrosine and finally within the protein molecule an oxidative ether linkage of two molecules of diiodotyrosine to form thyroxin (Fig 1) The last mentioned stage of this reaction seems to be mainly under the influence of the pituitary gland (Morton Perlman Anderson and Chaikoff 1942 Chaikoff and Taurog 1919) and is little if at all disturbed by the compounds under consideration Since iodine accumulates in vitro in thyroid slices treated with thiouracil but cannot be converted to diiodotyrosine or thyroxin it is clear that thiouracil stops the formation of thyroglobulin at an early stage (Franklin and Chaikoff 1913 Schachner Franklin and Chaikoff 1913 Keston et al 1911 Franklin and Chaikoff 1911 Schachner Franklin and Chaikoff 1911 Franklin Lerner and Chaikoff 1911 Rawson Tannheimer and Peacock 1911 Astwood 1911 1915 Taurog Chaikoff and Franklin 1915) Indeed when all the evidence is considered it appears that the oxidation of iodide to iodine is prevented by each of the thyroid active thiourea derivatives The work of Paschkis and his associates (Paschkis et al 1911a b 1915a b

The thiocyanates act solely upon the first two of these functions Both potassium and sodium thiocyanate inhibit the collection of iodine by the thyroid (Lunde Chaikoff and Lerner 1941 Wolff Chaikoff Taurog and Rubin 1946 Vanderlaan and Bissell 1946 Astwood 1949) Furthermore if the thyroid has already been packed with inorganic iodine the thiocyanate ion will cause its immediate discharge (Vanderlaan and Vanderlaan 1947, Stanley and Astwood 1948 Astwood 1949) This capacity for purging the gland of inorganic iodine is so marked that Stanley and Astwood (1948) have made it the basis of a test for the effectiveness of treatment with antithyroid compounds of the thiouracil type (see hyperthyroidism Chapter XXXVI) in the following way Thiouracil prevents the organic binding of iodine but when given in relatively large amounts does not inhibit its uptake and concentration by the thyroid Thiocyanate does not cause the discharge of organically bound iodine diiodotyrosine and thyroxin *Thus by following the course of tracer doses of radioiodine before* and after a dose of thiocyanate the capacity of the thyroid to form hormone is ascertained and thereby the effectiveness of thiocarbamyl medication can be readily checked At this point it should be emphasized that while the goitrogenic action of the thiocyanates can only be evoked by a low or relatively low intake of iodine that of the aniline and thiocarbamyl compounds while occurring in the face of relatively large intakes of iodine roughly varies inversely with the amount of iodine ingested particularly as regards the degree of thyroid block and the rapidity with which it is attained

How thiocyanate prevents the uptake of iodide by the thyroid is not known despite its proved ability to substitute for iodine in the diiodotyrosine molecule (Easterwood and Wood 1949) There is no increase in the concentration of the radicle within the gland nor are the processes of synthesis of thyroxin from *iodine already present in the gland* in any way disturbed (Astwood 1949) There is no palpable effect from thiocyanate with an adequate intake of iodine a striking effect if its ingestion is low Since many plants contain thiocyanates it is intriguing to speculate upon their role in producing goiters even in the presence of ordinarily adequate amounts of iodine

From what has been said it is clear that the thiocyanates have no place in the clinical management of thyrotoxic states for their action it too readily overcome even by modest increases in the intake of iodine Moreover when effective the action in blocking the formation of thyroid hormone is almost invariably accompanied by the formation of a goitrous swelling—certainly an undesirable side effect of any treatment

The action of the aniline and mercapto derivatives differs radically from that of thiocyanates and nitriles In neither instance is there any serious interference with the uptake of inorganic iodide although the turnover of iodide may be more rapid under their influence (Charipper

from organically combining to form thyroid hormone and its precursors but is also prevented from oxidizing or inactivating the thyrotrophin Under such circumstances the latter continues to act unopposed causing an increase in the already present sulf induced hypertrophy and hyperplasia However *if the action is long continued* the hyperplasia and hypertrophy may diminish (Mackenzie 1917) possibly through a decrease in the formation of thyrotrophin by the pituitary

The essential reactions in the behavior of the thyroid to antithyroid compounds plus iodine are schematically indicated in Fig 16 In using these and the figures already mentioned (Figs 1 11) it must be fully understood that they represent only one possible arrangement of the facts and that while valid they are not all inclusive but merely illustrative

For practical reasons from this point forward the antithyroid action of the thiocyanates the anilines and the mercapto compounds may be best considered separately Their probable point of attack upon thyroid function is suggested in Table VI

A THE ANTITHYROID ACTION OF THE THIOCYANATES AND NITRILES

Experimentally a number of cyanide and cyanate compounds have been tested for their goitrogenic effect (Astwood 1943) Of these sodium and *potassium thiocyanates are by far the most important clinically* because of their recent extensive use in the treatment of hypertension Williams (1944a) has collected from the literature no less than 20 instances of thiocyanate goiter occurring during treatment for hypertension and states that of 246 patients treated by Barker and his associates (1941) 11 were found to have goiters The mode of development of these goiters appears to be identical with that obtained by the administration of Brassica seeds although it is thought by some to evolve less

1) I + Ox E of Thyroid → I → Diodo → Thyrox → T H
2) Active (Pituitary) Thyrotrophin (T S H) + Ox F of Thyroid or I → Inactive (Urinary) T S H
3) Thiocarbamyl Compound + I → I + Ox Thiocarbamyl (Inactive)
4) Aniline Compound + Ox E of Thyroid → Inactive Enzyme System
5) Inactive Thyrotrophin + Thiocarbamyl → Active Thyrotrophin

Fig 16.—Schematically represented interrelations and antithyroid compounds upon the function of the thyroid gland

I = Iodide
I = Iodi
O E = Oxidizing enzyme
Di do = Di dotyrosin
Thy x = Thyroxin
T H = Thyroid hormone
T S H = Thyrotrophic hormone

Paschkis Cantarow and Tillson, 1945) and of Chaikoff and his associates (Taurog Chaikoff, and Franklin 1945, Franklin and Chaikoff 1943 Morton and Chaikoff 1942 1943 Morton et al 1942 1943 Morton Chaikoff, and Rosenfeld 1941 Morton Perlman and Chaikoff 1941 Perlman Morton and Chaikoff 1941 a b 1942 Schachner Franklin and Chaikoff 1943 1944) as well as that of other investigators (Dempsey 1941 Williams R H 1941a) confirms such a concept

It is believed that both the aniline and thiocarbamyl substances permit the oxidation of iodide to iodine but from that point onward they differ considerably in their mode of action (Figs 8 and 10) Indeed the details of their action are far from clear and any statement made now may be proved wrong tomorrow However it seems likely that both types of compounds influence peroxide peroxidase systems the thiocarbamyl derivatives to reduce nascent iodine to iodide as fast as it is formed (*Miller Robbin and Astwood 1943 Astwood 1949*) and the aniline compounds to stop the iodination of tyrosine by competing for the oxidative enzyme systems involved (Figs 8 and 10) (Mackenzie and Mackenzie 1943 Mackenzie 1947) Some exceptions already have been taken to this concept and not all of the compounds of either group behave alike For instance para aminobenzoic acid one of the simplest and more active of the aniline compounds acts more like the thiocarbamyl derivatives particularly in its responses to ingested iodine (*Mackenzie 1947*) *Despite the fact that large doses of iodine administered to a subject with a thiouracil blocked thyroid are picked up and held by it in an inorganic form they act upon the thyroid to reduce the hyperplasia and to further the storage of colloid* (Fig 9) Inasmuch as the iodine does not enter into organic combination this colloid is poor in thyroid hormone (Fig 9) The changes thus brought about by iodine in the thyroid controlled by thiouracil are probably due mainly to the ability of the former in large amounts to suppress the action of *thyrotrophin* (*Albert Rawson Merrill Lennon and Riddell 1946* Albert and Rawson 1946, Albert et al 1947a b c Rawson and McArthur 1947)

The use of iodine in the aniline blocked thyroid gland is followed under proper conditions by a quite dissimilar chain of events If the amount of the goitrogen is submaximal and the doses of iodine are relatively large iodine increases the hyperplasia and hypertrophy and fails to cause a collection of colloid within the acini (Fig 11) Mackenzie (1947) believes that this action is due to inhibition of a specific oxidative enzyme concerned in the iodination of tyrosine and therefore does not follow the law of mass action which he ascribes to compounds of the thiocarbamyl group Inasmuch as the action of thyrotrophin upon the thyroid also depends upon its oxidation it may be possible that aniline compounds of the sulfa type inhibit the same oxidizing enzymes which oxidize or inactivate thyrotrophin Thus the iodine is not only blocked

Despite their ability to produce a hyperplasia of the thyroid associated with hypothyroidism neither Brassica seeds nor any of the thiocyanates have been used clinically for the treatment of thyrotoxicosis for reasons rather clearly implied above namely that their antithyroid action is commonly associated with the formation of a goiter often of considerable size

B THE ANTITHYROID ACTION OF THE ANILINE COMPOUNDS

It was concluded earlier that this series of compounds owes its antithyroid activity to the presence of an appropriately substituted amino benzene grouping $NH_2C_6H_4$ (Astwood 1944 1945 Taurog Chaikoff and Franklin 1945) Anderson (1949) notes that this concept must be expanded to include methylated aniline derivatives and amino-heterocycles

Aniline itself is highly toxic and not goitrogenic in the intact animal in the small dose tolerated although partially inhibiting the formation of diiodotyrosine and thyroxin in thyroid tissue slices (Taurog Chaikoff and Franklin 1945) Para aminobenzoic acid was the simplest compound in this series showing a goitrogenic action but relatively large doses were needed to bring out its full effects (Fig 17)

All of the sulfa drugs belong to this series of compounds and of those in common clinical usage sulfadiazine and sulfapyridine are the most active in rats but still only one tenth as potent as thiouracil (Astwood 1944 1945) Of the aminoheterocycles promizole with one third the goitrogenic action of thiouracil was not surpassed in activity in the rat by any of the anilines thus far tested (McGinty and Bywater 1945a b Astwood 1944 1945 Higgins and Larson 1944) It was however equalled in thyroid blocking effect by two of the methylated anilines (Anderson 1949) not thus far introduced into clinical medicine

The chemical relationship between the five compounds named above is shown in Fig 18 It is readily seen that the aniline grouping is the only complex which they share in common The effects of para amino benzoic acid in the treatment of human hyperthyroidism are shown graphically in Fig 17 While in the rat this compound appears to possess not more than 2 per cent of the activity of thiouracil in man it has been reported about one fourth as effective (Gualco and Patrono 1947 Popp 1947) These workers did not mention any toxic effects

C THE ANTITHYROID ACTION OF THE MERCAPTO COMPOUNDS

a General Structure Characteristics and Species Behavior of Active Compounds

With the exception of aminothiazole it is from the group of thiocarbamyl derivatives that all the agents thus far satisfactory clinically

TABLE VI

SUMMARY OF THE PROBABLE NATURE OF ACTION OF SEVERAL TYPES OF ANTITHYROID COMPOUNDS

AGENT	POINT OF ATTACK	FACTOR WHICH IS PROBABLY DEPRESSED
Thyroid hormone	Anterior pituitary	Production of thyrotrophic hormone and inhibition of its action
Iodine	Anterior pituitary and or Thyrotrophic hormone	Production of thyrotrophic hormone and/or its activity
Thiocyanate group	Thyroid cell	Iodine uptake by the thyroid
Thiouracil group	Oxidative enzyme systems in the thyroid cell	Conversion of iodide to nascent iodine
Sulfonamide group	Oxidative enzyme systems in the thyroid cell	Iodination of tyrosine and synthesis of thyroxine

rapidly As in the case of most *Brassica* goiters the goiter produced by the thiocyanates can be relieved by the administration of iodine or by stopping the cyanate It can be *prevented* if there is an adequate or average ingestion of iodine hence the infrequency with which it is seen

The thyroid made goitrous by potassium thiocyanate has a much greater capacity for absorbing iodine when given in large quantities than does the normal gland (Rawson Tannheimer and Peacock 1944 Salter Cortell and McKay 1945) The average uptake of tracer doses of radioactive iodine with carrier by the thyroids of control rats in the experiments of Rawson Tannheimer and Peacock (1944) was 56 per cent of the administered dose while that of the thyroids of rats treated by thiocyanate was 87 per cent and that of thiouracil treated animals 10 per cent This suggests one fundamental difference between the thiouracil and the thiocyanate goiters namely that the latter are readily prevented and relieved by the administration of adequate doses of iodine

Rawson Hertz and Means (1943) state that thiocyanate goiters are characterized by (a) hyperplasia of the thyroid (b) symptoms of hypothyroidism (c) exophthalmos (seen in one case) (d) low basal metabolic rate (e) low blood iodine (f) decreased urinary excretion of labeled iodine, (g) increased urinary excretion of *thyrotrophic hormone* in the inactivated form

in the management of thyrotoxicosis have been derived These compounds have in common the structure

$$-NH-C(=S)-R$$

where R is usually a nitrogen rarely a carbon atom with single and double linkages respectively ($-N=$) but which may be an S or an O with single linkages respectively ($-S-$ or $-O-$)

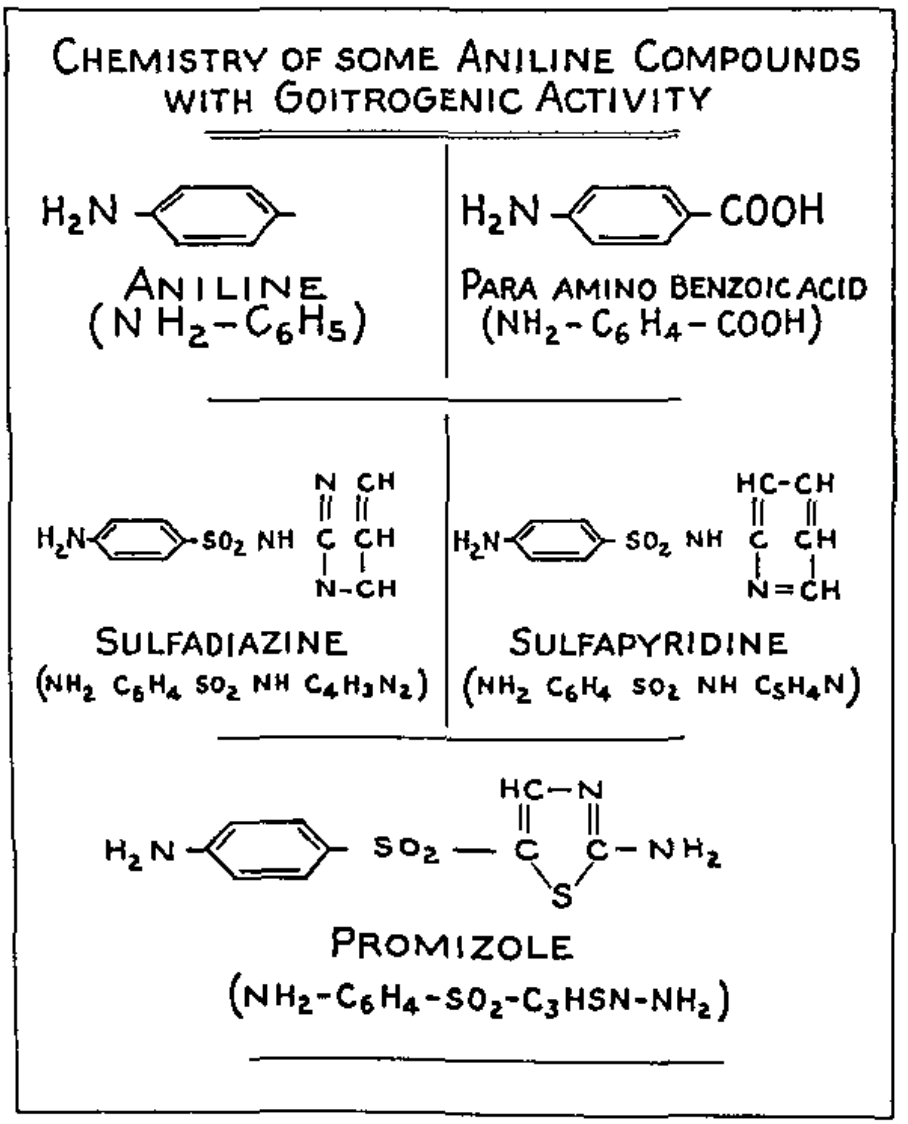


Fig 18 —Ch mi t y of m n line comp unds with g it genic ctivity Th a e among the most effect v f thi i f substan e Note that the nilin g ouping i the only p rtion f th l st ctu \ hi h th y h i commo

Of such compounds it was soon found that those of an open chain type the thioureas were f r inferior in activity to analogous ring structures *For instance the open chained propionyl thiourea* is but one

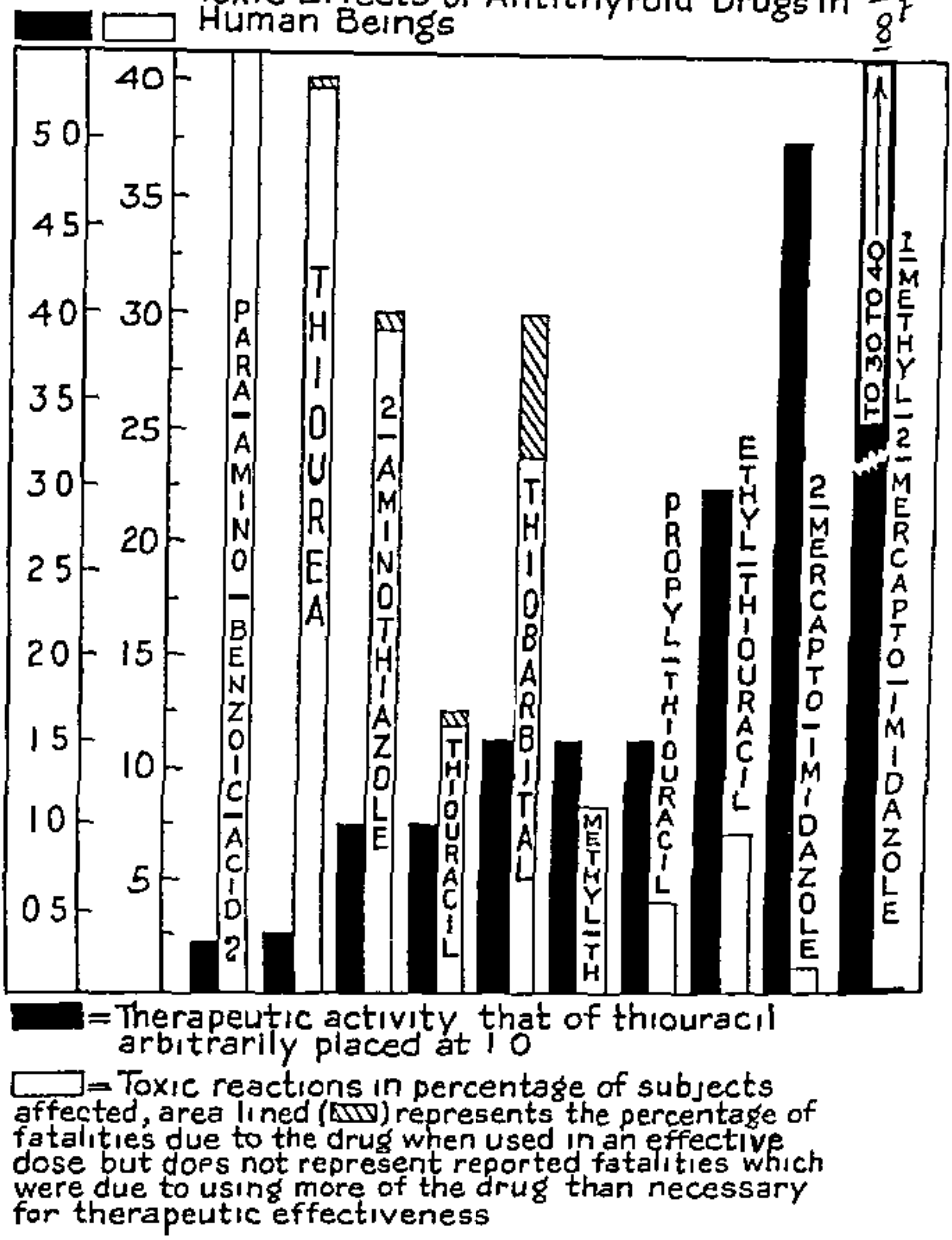


Fig 17 —A comparison of the th rapeuti a d toxi ff ts of antithy oid drugs in hum n b e ngs The comp risons are made o the b s of th linical ports ment ne l in the leg nd to Tabl VII In so f a poss ble the reco l of t xic n a ife tat n and of fataliti hav been ignored when th y were obtain d fr y do es which w obviou ly la g r th n nec a y to p oduce a satisfactory antithyroid effect The th apeut activity h b n mea ur d weight for w ight in te ms of thiou a ll th eff tiv n of which ha bee a bitrarily placed at 1 0 Toxic reaction are exi ressed as a pe c nt g f th numb r of subj ct t ated and th p rti n of this col imn which is cross hatch d approx n ates th pe centage of fatal t f all thos to whom the drug ha been given i a th rap utic r nge of dosag

(Astwood Bissell and Hughes 1945) but has proved to be about one and one half times as effective in the control of human thyrotoxicosis (Astwood and VanderLaan 1945 McCullagh Ryan and Schneider 1946 McGavack Gerl Vogel and Schutzer 1947) and by assay in man about three fourths as potent (Stanley and Astwood 1947)

These variations in the effects of the thiourea derivatives from one species to another particularly as regards the influence upon the thyroid make it impossible to apply quantitatively facts derived from work with small laboratory animals to the management of human thyrotoxicosis Assays of iodine uptake in man using the general principles employed by Stanley and Astwood (1947) appear to afford the best manner of arriving at the usefulness of a preparation in human hyperthyroidism However McGinty and Wilson (1949) have recently employed the rhesus monkey as a test subject and have found the activity of ten antithyroid compounds to be closely identified with that in human beings This is an important observation as it will probably enable the pharmacologist to test the potency of his drug accurately from the standpoint of human usefulness before he is put to the necessity of fully checking its toxicity in man Furthermore it may later be found that the reaction of the monkey to the toxic action of these drugs is sufficiently close to that of man as to permit a thorough preliminary study of value in their later human application

Other factors which complicate a comparative appraisal of these highly active antithyroid compounds include their rate of absorption their duration of action their fate in the body their rate and manner of excretion their toxicity and the amount of iodine present in the organism at the time the assay is made A systematic study of some of these problems with the more potent of these drugs has recently been initiated (McGinty Sharp Dill and Rawson 1948) In all the assay methods now in use every effort is made to control the iodine intake but still all too little is known about many of the other conditions which influence the effects in the human being Inasmuch as further work needs to be done in the assay of these compounds in man there is summarized below the technic we have adapted from Stanley and Astwood (1947) for detecting the potency of an unknown material on the uptake of radioiodine by the human thyroid

b Technic for Estimating the Relative Potency of Antithyroid Compounds in Man by the Aid of Radioiodine (I^{131})

1 *The subject*

i Normal healthy persons of either sex or age will do

ii These may be fasting or equally satisfactory may present themselves one hour after a normal breakfast

seventh is active as its closed chain thiouracil analogue (McGinty and Bywater 1915*a*) Similarly *2* thiobenzimidazole has been proved ten times as active as a goitrogenic agent as its open chain analogue phenyl thiourea (Bywater McGinty and Jenesel 1915) Of the closed chain compounds the most active have been found among the thiouracils imidazoles and thiazoles

While the results of assay in rats (McGinty and Bywater 1915*a* b Bywater McGinty and Jenesel 1915 Astwood Bissell and Hughes 1943) and in human beings (Stanley and Astwood 1917) and the action against the thyrotoxic state in man vary considerably there seems to be general agreement that thus far certain five membered rings (imidazoles and thiazoles) afford the most potent antithyroid preparations for use in man while 6 alkyl substituted compounds of the six membered ring thiouracil are the next most active group Judged according to their activity in man 6 methyl and 6 ethyl compounds are the most powerful of the thiouracil series while 1 methyl *2* mercapto imidazole is by far the most active of the preparations with a five membered ring and apparently exerts an antithyroid effect in man greater than that of any substance thus far studied (Stanley and Astwood 1917 McGavack 1919)

A series of iodinated thiouracils has now been tested for effectiveness in hyperthyroidism (Williams Towery Rogers Tagnon and Jaffe 1919) It was thought that the known avidity of the thyroid for iodine might enable the thyroid to concentrate such compounds thus lessening the effective dose and protecting other portions of the body from the known toxic action of thiouracil Of these compounds 5 iodo 2 thiouracil proved most active its effects qualitatively resembling those of iodine Of *29* patients treated with it *fifteen* had successful remissions Whenever the compound was effective results were observed within 15 days If the control was not established by that time further therapy appeared to be useless Although effort was made to collect data on the ability of the thyroid to concentrate the material no satisfactory determinations were obtained The idea of concentrating an antithyroid compound other than iodine in the thyroid gland is intriguing but with several apparently nontoxic imidazoles now available for therapy may no longer justify the effort involved in the search

It is not easy to determine the relative and absolute potencies of the antithyroid compounds nor to decide which will in the long run prove most beneficial in the clinical management of thyrotoxicosis The results of assays on rats and other small laboratory animals cannot be transferred quantitatively to human beings indeed they may often be misleading as for instance in the case of propylthiouracil which was found to be 11 times as active a goitrogen in the rat as thiouracil

Since this was written Atwood (J. Biol. Chem. 88 1929) found that 1 part in 100 000 was as effective as thiouracil in preventing the uptake of iodine by the thyroid

ent C the counts per second at the end of the period C the counts per second and the beginning of the period M and M the square root of the elapsed time since ingestion of the radioiodine at the end and at the beginning of the period respectively For example if the counts per second at the end of 225 minutes were 110 and at the end of 25 minutes had been 22 then

$$G = \frac{110 - 22}{\sqrt{225} - \sqrt{25}} = \frac{88}{15 - 5} = 8.8$$

4 *Testing unknown compounds for antithyroid potency*

i Dosage As a result of studies of toxicity and potency in animals a presumptively effective dose will be given to the first subject tested From the alteration produced in the accumulation gradient the dosage for subsequent subjects will be determined from which the effectiveness of the drug can be compared with that of thiouracil the activity of which will be arbitrarily set at 1.0

ii Grading of effects As soon as the accumulation gradient of radioiodine has been established a dose of the antithyroid drug will be given The degree to which this modifies the predicted accumulation will be graded according to an arbitrary system wherein scores of 0 to 5 will be assigned on the basis of the completeness and the duration of the inhibition Stanley and Astwood (1947) define these degrees as follows

0—No effect
1—Slight or questionable inhibition
2—Definite but incomplete inhibition
3—Complete inhibition lasting less than 1 hours
4—Complete inhibition for more than 1 but less than 24 hours
5—Complete inhibition for more than 24 hours

Despite widely varying accumulation gradients in different subjects the degree of inhibition from subject to subject is remarkably uniform when appraised in this manner For example thiouracil in a dose of 100 mg gives a type 1 reaction in a majority of subjects 2 mercaptoimidazole gives a similar response following the ingestion of 10 mg Therefore the estimated activity of the latter in terms of thiouracil is 10

iii Subjects From 12 to 30 subjects will probably be the minimum necessary to test any single drug No subject should be used twice This is important as it completely obviates hazard from the toxic effects of the antithyroid compound and any untoward cumulative effects from the radioiodine

iii A tracer dose of 100 microcuries (0·1 millicurie) of I^{131} is given in approximately 25 c.c. of saline and, immediately after, a similar amount of water is ingested to wash the material from the mouth and esophagus

2 *The counting*

i Measurements are made with a shielded Geiger Muller counter (the arrangement of Stanley and Astwood [1947] should be satisfactory) and the counts are recorded by the use of an instrument of the Autoscaler (Tracerlab) type

ii During the actual counting the subject is seated erectly in a straight chair

iii The counter is pressed against the front of the neck in such a position that its edge rests upon the sternal notch. In general this position affords readily reproducible determinations and is usually the position in which maximal counts can be obtained

iv Background counts are of relatively little importance if the uptake of iodine by the thyroid is satisfactory. However such counts should be made shortly after the ingestion of the iodine as its presence in the soft tissues of the neck outside the thyroid may add 10 to 15 counts per second to the determination. Moreover we have found it wise to repeat such background counts several times during the test

3 *Calculation of the accumulation gradient*

i The actual curve of uptake of iodine by the thyroid is a much distorted S shaped affair. However if counts per second (ordinate) are plotted against the square root of elapsed time (abscissa) then for the first 24 hours at least the relationship becomes that of a straight line. To obtain the data for constructing this curve

a Counts are made every half hour or oftener if desired and the values plotted as above mentioned

b This is continued until the straight line relationship has become established (usually takes from one to two hours)

c The accumulation gradient can then be calculated from values corresponding to any two points on the line by the formula

$$G = \frac{C - C}{\sqrt{M} - \sqrt{M}}$$ where G represents the gradi

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The records in such a fashion that the rate of counting can be calculated and the results expressed as number of counts per second

(Legend to Table VII—Continued)

(b) *Thiourea*

1943—Astwood (a b) Himsworth

1944—Campbell Landgrebe and Morgan Goldsmith Gordon Finkelstein and Chaffee Himsworth Horlick Johnston Maxwell Newcomb and Deane Poate Ritchie and Geddes St Johnston

1945—Beard Cruz Cole Rojas Mujica and Diaz de Valdes Danowski Man and Winkler Gibson and Quinlan Williams and Frame Williams and Kay

1946—Hendon Lundback Netter Poate and Spencer Vilaclara Mir Winkler and Danowski

1947—Danowski Man and Winkler Morgans Stanley and Astwood

1948—Beebe Danowski et al Hertz

1949—Kent Shipley and Rundell Rachmilewitz and Rosin

(c) *Aminothiazole*

1944—Perrault Bovet and Droguet

1945—Bovet Bablet and Fournel Joliot et al (b) Perrault Perrault and Bovet

1946—Bastenie and Tagnon Himsworth and Morgans Perrault Perrault and Bovet Vilaclara Mir

1947—Albeaux Fernet and Deribreux Amyot de Gennes et al Gayral Gualco and Patrono Lederer and von Den Broucke Morgans Paolino and De Sario Stanley and Astwood

1948—Azerad and Berthaud Faradji Andik and Farkas Messiny Uzan et al Pietra

1949—Fangeron Perrault Ravault Planchu and Cuinet Romagny

(d) *Thiouracil*

1943—Astwood (a b) Williams and Bissell

1944—Astwood (a b) Bartels Gabrilove and Kert Himsworth McGavack Gerl Vogel and Schwimmer Palmer Rawson Evans Means Peacock Perman and Cortell Rubinstein Sloan and Shorr Williams (a b)

1945—Bartels (b) Birch Boyd and Connell Cookson Dunlop Eaton Grainger Gregson and Pemberton Kennie Lesses and Cargill McArthur Rawson and Means McGavack et al Montague and Wilson Muether and Anderson Muether Sexton et al Palmer Rinkoff and Tandatnick Vorhaus and Rothendler Williams and Frame

1946—Aranow et al Barclay and Feathem Carns and Poser Fowler Fessler Harris and Robertson Jackson Limarzi and Ricewasser Markby Maxwell Gunter and Schwarz Moore Newman and Jones Reveno Sexton Sikkema Theros and Meyer Trasoff Wohl and Mintz Tyson Vogel and Rosenthal Van Winkle et al Vilaclara Mir

1947—Bartels Bartels and Bell Cookson and Staines Davison and Fetton Eaton Himsworth Morgans and Trotter Fahey Lederer and von Den Broucke Morgans Morton Soley Stanley and Astwood Thompson Thompson and Mandernach Thyssen Williams et al

1948—Bartels (a) Beebe Blackburn Blackburn Goodwin and Canter Curtis and Swenson Himsworth Kurth Fahey Regniers and Libbrecht

1949—Anglem and Kenney Branwood El Badry Fischer 1949 Rachmilewitz and Rosin Williams

TABLE VII

ACTIVITY OF ANTITHYROID COMPOUNDS COMPARED IN RAT AND MAN

COMPOUND	APPROXIMATE ACTIVITY (THIOURACIL = 1.0)		
	RAT[1]	MAN	
	THYROID I^{-} AND WEIGHT	RATE OF I^{-} UPTAKE BY THYROID[2]	EFFECT ON HYPERTHYROIDISM[3]
Para aminobenzoic acid	0.01	—	0.25
Thiourea	0.1	1.0	0.3
2-Aminothiazole	0.1	2.5	1.0
2-Thiouracil	1.0	1.0	1.0
Thiobarbital	1.7	2.0	2.0
6-Methyl-2-thiouracil	1.0	2.0	2.0
6-N-propyl-2-thiouracil	11.0	0.5	2.0
6-Ethyl-2-thiouracil	8.0	1.0	3.0 (?)
2-Mercaptoimidazole	2.0	10.0	5.0
1-Methyl-2-mercaptoimidazole	2.0	100.0	40
2-Mercaptobenzimidazole	0.5	2.5	—
2-Mercaptothiazoline	1.3	2.5	—
2-Thiohydantoin	0.4	2.5	—
Thiocarbamyl thioglycollic acid	0.4	2.5	—

(1) Method of McGinty and Bywater (1945a,b) and Bywater McGinty and Jenesel (1945). Data are recorded as compiled by Anderson (1949).

(2) Method of Stanley and Astwood (1947). Data are recorded as compiled by Anderson (1951).

(3) From reports in the literature which are concerned with the use of antithyroid compounds in the control of hyperthyroidism in man as noted *below*.

(a) *Para aminobenzoic acid*

1947—Cualco and Patrono Popp

(Refer to Table VII—Continued)

(b) *Thiourea*

1943—Astwood (a b) Himsworth

1944—Campbell Landgrebe and Morgan Goldsmith Gordon Finkelstein and Chaffee Himsworth Horlick Johnston Maxwell Newcomb and Deane Poate Ritchie and Geddes St Johnston

1945—Beard Cruz Colon Rojas Mujica and Diaz de Valdes Danowski Man and Winkler Gibson and Quinlan Williams and Frame Williams and Kay

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1947—Danowski Man and Winkler Morgans Stanley and Astwood

1948—Beebe Danowski et al Hertz

1949—Kent Shipley and Rundell Rachmilewitz and Rosin

(c) *Aminothiazole*

1944—Perrault Boyet and Droguet

1945—Boyet Bablet and Tournel Joliot et al (b) Perrault Perrault and Boyet

1946—Bastenie and Pagnon Himsworth and Morgans Perrault Perrault and Boyet Vilaclara Mir

1947—Albeaux Fernet and Deribreux Amyot de Cennes et al Gayral Cualco and Patrono Federer and von Den Broucke Morgans Paolino and De Sario Stanley and Astwood

1948—Azerad and Berthaud Faradji Andik and Farkas Messiny Uzan et al Pietra

1949—Fangeron Perrault Raynaud Flanchu and Cuinet Romagny

(d) *Thiouracil*

1943—Astwood (a b) Williams and Bissell

1944—Astwood (a b) Bartels Gabrilove and Kert Himsworth McGavack Gerl Vogel and Schwimmer Palmer Rawson Evans Means Peacock Perman and Cortell Rubinstein Sloan and Shorr Williams (a b)

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1946—Aranow et al Barclay and Leathem Cairns and Loser Fowler Gessler Harris and Robertson Jackson Limarzi and Riccwasser Markby Maxwell Gunter and Schwarz Moore Newman and Jones Reveno Sexton Sikkema Theros and Meyer Trasoff Wohl and Mintz Tyson Vogel and Rosenthal Van Winkle et al Vilaclara Mir

1947—Bartels Bartels and Bell Cookson and Staines Davison and Letton Eaton Himsworth Morgans and Trotter Lahey Federer and von Den Broucke Morgans Morton Soley Stanley and Astwood Thompson Thompson and Mandernach Thyssen Williams et al

1948—Bartels (a) Beebe Blackburn Blackburn Goodwin and Canter Curtis and Swenson Himsworth Kurth Lahey Regniers and Tibbrecht

1949—Anglem and Kenney Branwood El Badry Fischer 1949 Richmilewitz and Rosin Williams

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COMPOUND	APPROXIMATE ACTIVITY (THIOURACIL = 1.0)		
	RAT[1]	MAN	
	THYROID I⁻ AND WEIGHT	RATE OF I⁻ UPTAKE BY THYROID[2]	EFFECT ON HYPERTHYROIDISM[3]
Para aminobenzoic acid	0.01	—	0.05
Thiourea	0.1	1.0	0.3
2-Aminothiazole	0.1	2.5	1.0
2-Thiouracil	1.0	1.0	1.0
Thiobarbital	1.7	2.0	2.0
6-Methyl-2-thiouracil	1.0	2.0	2.0
6-N-propyl-2-thiouracil	11.0	0.8	2.0
6-Ethyl-2-thiouracil	8.0	1.0	3.0 (?)
2-Mercaptoimidazole	2.0	10.0	5.0
1-Methyl-2-mercaptoimidazole	2.0	100.0	40
2-Mercaptobenzimidazole	0.5	2.5	—
2-Mercaptothiazoline	1.3	2.5	—
2-Thiohydantoin	0.4	0.5	—
Thiocarbamyl thioglycollic acid	0.4	2.5	—

(1) Method of McGinty and Bywater (1945a b) and Bywater McGinty and Jenesel (1945). Data are recorded as compiled by Anderson (*1949*)

(2) Method of Stanley and Aslwood (1947). Data are recorded as compiled by Anderson (1951)

(3) From reports in the literature which are concerned with the use of antithyroid compounds in the control of hyperthyroidism in man as noted below

(a) *Para aminobenzoic acid*

1947—Gualco and Patrono Popp

(Legend to Table VII—Continued)

(e) *Thiobarbital*

1945—Astwood (a b) Bartels (a)
1947—Guthrie Lahey Stanley and Astwood
1948—Lahey

(f) *Methylthiouracil*

1945—Levs Westergaard
1946—de Gasperis de Nogales Frisk Glock (b) Hadorn Hadorn and Beer Lundback Magnusson and Srenson Poate (a b) Ritchie Wilson
1947—Abelin Barfred Lalon Frisk Gualco and Patrono Lederer and von Den Broucke Morgans Piercy Poate Spuehler Stanley and Astwood Thyssen
1948—Anderson Clarke Corti Frisk Curdini Hone and Magarey Kelemen Kellner Loicq and Martin McCullagh and Schneider McCullagh and Sirridge Meulengracht and Kjerulf Jensen Meulengracht Kjerulf Jensen and Schmith Stronk Wegelin
1949—Bartels and Ingham Malmberg McGavack

(g) *Propylthiouracil*

1946—Astwood and Vanderl ian (a b) Crile and Dunsmore Kjerulf Jensen and Meulengracht McCullagh Watson
1947—Baird Crile (a b c) Curtis Davison and Letton Deneen Drennen and Kahn Eisenmenger and Steele Jackson (a b) Lahey Livingston and Livingston McCullagh Hibbs and Schneider McGavack Gerl Vogel and Schulzer Reveno Scales Stanley and Astwood Taylor West Wilson and Goodwin
1948—Azarnoff and Leathem Barr Bartels (a b c) Beebe Cod ington and Bondy Crile Grauer De Wall and Elkin Greenhouse Harding Hibbs and McCullagh Kincov and Dugan Kjerulf Jensen and Meulengracht Lahey McCullagh and Schneider Reveno Richardson and Richardson Sex ton and Murphy
1949—Beierwaltes and Sturgis Friedenberg Jackson and Haley Lahey Lederer Peters Man kydd Engstrom and Waters Rowe Williams
1950—Merikangas

(h) *Ethylthiouracil*

1944—Astwood
1945—Astwood (a)
1946—Watson
1947—Stanley and Astwood

(i) *2 Mercaptoimida ole*

1947—Stanley and Astwood
1949—McGavack

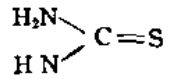
(j) *1 Methyl 2 Mercaptoimida ole*

1949—Stanley and Astwood
1950—Astwood McGavack

c Compounds Which Now Are or Have Been Employed in the Management of Hyperthyroidism in Man

By assay in the rat according to the method of McGinty and Bywater (1943 b) adapted by Astwood Bissell and Hughes (1945) 25 preparations were found with greater antithyroid activity than thiouracil Of 32 compounds tested in man by the method of Stanley and Astwood (1947) employing radioiodine ten showed an activity greater than thiouracil The value for the antithyroid activity of a given compound varies considerably depending upon which of these two methods is used in the assay Let us consider several of the antithyroid compounds that have been successfully employed in human beings for the control of thyrotoxicosis with a view to giving them a therapeutic rating as to efficiency and toxicity (Table VII and Fig 17) In doing this thiouracil the first of these drugs widely studied and applied will arbitrarily be assigned a therapeutic index of 1 0 Toxicity will be reported in approximate percentage of cases affected (Fig 17) There are several compounds that have been thus tried which proved too toxic for continued use such as diethylthiourea (Williams 1945) and tetramethyl thiourea (Williams 1945) No further mention will be made of them Others will be considered in the ascending order of their known ability to relieve and control human hyperthyroidism In Fig 17 para aminobenzoic acid with a therapeutic activity in terms of thiouracil of 0 25 has already been mentioned under the group of amline derivatives to which it belongs Continuing to read this figure from left to right we find

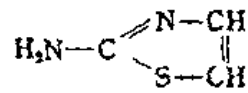
1 *Thiourea* (Table VII Fig 17)



This was one of the first of the thio compounds to be employed in treating thyrotoxicosis and was widely used because of its ready availability The amounts given have varied widely from investigator to investigator Effective initial daily doses have ranged from 0 6 Gm (Cruz Coke et al 1945) to 3 0 Gm (Ritchie and Geddes 1944) with an average of 2 0 Gm The exception to these statements are the very much smaller doses used by Danowski Man and Winkler (1945 1947) in conjunction with the administration of iodine They claim a potentiation of effect which permits the lowering of the dose to an average of 0 3 Gm daily or below The frequency of toxic febrile and urticarial reactions has made continued clinical use of this compound unwise

However agranulocytosis is rare and death is not common probably occurring in 0 25 per cent of the cases treated

2 *Aminothiazole* (2 iminothiazole) (Table VII Fig 17)



One group of French workers have found this drug most satisfactory for the control of hyperthyroidism (Perrault 1915 1916 1919, Boyet Bablet and Lommel, 1915 Perrault and Boyet 1915 1916) However the majority of workers (see references bottom of Table VII) consider the drug much too toxic for continued use in man particularly as there are a number of other more efficient and less harmful antithyroid substances available Jaundice is one of the most serious toxic effects one observer alone having reported 13 instances of the condition which ended fatally in four (Messimy 1918) Agranulocytosis occasionally occurs The percentage of deaths from its clinical use varies between 0 5 and 0 75 per cent (Fig 17)

3 *Thiouracil* (2 thiouracil) (Table VII Fig 17) Thiouracil although now no longer manufactured for clinical use in the United States has become the drug of standard for other antithyroid compounds so that its structural formula is given in Fig 19 with the carbon atoms numbered The other compounds here grouped are studied arranged

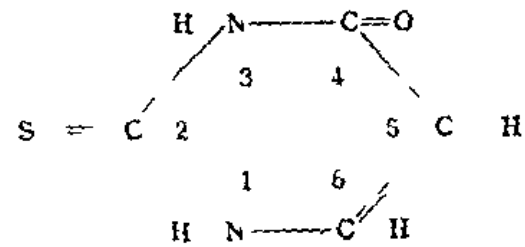


Fig 19—Structural formula of thiouracil (2 thiouracil) The numbering of the carbon atoms is similar for this and the six remaining structures which follow

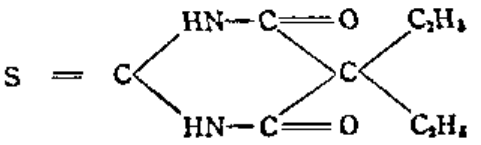
Thiouracil was the first of the antithyroid compounds to have extensive clinical trial In the rat it is ten times as active as thiourea but less active than a number of other compounds of the thiouracil series (Astwood 1941-1945 Astwood Bissell and Hughes 1945 Astwood and VanderLaan 1945 McGinty and Bywater 1945a b Bywater McGinty and Jenesel 1945 Greer and Astwood 1948 McGinty 1949) When compared in the human being by their ability to inhibit the uptake of

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This drug rightfully belongs to the aminoheterocyclic series and does not have the capacity of the mercapto compounds for forming SH or equivalent However in clinical appraisal it has seemed to be appropriate to consider it for comparison with members of the mercaptoglycosuria series the only material outside this series which has been afforded extensive clinical trial in the human being

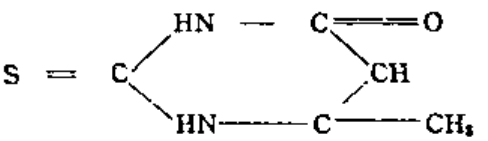
iodoiodine by the thyroid the activity of thiourea and thiouracil is approximately equal (Table VII) In hyperthyroidism (Fig 17) thiouracil is three times as effective as thiourea and about one fourth as toxic (12 5 per cent toxic reactions) Agranulocytosis is the most dangerous of its complications death having occurred in 0 5 per cent of all cases in which the drug has been employed

4 *Thiobarbital* (5 5 diethyl 2 thiobarbituric acid) (Table VII Fig 17)



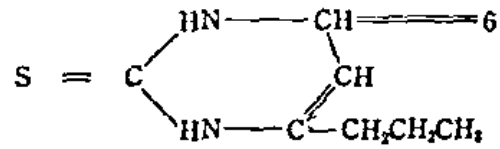
Thiobarbital the structural formula of which is given above has an antithyroid effect (Astwood 1944 1945 1945a b Bartels 1945) reportedly 3 (Astwood 1945a) to 12 (Bartels 1945) times that of thiouracil in the management of thyrotoxicosis in man but only 1 2 (McGinty and Bywater 1945a) to 1 7 (Astwood Bissell and Hughes 1945) times as active in the rat In effective dosage it is more toxic than the latter drug (Astwood 1944 1945 1945a b) Despite this fact seven of nine patients who developed toxic reactions to thiouracil tolerated thiobarbital well (Bartels 1945) Further clinical trial with it is hardly justified

5 *Methylthiouracil* (6 Methyl 2 thiouracil) (Table VII Fig 17)



Methylthiouracil was at first thought to be more toxic than thiouracil but the dosages used at that time were comparatively large More recently rather extensive study (see references with Table VII) indicate that it is from one and one half to two times as effective and about *two thirds as toxic as the latter compound* *In our own experience* (McGavack 1949a b) toxic effects are mild occur in about 1 per cent of cases and rarely require the discontinuance of the drug We have not used doses above 600 mg per day and these only for short periods of time McCullagh and Surridge (1948) have had a somewhat similar experience Agranulocytosis is the most serious complication which can occur in connection with its administration but has not been reported where the doses now recognized to be effective have been employed Since it can be manufactured at relatively low cost and used with very little danger to the patient it will probably continue to be used extensively by the clinician

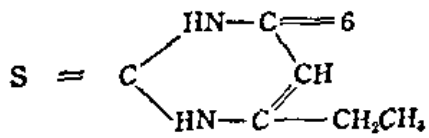
6 *Propylthiouracil* (6 N propyl 2 thiouracil) (Table VII Fig 17)



Extensive clinical trial was afforded this drug because of its very high activity in the rat It seems to be about one and one half to two times as effective in hyperthyroidism as thiouracil although further revision downward in this appraisal of its action may be necessary in view of the fact that most clinicians find its influence in currently recommended doses somewhat uncertain

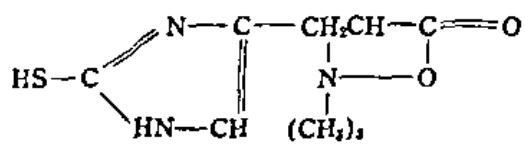
As a matter of fact because of the small dose employed and the concomitant use of large doses of Lugol s solution some reports of the ineffectiveness of propylthiouracil such as that of Borgstrom (1949) must be considerably discounted We believe its action is reliable in proper dosage and inasmuch as the side effects appear in not more than 1 per cent of patients and are never serious it will undoubtedly be used in clinical medicine for some time to come

7 *6 Ethyl-2 thiouracil* (Table VII Fig 17)



Clinical application of this drug has been confined to a study of 11 patients with hyperthyroidism (Astwood 1943a) Instances of toxicity were recorded (7 per cent of cases) Further trial will be necessary to show its usefulness and to determine more accurately its therapeutic index Its manufacture is said to be rather difficult so that in view of the relatively large number of more active compounds it is doubtful that this one will ever be used further by the internist

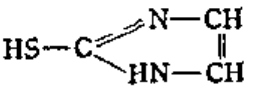
8 *Ergothioneine* (not included in Table VII)



From the above structural formula it is obvious that ergothioneine is closely related chemically to histidine and is known to occur in the body of human beings under normal conditions The report of Lawson and Rimington (1947) that this material could exert a very definite antithyroid effect has raised the question whether or not this naturally occurring material might be one of the normal regulators of thyroid

activity in man This seemed all the more reasonable since Rivers (1948) has found that the compound inhibits the conversion of acetyldiiodotyrosine to acetylthyroxin in vitro However Astwood and Stanley (1947) failed to observe any influence of the drug upon the uptake of radioiodine by the thyroids of normal human subjects even though the doses were large and given intravenously (100 mg) In discussing Astwood and Stanley's communication Lawson and Rimington stated that 100 mg daily was without effect in two patients with thyrotoxicosis Wilson and McGinty (1949) have carefully evaluated the action of ergothioneine in rats and in rhesus monkeys and have failed to demonstrate any *antithyroid activity in doses substantially larger than effective* amounts of thiouracil Despite these disappointing results we have felt justified in mentioning ergothioneine somewhat at length because of its presence normally in the tissues of the body and because it is closely related chemically to imidazole derivatives possessing high antithyroid activity in man Two of these compounds will now be considered

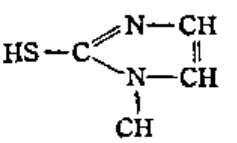
9 *2 Mercaptoimidazole* (Table VII Fig 17)



2 Mercaptoimidazole is the first of a series of five membered heterocyclic mercapto compounds to be investigated in man In the rat several of the thiouracil derivatives have shown the highest antithyroid activity *of all compounds studied But in man using the uptake of radioactive* iodine as described by Stanley and Astwood (1947) as an indicator several imidazole derivatives have proved much more active than any drugs previously studied Anderson (1949) has reviewed the literature regarding work with these in rats and man to the date of his report More recently Jones Kornfeld McLaughlin and Anderson (1949) have described the synthesis of many more members of this group and report preliminary tests of their antithyroid activity in rats

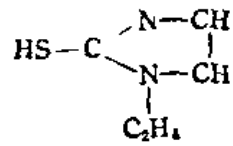
Stanley and Astwood (1947) found 2 mercaptoimidazole ten times as active as thiouracil in inhibiting the uptake of radioiodine by the thyroid of human subjects In limited clinical trial we have found a dose of 20 mg four times daily sufficient to control thyrotoxicosis and have employed maintenance doses of between 10 and 30 mg Thus in clinical practice the compound is between six and seven times as active as thiouracil In the doses used no toxic reactions have been observed

10 *1 Methyl 2 mercaptoimidazole* (Table VII *Fig* 17)



In inhibiting the uptake of radioactive iodine by the thyroid of normal human beings Stanley and Astwood (1949) found 1 methyl 2 mercaptoimidazole 100 times as active as thiouracil At that time they had used the drug successfully in the management of 30 patients with thyrotoxicosis During the past year we have employed the drug in more than 50 patients with hyperthyroidism (McGavack 1950) Five milligrams three times daily has been sufficient to control the condition in all but three individuals *one of whom needed 25 mg daily and two 20* mg daily Astwood (1950) states that he has now treated more than 60 patients and employs 5 mg every 8 hours as an initial dose As a rule the thyrotoxic state comes under control quite rapidly first signs of improvement often being observed by the third day Complete control is rarely delayed beyond the third week Maintenance doses have varied from 1 to 8 mg daily There has not been a single toxic reaction in any patient for whose thyrotoxicosis this drug has been employed

11 *1 Ethyl-2 mercaptoimidazole*



We have now employed this drug in eleven patients The initial effective daily dose has been *approximately 30 mg* The action is neither as rapid nor as certain as with the methyl derivative above mentioned Maintenance doses have ranged from 8 to 15 mg No toxic reactions have been observed

12 *Other compounds* (Table VII) Among the other compounds which should be given clinical trial on the basis of their activity when tested in man by the technic of Stanley and Astwood (1947) are 2 mercaptobenzimidazole 2 mercaptothiazoline 2 thiohydantoin and thiocarbamylthioglycolic acid Their respective antithyroid potencies as antithyroid compounds are recorded in Table VII

Among the long acting antithyroid substances 2 mercaptothiazoline must be mentioned as its effects can be demonstrated for as long as 18 hours after the administration of a single dose (Astwood 1941 1945) Duration of action is one of the major factors not appraised now by a comparative testing procedure so that this drug may be *much more* useful clinically than its activity index of 2 5 in man indicates

Chapter XVII

RADIOACTIVE ISOTOPES OF IODINE AND THE THYROID

During the same year that Joliot and Curie (1934) discovered artificial radioactivity and described methods for producing radioactive isotopes Fermi prepared radioactive iodine which rapidly became available to investigators following the development of the cyclotron by Lawrence and Cooksey in 1936 In 1938 the first two reports of radio iodine as a tool for studying human physiology appeared almost simultaneously (Hertz Roberts and Evans Hamilton) and four years later the results of the application of such isotopes to the treatment of thyroid disease were recorded (Hertz and Roberts Hamilton and Lawrence) Since that time a relatively large number of investigators have contributed to our knowledge of thyroid physiology and therapy as influenced by the use of radioactive isotopes of iodine and two very excellent reviews of this subject have appeared (Rawson and McArthur 1947 Kelsey Haines and Keating 1949)

DEFINITIONS

Through radioactive isotopes there has been introduced into medicine an entirely new discipline that of nuclear physics While the body of facts thus concerned will remain for the most part within the province of the physicist and chemist there is an irreducible minimum of terminology with which the physician must fortify himself

For descriptive purposes *atoms* may be looked upon as composed of *protons neutrons* and *electrons* The nucleus of an atom is comprised of protons or of protons plus neutrons (*nucleons*) Because of the small size of the electron for all practical purposes the weight of an atom i e the *atomic mass* equals the combined mass of the protons and neutrons it contains This figure is written as a right superscript beside the symbol of the element Thus H or I^{127} means that there are 1 proton and 127 protons and neutrons in these atoms of hydrogen and iodine respectively

Despite the tremendous difference in mass (a proton is 1 838 times as large as an electron) the positive charge of a proton is exactly counterbalanced by the negative charge of an electron or beta particle A neutron is comprised of a proton and an electron in immediate contact with each other and thus possesses no electrical charge

The number of protons in the nucleus and therefore the number of electrons required to balance their positive charge is spoken of as the *atomic number* of the substance The number of such protons indicated by the atomic number predetermines the chemical qualities characteristics and behavior of the substance and is usually written as a left subscript to the elemental symbol Thus the hydrogen nucleus contains 1 proton and that of iodine 53 protons so that the full designation of these substances showing both atomic *numbers* and *weights* would be $_{1}H$ and $_{53}I^{127}$ respectively By the definitions noted above, it is clear that the number of neutrons in these two substances are 0 and 74, respectively their number represents the difference between the atomic weight and the atomic number It is equally pertinent to note that any element can be fully designated simply by giving its atomic number and atomic weight as its chemical qualities are implied in the former and its physical equilibrium denoted by the latter Thus the figures and $_{1}^{127}$ indicate clearly the structure of the two substances above mentioned long continued usage however justifies the retention of the lettered symbol as well which will be retained in our further discussion

Isotopes are substances which possess identical atomic numbers but vary as to atomic weight In other words each is a substance with a given number of protons to which neutrons have been added or from which they have been removed Such an addition or subtraction may result in a stable or an unstable compound the latter type is radioactive As a simple illustration when a neutron is added to hydrogen deuterium or heavy hydrogen results the nucleus of which contains one proton and one neutron ($_{1}H^{2}$) The reception of this neutron is accomplished without upsetting the previous equilibrium of the nucleus the compound is stable If a second neutron is added thereby making the atomic weight three ($_{1}H^{3}$) satisfactory equilibrium is achieved only by a rearrangement of the nuclear structure associated with which an electron or beta particle is ejected at high speed Therefore this isotope is unstable or radioactive In some instances such ejection of an electron is associated with or followed by the emission of energy in the form of the *gamma ray* Such a change accompanies the disintegration of the unstable or radioactive nuclei of $_{53}I^{130}$ and $_{53}I^{131}$ Through their impingement upon other atoms these electromagnetic gamma rays may give rise to further beta radiation *(conversion electrons)* by knocking high speed electrons off surrounding atoms and so causing ionization of the tissues through which they pass

When electrons or beta particles escape from the atom it is obvious that they change the electrical charge and the number of protons present Thus eventually the atomic number is altered a nuclear transformation has occurred and an entirely different substance may have been formed For instance in the example of radioactive hydrogen above mentioned the nuclear transformation is such that one electron

escapes and two protons are left so that the atomic number becomes two thus the atom is no longer that of hydrogen but has become helium the *only* element with an atomic number of two Perhaps a more appropriate illustration is that involved in the formation of radioactive iodine (I) from the bombardment of tellurium with slow neutrons and the subsequent spontaneous disintegration to xenon (Fig 20) Here we see that unstable conditions are set up when an additional neutron is introduced into the previously stable atom of tellurium The resulting nuclear rearrangements involve the formation of an *unstable isotope* of tellurium which following the discharge of a beta particle or electron, *loses a neutron and gains a proton* The element thus changes its chemical characteristics and behavior to those of an unstable isotope of

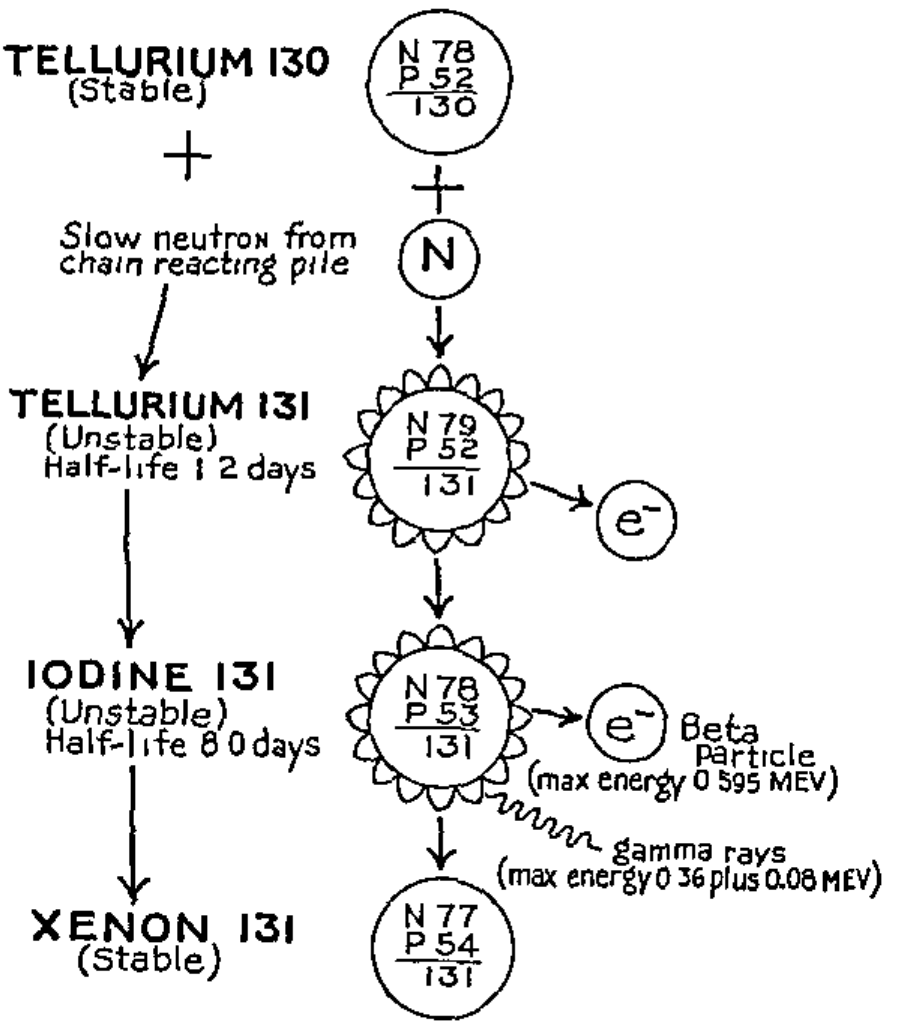


Fig 0 —Simplified chematic representation of the production and disintegration of I¹³¹ The large circles represent atomic nuclei those with the smaller dots indicate an unstable radioactive nucleus N equal the number of neutrons and P the number of protons in each nucleus respectively Many features of the reactions are not indicated for instance the steps of isomeric decay through which the fission fragments finally give the stable isotope of xenon although light on the uranium chain reacting pile with I¹³¹ and possibly other radioactive nuclei the production of neutrons (probably less than 1 per cent of additional nuclei in the xenon produced (See Metzger and Duane 1948)

The number of protons in the nucleus and therefore the number of electrons required to balance their positive charge is spoken of as the *atomic number* of the substance The number of such protons indicated by the atomic number predetermines the chemical qualities characteristics and behavior of the substance and is usually written as a left subscript to the elemental symbol Thus the hydrogen nucleus contains 1 proton and that of iodine 53 protons so that the full designation of these substances showing both atomic *numbers* and *weights* would be $_1H^1$ and $_{53}I^{127}$ respectively By the definitions noted above it is clear that the number of neutrons in these two substances are 0 and 74, respectively their number represents the difference between the atomic weight and the atomic number It is equally pertinent to note that any element can be fully designated simply by giving its atomic number and atomic weight, as its chemical qualities are implied in the former and its physical equilibrium denoted by the latter Thus the figures $_1$ and ^{127} indicate clearly the structure of the two substances above mentioned long continued usage however justifies the retention of the lettered symbol as well which will be retained in our further discussion

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This is high in comparison with the 2000 to 3000 roentgen units commonly employed when external radiation has been used Numerous factors may be concerned in this difference of biological effect many of which have been summarized by Nelson (1948) and need not concern us here The actual application of this formula to therapy is given under our discussion of the treatment of hyperthyroidism (Section III Chapter XXXVIII)

Using the above formula exclusive of the secondary gamma radiation Marinelli Brinckerhoff and Hine (1947) have created a chart (Fig 21) from which the roentgen equivalents can be read directly if the total dose of I in microcuries and the weight of the thyroid are known This is highly convenient for the busy clinician and is only in error to that extent that the earlier calculations of particle energy have been used in its elaboration

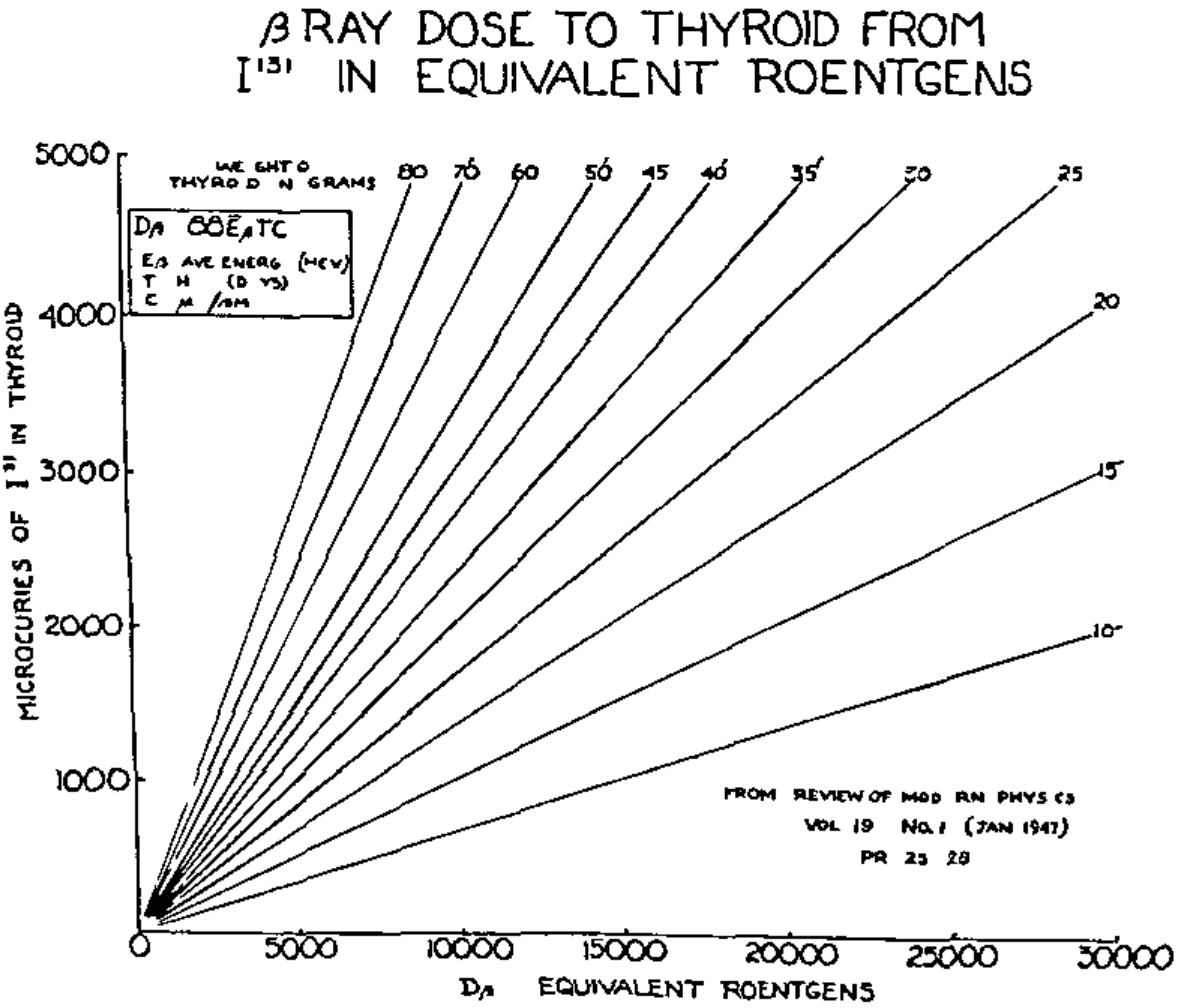


Fig 21—Beta ray dose delivered to the thyroid for I131 at various equivalent roentgen (rem) The total dose of I131 in microcuries is plotted against the weight of the thyroid in grams (abscissa) and the scale is adjusted that from the two factors the roentgen equivalents are added directly Although based directly on integration of the formula (see Fig 20 p 19 and p 196 ff) the figure will afford a close approximation of dosage for microcuries to equivalent roentgen (After Marinelli Brinckerhoff Hine 1947)

iodine This radioactive iodine decays by further beta particle ejection and gamma radiation to become stable xenon with an atomic number of 54 (Fig 20)

The quantitative measurement of these nuclear transformations is usually designated in curies or some fraction or multiple thereof A *curie* is a measure of the rate of atomic disintegration and represents that quantity of potentially radioactive atoms in which 3.7×10^{10} nuclear transformations will take place per second Some of the uses and abuses of this unit have been described by R D Evans (1947) and more recently Eichelberg (1948, 1949) has called attention to problems involved in arriving at the value of the curie in relation to radioactive iodine

A *roentgen unit* is a unit of radioactive energy dissipation in an arbitrarily chosen material air whereby one roentgen unit represents the loss of 83.8 ergs of energy per gram of air It is therefore not possible to express curies directly as roentgen units However since the clinician is more familiar with the latter than with the former a conversion to roentgen equivalents physical (r e p) gives an approximation of the energies involved by which rough though by no means accurate comparisons can be made The formula of Marinelli Quimby and Hine (1948) can be adapted in which the combined dose of radioactive material from the beta radiation ($D\beta$) and the conversion electrons (from the gamma radiation $D\gamma$) of I^{131} may be given as

$D\beta + \gamma = 88\ E\beta + \gamma T C$ equivalent roentgens (e r) where

$E\beta + \gamma$ = the average energy of the beta particle (0.190) plus the average energy of the conversion electrons (0.010) (Metzger and Deutsch 1948)

T = the effective half life in days of I^{131} in the thyroid and

C = the concentration of I^{131} in microcuries per gram of thyroid tissue

Thus if we assume that a patient with hyperthyroidism receives 6.0 millicuries of I that the gland weighs 40 grams that the effective half life in the gland is 6 days and that 60 per cent is retained by the gland then

$$D\beta+\gamma = 88 \times 0.200 \times 6 \times \frac{6000 \times 0.60}{40} \text{ e r}$$

$$= 9504 \text{ e r}$$

Metzger and Deutsch (1948) have recently redetermined the average energy per disintegration For the beta particle they found this to be 0.190 MEV (formerly thought to be 0.20 MEV) and for the conversion electron produced by the gamma radiation approximately 0.010 MEV (formerly thought to be 0.01 MEV) The figure must be sharply distinguished from the maximal energy of the beta particle which is reported to be 0.59 MEV and the maximal energy of the gamma rays which is estimated at 0.360 MEV

The detection and quantitation of this radioactivity is carried out by instruments the physical principles of which are based upon the ability of beta and gamma radiations to produce ionization effects in especially constructed chambers In view of the low penetrability of the beta particles a thin walled window must be employed for their detection direct counts of beta radiation in connection with the investigation of iodine metabolism are usually confined to a study of body fluids such as blood and urine Estimation of the amount of radio iodine in the tissues is usually accomplished by the use of a gamma ray counter The requirements for both beta particle and gamma ray determination are met by some one or more modifications of the Geiger-Muller counter the details of which are readily available to those concerned (Roberts and Irvine 1938 Kamen 1947 Soley and Miller 1948 Feitelberg 1949)

The second essential piece of apparatus is a scaling device for automatically counting and recording the ionization effects taking place within the Geiger Muller counter In using such equipment for making counts in patients periodic checking of equipment and proper control counts are essential (Oshry and Schmidt 1948)

b **Storing and Handling of Radioisotopes of Iodine** —All radioactive material is dangerous Iodine is far from an exception and should be handled with remotely controlled instruments of which some recently described are representative and practical (Morgan 1948 Tompkins 1948) Workers should employ tongs heavy x ray rubber gloves of 0 5 mm lead equivalent and heavy rubber aprons Transfer of solutions is best accomplished by remotely controlled pipettes The device described by Soley and Miller (1948) for this purpose is quite ingenious and should be satisfactory In view of the presence of some gamma radiation lead shields must be used in storing and transporting the material (Kamen 1947 Morgan 1948 Tompkins 1948)

c **Monitoring and Protecting Patients and Personnel** —All biological systems are continuously subjected to penetrating ionizing radiations which originate from the naturally occurring radioactive materials and from cosmic rays and their secondarily induced radioactivity This background radiation varies somewhat with altitude and with geographical location but at sea level is usually equal to or greater than 0 2 milliroentgens per 24 hours (Atomic Energy Commission Isotopes Division Circular B 6 1949) In addition to the precautions described above in connection with the storage and transport of radioiodine it is important that all laboratory personnel wear film badges which should be read at least once monthly More elaborate devices are also available (Morgan 1948) but are probably not necessary if radioiodine alone is to be handled

By *half life* is meant the period during which one half of the potentially radioactive atoms of an isotope will undergo disintegration or nuclear transformation

The *specific activity* of an unstable or radioactive isotope is an expression of the number of millicuries present per unit weight of material Errors inherent in our methods of standardizing radioactive iodine (Leitzberg 1918 1949) necessarily influence the determination of specific activity In any event as Trunnell (1919) points out such activity may often be impressively high For example, he remarks the largest single therapeutic dose of radioactive iodine 315 millicuries weighed approximately 2 5/1 000 000 of a gram This quantity which is too small to visualize without the aid of optical instruments is only slightly greater than the amount of stable iodine in a tumblerful of New York City tap water

RADIOACTIVE ISOTOPES OF IODINE

Fourteen radioactive isotopes of iodine have been identified (Kelsey Haines and Keating 1919) of which four have been employed in biological investigations—I^{131} with a half life of 13 days I^{132} with a half life of 25 minutes I^{130} with a half-life of 12 6 hours and I^{126} with a half life of 8 days Because of its convenient half life and the relatively pure form in which it can now be obtained from the uranium chain reacting pile I^{131} with a negligible contamination of I^{130} (Trunnell 1919) is now almost universally used in both investigation and therapy Therefore the remainder of our discussion will concern this isotope unless some other one is specifically mentioned by mass number

EQUIPMENT, STANDARDIZATION AND PRECAUTIONS

In so far as tracer studies with radioiodine are concerned it is remarkable how little space is necessary to carry on considerable work and how few *although extremely important* are the precautions which must be followed by the workers and their subjects Details are irrelevant here but essentially equipment consists of those articles required for (a) detecting quantitating and recording the radioactivity (b) storing and handling the radioisotopes and (c) monitoring and protecting personnel

a **Detecting, Quantitating, and Recording Radioactivity**—As above noted I^{131} gives off beta particles and gamma radiation The former have little power of penetration (e g not more than 2 mm of body tissue) and constitute more than 90 per cent of the radioactivity of the element The latter is capable of exerting effects at long distances thus enabling the operator to determine the amount present in the tissues of the subject at considerable distances below the surface as for instance in the thyroid gland

The detection and quantitation of this radioactivity is carried out by instruments the physical principles of which are based upon the ability of beta and gamma radiations to produce ionization effects in especially constructed chambers In view of the low penetrability of the beta particles a thin walled window must be employed for their detection direct counts of beta radiation in connection with the investigation of iodine metabolism are usually confined to a study of body fluids such as blood and urine Estimation of the amount of radio iodine in the tissues is usually accomplished by the use of a gamma ray counter The requirements for both beta particle and gamma ray determination are met by some one or more modifications of the Geiger Muller counter the details of which are readily available to those concerned (Roberts and Irvine 1938 Kamen 1947 Soley and Miller 1948 Feitelberg 1949)

The second essential piece of apparatus is a scaling device for automatically counting and recording the ionization effects taking place within the Geiger Muller counter In using such equipment for making counts in patients periodic checking of equipment and proper control counts are essential (Oshry and Schmidt 1948)

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laboratories should be routinely checked for contamination If any radiation greater than 0 003 roentgen equivalents per 24 hours per square foot is found in any place that area is not tolerable Morgan (1947) has devised procedures and mathematical formulas which deal with permissible concentrations and should be consulted in establishing a laboratory for radioactive isotopic work

Waste may be disposed of down the sink or into the sewer as long as the radioactivity per flush does not exceed 0 5 millicuries Further procedures for disposal as given by the United States Atomic Energy Commission (Isotopes Division Circular B 6 1949) are as follows

1 Radioiodine may be discharged from an institution into the main sewer provided that
   a The daily volume of water flowing from the sewage outlet of the institution to the main sewer is sufficient to dilute the radioiodine to 0 5 microcurie per liter
   b Maximum activity disposed of from any one institution will not exceed 200 millicuries per week
   c Regular radiation surveys are made of plumbing fixtures
   d Appropriate surveys are made before repairing the plumbing between the disposal outlet and the main sewer

or

2 Radioiodine as excreted from patients in the form of iodide may be discharged from an institution into the main sewer provided that
   a To each millicurie of radioiodine discharged one gram of potassium iodide is added at the time of disposal
   b The daily average volume of water flowing from the sewage outlet of an institution to the main sewer is sufficient to dilute the radioiodine to 10 microcuries per liter
   c Regular radiation surveys are made of plumbing fixtures
   d Appropriate surveys are made before repairing the plumbing between the disposal outlet and the main sewer

It is wise to segregate the person receiving radioiodine although when doses of I do not exceed 12 millicuries the danger of secondary irradiation to others is slight Urine should be collected and measured in calibrated collecting bottles later it may be disposed of down the sewer when the amount of radioactivity does not exceed 0 5 millicuries per flush Should bedclothes or linen become contaminated they should be kept in a room apart until significant decay has occurred

RADIOIODINE IN DIAGNOSIS

Germane to any appraisal of radioiodine as a diagnostic tool is its disposition by the body under normal conditions of ingestion in varying amounts

A The Fate of Radioiodine in the Body

Absorption of radioiodine from the gastrointestinal tract is complete within three hours but may be appreciably delayed by the presence of food in the stomach Three fourths of the radioactive material is absorbed within the first hour while quantities sufficiently great to be readily detected can be found in remote parts of the body within 3 to 6 minutes of ingestion

During absorption of a tracer dose of radioiodine the levels in the blood serum and other extracellular fluids of the body rise rapidly reaching a maximum at about the end of one hour and then falling exponentially as the iodine in the form of iodide enters the thyroid the urine (Fig 2) and other avenues of disposal Later following incorporation of the radioactive material into thyroid hormone there is a secondary although much lesser rise in the radioactivity of the blood

Now that relatively simple methods for counting the beta radiation of body fluids have afforded data concerning radioactivity which are comparable with those attendant upon the estimation of gamma radiation (Freedberg Buka and McManus 1949) it may be possible to use the behavior of serum precipitable iodine following a tracer dose of I as a gauge of the level of thyroid function (Freedberg Ureles and Hertz 1949 Potts et al 1949) It appears that the peak level of radioactive protein bound iodine of the serum is reached in myxedematous and normal subjects within two hours whereas those with hyperthyroidism show a continuous rise in such values up to the eighth hour after administration of the radioactive isotope

From 85 to 90 per cent of a tracer dose of iodine may be accounted for by its concentration within the thyroid and its excretion by way of the urine Small amounts are also lost by way of the sweat and feces Ten to fifteen per cent is distributed to the various organs and tissues of the body other than the thyroid (see Chapter VII on The Metabolism of Iodine)

Under normal circumstances that portion of the iodine which is taken up by the thyroid can be followed through the various stages involved in the synthesis storage and discharge of thyroid hormone (see Chapters VII and IX on The Metabolism of Iodine and Synthesis and Nature of Thyroid Hormone respectively) The metabolism of administered radioiodine can be dramatically influenced by the use of thyrotrophin antithyroid compounds the amount of iodine ingested and the functional status of the thyroid These factors have already been discussed (q v) The influence of the amount of iodine ingested is emphasized by Figs 22 and 23 which show the influence of added iodine upon the uptake by the thyroid and the excretion by the kidney respectively of a standard dose of radioiodine In our appraisal of the results of any tracer study these curves must be kept in mind However they are scarcely a factor when tracer doses without carrier are used as

laboratories should be routinely checked for contamination If any radiation greater than 0 003 roentgen equivalents per 24 hours per square foot is found in any place that area is not tolerable Morgan (1947) has devised procedures and mathematical formulas which deal with permissible concentrations and should be consulted in establishing a laboratory for radioactive isotopic work

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or

2 Radioiodine as excreted from patients in the form of iodide may be discharged from an institution into the main sewer provided that
   a To each millicurie of radioiodine discharged one gram of potassium iodide is added at the time of disposal
   b The daily average volume of water flowing from the sewage outlet of an institution to the main sewer is sufficient to dilute the radioiodine to 10 microcuries per liter
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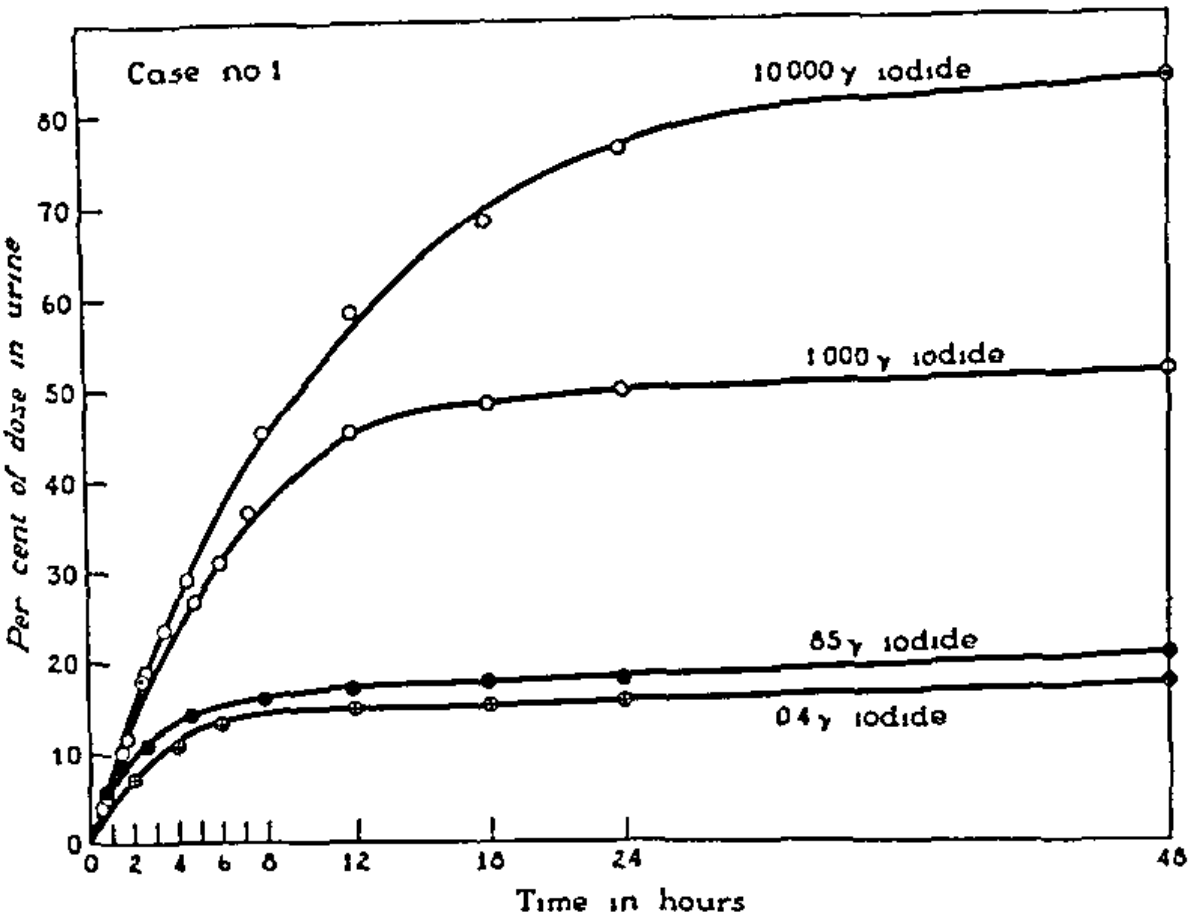


Fig. 3—Illustration of the percentage of dioxane (I¹³¹) excreted in given periods of time relative to the amount of iodide (I¹³¹) used as carrier. Note the latent period and the slight difference in the percentage of dioxane present in the urine during the first day after the administration of iodide. Above that figure the curves are essentially parallel, indicating that the rate of excretion of labeled radioxane is proportional to the activity of the thyroid at that time. Apparently the rate of uptake and concentration of iodine is not significantly altered by the presence of the radioxane. It is clear from the illustration that dosages of iodide as low as 85 γ suppress the function. (After Keston, Hamilton, Evans, and Hicks, 1949.)

the total amount of iodine involved in such studies is negligible as compared with that normally entering into body metabolism (Trunnell 1949)

B The Tracer Dose of Radioiodine

Much of the tracer work with I^{131} in human beings has been done with 100 microcuries of material However there is now evidence that such doses may not be without an appreciable radiation effect which itself may modify the results of the study and possibly alter the activity of the gland (Skanse 1948b Skanse Merrill and Evans 1948) For this reason Werner Quimby and Schmidt (1948 1949) now use 40 microcuries as a tracer dose and as little as 10 microcuries has been reported as sufficient amount for satisfactory calculation (Mason and Oliver 1949)

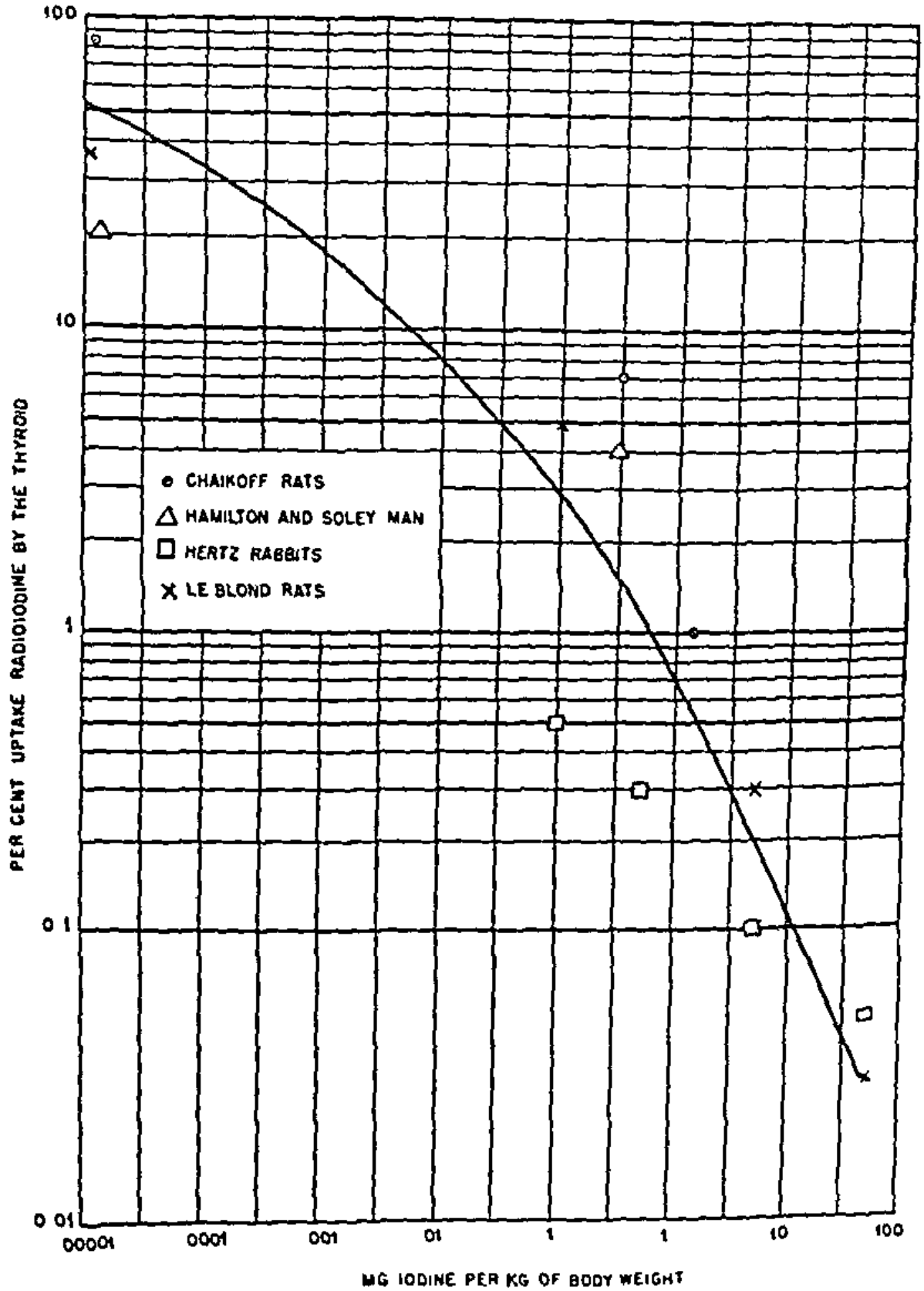


Fig. 2.—The influence of ingested iodine upon the ability of the thyroid to take up and concentrate iodine. This is a composite curve taken from the data of several investigators. The larger the dose of iodine the smaller the percentage which is taken up and concentrated by the thyroid. This blocking effect of iodine upon the thyroid function of the iodine mechanism regulating its activity under normal conditions. (After Hamilton, 1914.)

It is now clear that age and sex both influence the capacity of the thyroid to pick up iodine (Quimby and McCune 1947 Perlmutter and Riggs 1949) Perlmutter and Riggs demonstrated that the gradient for the uptake is the same in boys and girls up to puberty but is consistently higher in the latter following that event They found a rapid drop in the mean gradient to low levels after the menopause whereas in the male there was a gradual decrease from puberty to old age

Dyes containing iodine used in gall bladder visualization or bronchography may alter the behavior of body iodine for several months those used in excretion urography for several weeks and any inadvertent absorption of extraneous iodine may be sufficient to vitiate all the results obtained Of the hormones thyrotrophin exerts the greatest influence in increasing the uptake of iodine by the thyroid but other substances may later be proved of importance in this connection as has already been reported for epinephrine and certain adrenocortical steroids (Reiss Forsham and Thorn 1949 Soffer Gabrilove and Jailer 1949)

Beierwaltes et al (1948) have called attention to a number of factors of error involved in estimating the uptake of iodine by the thyroid through the use of an externally applied Geiger Muller counter for instance errors of 200 per cent in estimating the weight of the thyroid are not uncommon and inaccuracies amounting to 400 per cent have been admitted Fortunately a method has been devised recently in the carrying out of which estimations by palpation of the size of the gland are not necessary for determining the percentage uptake and its concentration (Freedberg Ureles and Van Dilla 1949)

i Thyroid Uptake of I in Hyperthyroidism —A technic designed to accentuate the effects of hyperthyroidism on the uptake of radioiodine is described under the diagnosis of hyperthyroidism (Chapter XXXVI) as it is in connection with this state that radioiodine will probably have its most liberal usage as a diagnostic and therapeutic tool These technics are based primarily on the work of Astwood and his associates (Astwood and Stanley 1947 Stanley and Astwood 1947 1948 1949 Stanley 1948 Greer and Astwood 1948)

ii Thyroid Uptake of I in Malignancy —The method of detecting radioiodine uptake by the thyroid can also be applied in cases of malignancy (Hamilton Soley and Eichorn 1940 Keston Ball Frantz and Palmer 1942 Frantz Ball Keston and Palmer 1944 Seidlin Marinelli and Oshry 1946 Marinelli Foote Hill and Hocker 1947 Ward 1947 Reinhard 1947 Rawson McArthur Dobyns Fluharty and Cope 1948 Seidlin Oshry and Yalow 1948 Dobyns and Lennon 1948 Rawson Marinelli Skanse Trunnell and Fluharty 1948 Rawson and Skanse 1948 Frantz Quimby and Evans 1948 Marinelli Trunnell Hill and Foote 1948 Rawson Skanse Marinelli and Fluharty 1949)

While it is admittedly not possible to transfer *part passu* our results from small laboratory animals to human beings it does seem worthwhile to mention here the recent careful study of the functional (Goldberg and Chaikoff) and histological (Goldberg Chaikoff, Lindsay and Feller 1950) changes found in the thyroids of rats to whom graduated doses of radioiodine have been given In rats weighing about 250 grams there was no evidence of damage to the thyroid or pituitary tissues when a dose of 18 microcuries of I was administered When 300 or 520 microcuries were used there was a suppression of thyroid function with considerable tissue change finally resulting in the case of the smaller dose in complete functional restoration With the larger amount permanent functional and histological alterations occurred Many factors enter into the transfer of such data to man if they can be transferred at all for instance the thyroid uptake and discharge of iodine are both much more rapid in the rat than in man the size of the thyroid in proportion to body weight is approximately five times greater in man than in the rat and so forth Nevertheless if we consider these two factors alone it seems likely that a 100 microcurie dose in man will not materially influence the physiological activity of the thyroid nor its histological status either temporarily or permanently

C Diagnostic Procedures Based Upon Radioiodine Tracer Technics

The general lines of procedure for employing radioiodine as a diagnostic tool include (a) measurement of the uptake of radioiodine by the thyroid during a given period of time under standardized conditions (b) measurement of the urinary excretion of labeled iodine in an arbitrarily fixed period under controlled conditions and (c) radioautographic prints of tissue

a Measurement of the Uptake of Radioiodine by the Thyroid During a Given Period of Time Under Standardized Conditions—In the result of Werner and his associates the normal range of uptake by the thyroid within 24 hours lay between 10 and 40 per cent with a mode between 15 and 30 per cent In nearly all cases of hyperthyroidism more than 40 per cent of the administered dose was found within the thyroid at the end of a 24 hour period and in subjects with myxedema the corresponding figure was usually less than 10 per cent These data confirm the earlier work of Hamilton (1942) and are generally accepted by the majority of investigators

It must be kept in mind that the values for the uptake of radioiodine by the thyroid can be considerably influenced by age sex the previous use of iodine antithyroid drugs other hormones environmental conditions such as heat and cold and last but by no means least factors of error involved in estimating the weight of the thyroid gland

screen the body for metastases using radioiodine as an indicator Needless to say a negative result on such a test does not exclude the possibility of a metastatic lesion but a positive result may lead to therapy of value—radioiodine

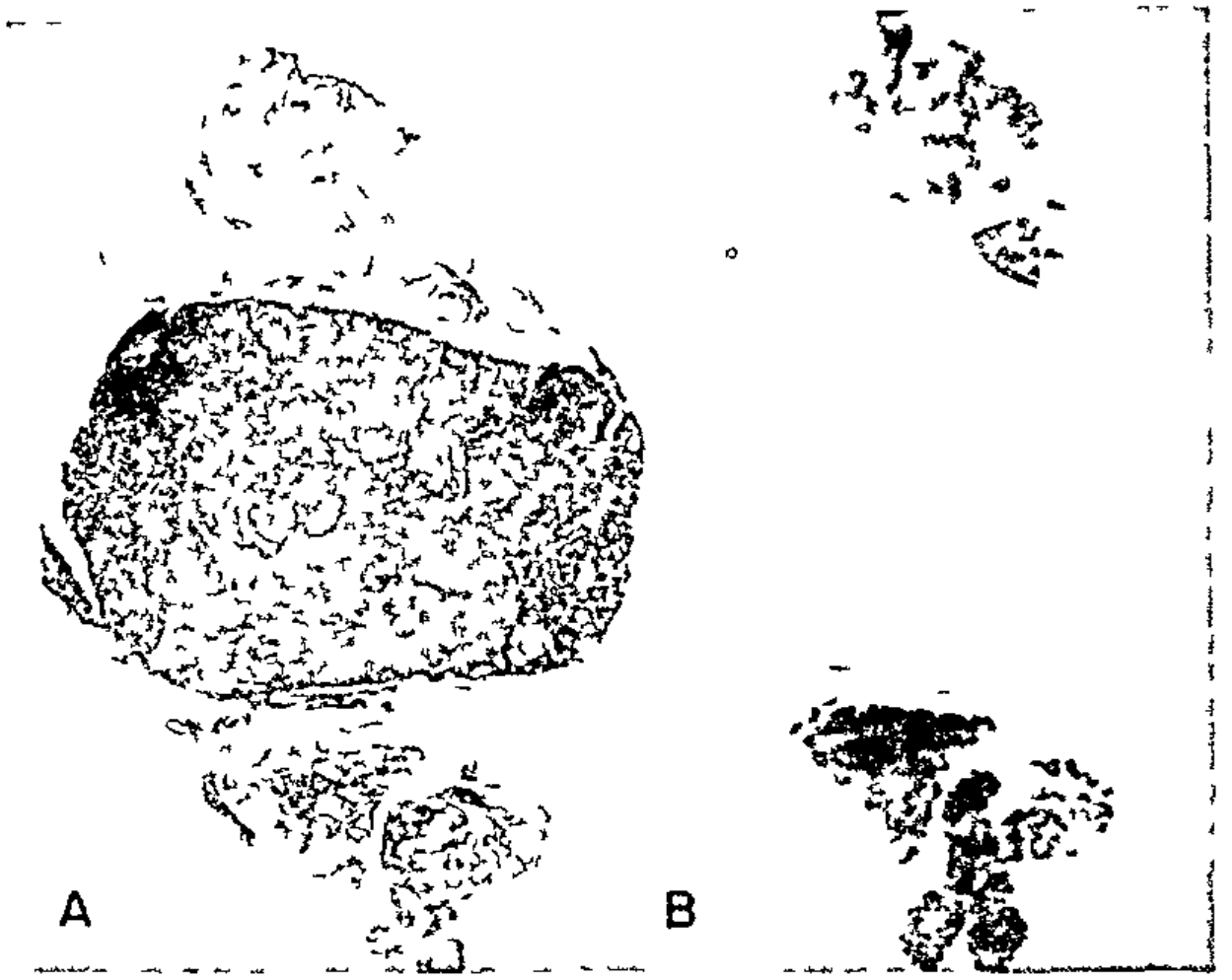


Fig 4—An undifferentiated cellular embryonal adenoma without function In this the following figure a histological section of thyroid tissue and tumor (A) is compared with a photograph (B) of the pertechnetate In B represent the location of the nodule It will be seen in Fig 8 that the degree of function of nadenomata may within certain limits be related to the degree of cellular differentiation that is the greater the approximation of the tumor towards the fully developed normal thyroid cell and follicle the greater the efficiency of trapping and the clearer the photograph In the post figure there is no picture of radiation by the tumor since it is composed of embryonic thyroid tissue undifferentiated in nature of its cellular structure (After Dobyns and Lennon 1948)

Dobyns Skanse and Maloof (1949) have so adjusted their apparatus for counting radioactivity that a very small area can be isolated from the surrounding tissue This means that the radioactivity of thyroid nodules may be quantitatively determined and compared with that of the surrounding parenchyma When the accuracy of their observations has been checked against the radioautographs of the tissues the correspondence has been sufficiently close to justify the clinical application

and in search for aberrant or metastatic thyroid tissue provided of course that some degree of thyroid function has been preserved Inasmuch as this technic involves the detection of the gamma radiation emitted by I there is no part of the body that cannot thus be searched There are now several reports in which metastatic growths have been discovered (Keston Ball Frantz and Palmer 1942 Frantz Ball Keston and Palmer 1944 Seidlin Marinelli and Oshry 1946 Marinelli Foote Hill and Hocket 1947 Rawson McArthur Dobyns Lahey and Cope 1948 Seidlin Oshry and Yalow 1948 Rawson Marinelli Skanse Trunnell and Lahey 1948 Rawson and Skanse 1948 Frantz Quimby and Evans 1948 Marinelli Trunnell Hill and Foote 1948 Rawson Skanse Marinelli and Lahey 1949) and the course of their activity followed by such a procedure (Keston Ball Frantz and Palmer 1942 Frantz Ball Keston and Palmer 1944 Seidlin Marinelli and Oshry 1946 Seidlin Oshry and Yalow 1948 Rawson Marinelli Skanse, Trunnell and Lahey 1948 Rawson and Skanse 1948)

Marinelli and his associates (1947) were of the impression that approximately one sixth of all thyroid malignancies were capable of accumulating radioiodine in some degree Seidlin and his co workers (1948 1949) found this figure above 50 per cent in metastatic lesions It has also been noted that uptake of iodine by metastases can be increased by thyroidectomy and the administration of thyrotrophin (Rawson and Skanse 1948 Rawson and his associates 1948 1949 Frantz Quimby and Evans 1948 Marinelli Trunnell Hill and Foote 1948 Seidlin Oshry and Yalow 1948 Rawson Skanse Marinelli and Lahey 1949 Seidlin Rossman Oshry and Siegel 1949 Trunnell Marinelli Duffy Hill Peacock and Rawson 1949) It seems quite likely that a low intake of iodine and the prior administration of an antithyroid compound may also be of use in increasing the concentration of radioactive material in thyroid carcinomas of some types as well as in their metastases (Marinelli Trunnell Hill and Foote 1948 Rawson and Skanse 1948)

Within certain limits it has been demonstrated that iodine uptake by the thyroid gland and the histopathological picture of the tumor are correlated (Dobyns and Lennon 1948 Rawson 1948 Rawson and his associates 1948 1949 Frantz Quimby and Evans 1948 Marinelli Trunnell Hill and Foote 1948 Seidlin Rossman Oshry and Siegel 1949 Trunnell Marinelli Duffy Hill Peacock and Rawson 1949 Fitzgerald and Foote 1949 Dobyns Skanse and Maloof 1949)

It appears that the more anaplastic or embryonal the cellular elements of the growth and the less it resembles normal thyroid tissue the less likely is it or its metastases to pick up iodine (Figs 21 28) However a highly undifferentiated primary tumor in the thyroid may develop metastases with a reasonable degree of function Therefore in every case of primary malignancy of the thyroid it seems worth while to

high while serum protein bound iodines were entirely within the normal range

b Measurement of the Urinary Excretion of Labeled Iodine Over a Fixed Period Under Controlled Conditions—It was at first believed that curves for the urinary excretion of radioiodine would prove to be of much more value as a method for determining thyroidal functions than the estimated uptake of iodine by the gland itself However this estimation also has many disadvantages Treatment with thyroid hormone the administration of antithyroid compounds including iodine and the presence of renal disease or congestive heart failure may be among the common causes which upset the results Nevertheless in the present state of our knowledge no avenue for obtaining information regarding so promising a diagnostic and therapeutic tool as radioiodine should be overlooked

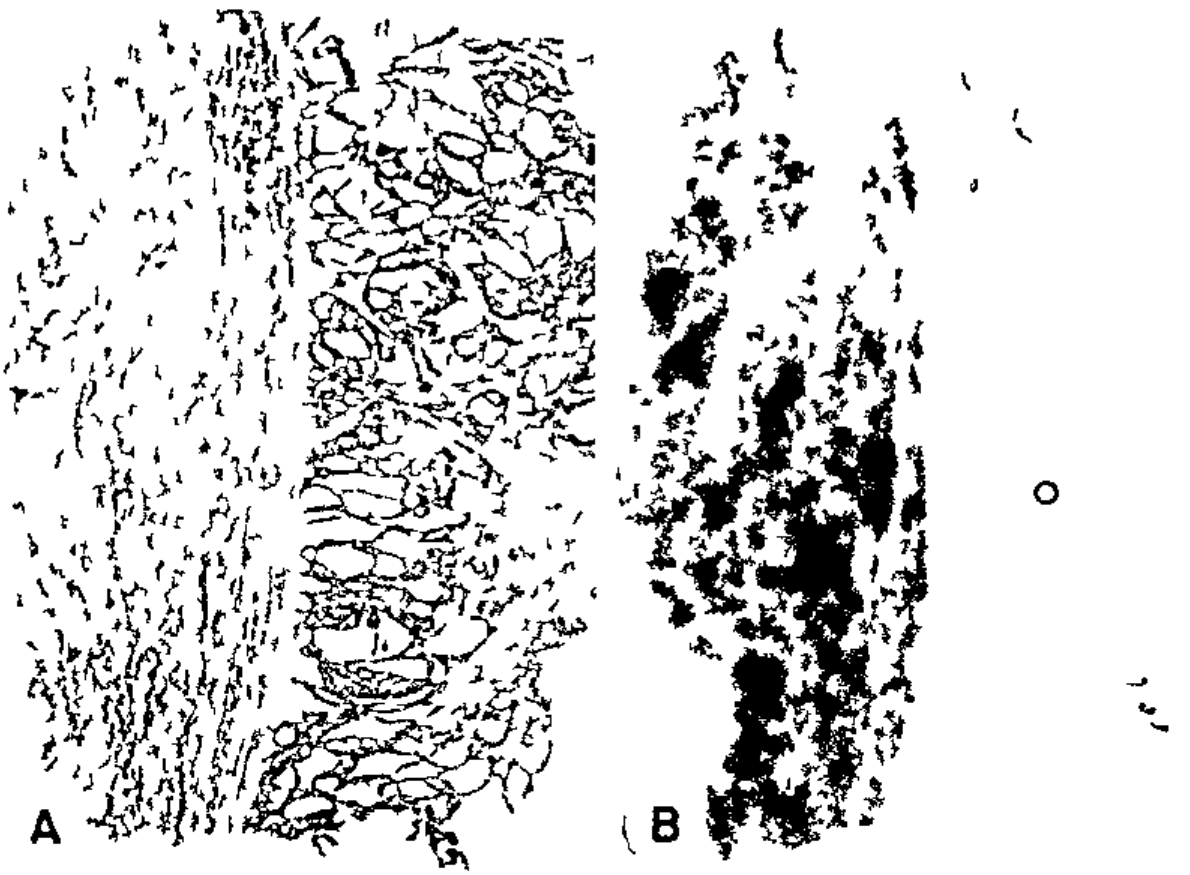


Fig 6—Thi a hyp pla t d w th ut f n t In both ti s (*A* nd *B*) th de n a s on tl ght d th rm ity functi ing p an d l r t sue on the l ft In th adenon tl e ll l l n d bly e (to 18 nicr) th aj t l ing larg th s th norm l cell (a a e ab ut m e t) (Aft D b ns and L n 1948)

The technic for estimating the urinary excretion of radioiodine is described under a discussion of diagnostic tests useful in the study of hyperthyroidism (Chapter XXXVI) Several modifications of the one

of the method In general it has been found that (1) carcinomatous tissue takes up less iodine than the surrounding normal structure (2) solitary hyperfunctioning nodules with or without thyrotoxicosis are easily detected and are advisedly removed surgically (3) thyrotoxicosis due to generalized hyperplasia for which radioiodine is often satisfactory therapy may be distinguished from thyrotoxicosis due to a hyperfunctioning nodule



Fig —Two follicles one of which shows no function and the second (left) a slight amount of function as compared with the normal parenchymal tissue The heights of the cells in both the lesions and in the surrounding normal tissue were compared Variations ranging from 4 to 9 microns were noted for the nonfunctioning tumor while those of the normal tissue varied from 2 to 8 microns Only 40 per cent of the total around microns The cells of the slightly functioning tissue were from 3 to 0 microns in height with more than 6 per cent between and 10 microns Exceptionally cells of an even greater height are believed to be interpolated (After Dobyns and Lemon 1948)

iii Thyroid Uptake of I in Mental Diseases—Some attempt has been made to study thyroid function in patients with mental diseases particularly schizophrenia by observing the maximum *concentration* of I in the thyroid following the oral administration of a carrier free tracer dose (Bowman Miller Dailey Simon Frankel and Lowe 1950) Such concentrations were usually within the normal range and in no case did the uptake curves on our subjects resemble the types found in myxedema or thyrotoxicosis Concomitantly determined basal metabolic rates were somewhat low and plasma cholesterols somewhat

above (Lourey et al 1949 Arnott et al 1949) Inasmuch as rather wide individual variations occur in both the glandular uptake and urinary excretion of iodine Williams Jaffe and Bernstein (1949) have proposed a correlation of the I in urine and in blood following a test dose of 100 microcuries as an aid in diagnosis The product of urinary radioiodine for the first 24 hour period and serum inorganic iodine at the end of 24 hours was found to be highest in athyreosis less elevated in thyrotoxicosis and least in the normal subject The ratio of urine radioiodine to serum inorganic iodine was less in thyrotoxicosis than in euthyroidism or athyreosis Fractionation of the serum at the end of 24 hours revealed supernormal values in the serum of thyrotoxic subjects for total radioiodine protein bound iodine and inorganic iodine The ratio of diiodotyrosine to thyroxin was also lowered in such individuals By contrast the serum inorganic iodine was markedly increased over normal in the athyreotic patient

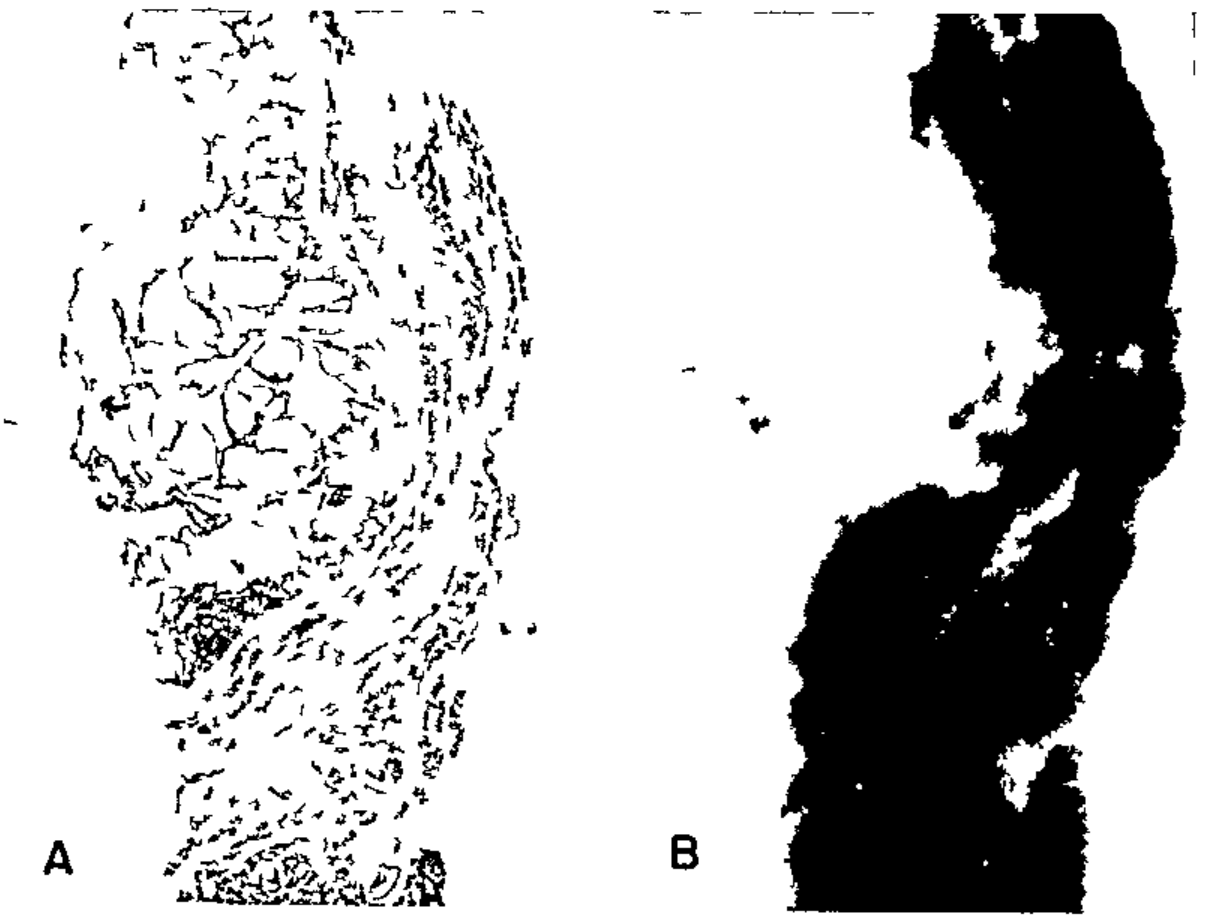


Fig 8—Gross di which th hyperplast gland nt n n functioni g n d l N t th hasyn of th ad ut g l ndicati s a y n ark d n t ation f rad d d Th cell h ght f ll e n dule w s l w on n f id g a oll d adenom In th m nd f tl gl l th ll w rs h hyp t ph d with n rag h ght f 11 c ns Il r tle d n m w s n d tal t h t pi t vl il F tl ut o nousl ting l n w f t i g o ig ly to surp the r a uf t of tl d l o by oth po ts of th l nd (After D by s d L n n 1948)

described have been used by various investigators Using tracer doses of 100 microcuries of I and a 48 hour excretion period Sharpe (1918a b) found that euthyroid subjects excreted from 52 to 81 per cent of the administered dose with an average of 66 per cent For thyrotoxic subjects the range of excretion was 6 to 32 per cent with an average of 19 per cent and for myxedematous patients the excretion was very much greater and varied from 72 to 91 per cent in individual subjects Using a 72 hour period of excretion and a 100 microcurie test dose Keating Power Berkson and Haines (1917) found that most of their hyperthyroid patients retained from 75 to 90 per cent of the tracer dose their euthyroid subjects excreted an average of 65 per cent and their cases of myxedema an average of 85 per cent of the administered radio iodine Typical curves of excretion for normal men are shown in Fig 2 The results of other workers are in accord with those mentioned

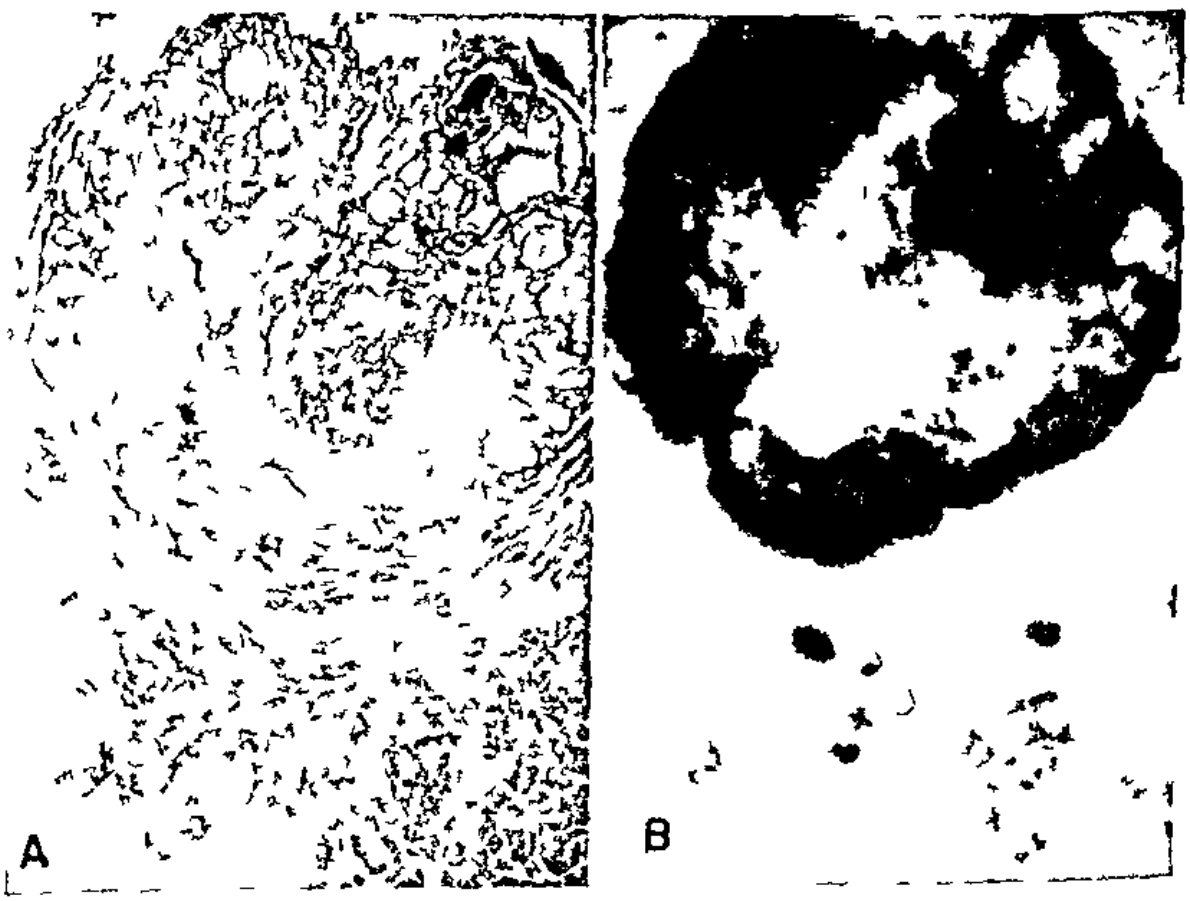
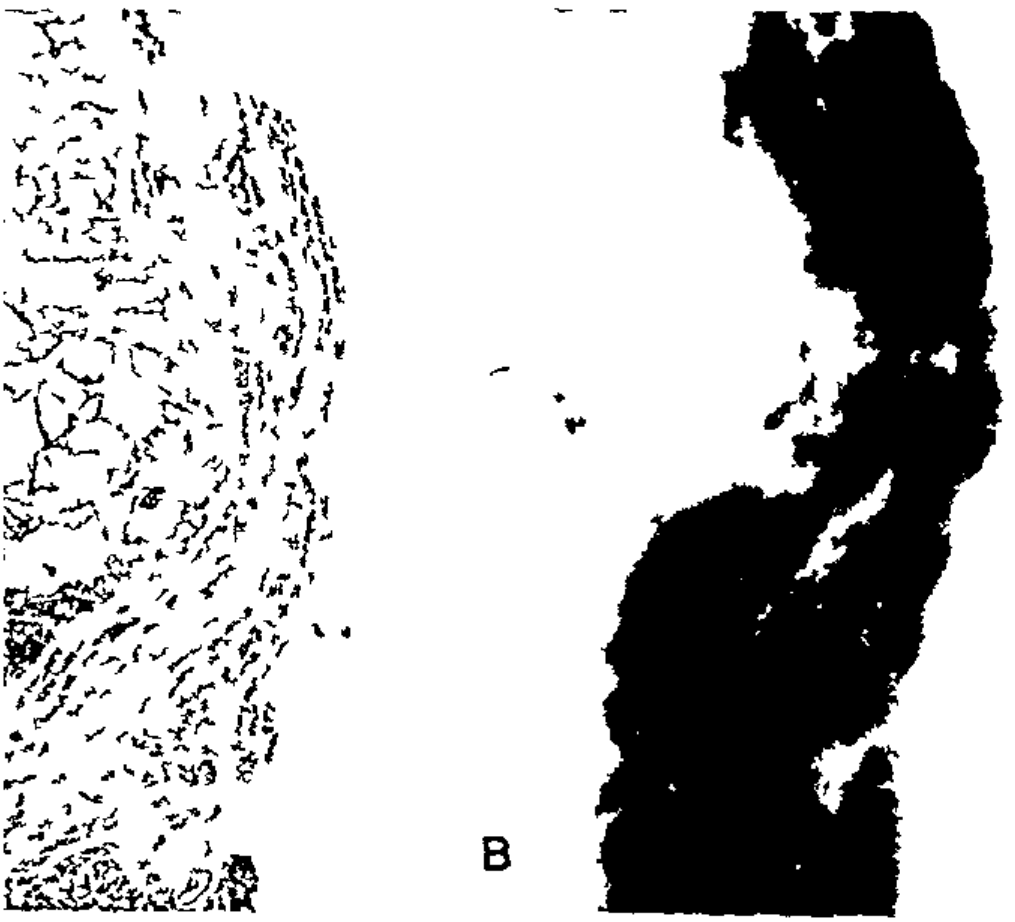


Fig 2 — This is a hyperfunctioning single adenoma of the thyroid Note the necrosis in the center of the nodule (section 4) which is sharply outlined in B by its failure to take up any radioiodine With the adenoma cell height varied from to 11 microns with approximately 80 per cent of the cells between 6 and 8 microns in height This is in sharp contrast to the wide variation in the hyperplastic but nonfunctioning cell of the carcinoma shown in Fig 2C There appears to be little relationship between uniformity of cell and nuclear size and functional polarity Note the uniformity of the activity of the surrounding thyroid tissue to one activity of the adenoma Cell height within the parenchymatous tissue was while quite uniform was low with an average of 3 microns as compared with a normal of microns (at opposite) (After Dobyns and Lahey 1918)

ney et al 1949, Arnott et al 1949) Inasmuch as rather dural variations occur in both the glandular uptake and urin ion of iodine Williams Jaffe and Bernstein (1949) have pro relation of the I^{131} in urine and in blood following a test dose rocuries is m ud in diagnosis The product of urinary for the first 24 hour period and serum inorganic iodine at 24 hours was found to be highest in thyreosis less elevated reosis and least in the normal subject The ratio of urine to serum inorganic iodine was less in thyrotoxicosis than in m or thyreosis Fractionation of the serum at the end of vealed supernormal values in the serum of thyrotoxic sub tal radioiodine protein bound iodine and inorganic iodine of diiodotyrosine to thyroxin was also lowered in such indi by contrast the serum inorganic iodine was markedly in er normal in the thyreotic patient



e li e in wh i th b pl ti gla d ontains a rot fu t onl g n dule f th f a tosra l ind ating a ery n a ked o t t o of adiot di f th nod l w l w a ou f nding in a oll id ad b n It th e ab d th ell wer ery l ly o tr thied w th n e g l ight of 11 mlero is o w f fi tal to th to ti tur whil l Fig 7 tle ulo usly tu g f fi fi s o vigo ou ly a to supr ss the a uf t e of tl d lor i by the gl d (*Alle Dobyns d L r non 1948*)

c **Radioautographic Prints of Tissue**—By radioautography, we mean the picture produced by radioactive containing tissue on a sensitized photographic film or emulsion closely clamped against the mounted tissue (Boyd 1947)—or printed as in emulsion on the section (Belanger and Leblond 1946) Factors concerned in the underlying physical principles of such technics and the accuracy of definition obtained thereby have been reviewed by Boyd (1947) Suffice it to say that in the case of radioiodine these pictures enable us to locate with accuracy satisfactory for clinical purposes, the disposition of the tagged material in histological specimens As applied to thyroid function Hamilton Soley and Eichorn (1940) were the first to employ this method of study Since then several investigators have employed some modification of the procedure (Hamilton 1942 Leblond 1943a b Belanger and Leblond 1946 Cope Rawson and McArthur 1947 Evans 1947 Dobyns and Lennon 1948 Rawson McArthur Dobyns Lahanty and Cope 1948 Kelsey Hames and Keating 1949 Fitzgerald and Foote 1949) with the addition of the following facts to our knowledge of thyroid physiology and pathology

1 Degrees of radioactivity not ordinarily amenable to localization by means of a Geiger Muller counter can be readily detected

2 A closer correlation has been made possible between the localization of radioactivity and the histological features of the tissue

3 In the normal thyroid gland the radioactivity is not evenly distributed some follicles and surrounding cells showing much greater concentration than others of a similar histological appearance On the basis of such observations it has been suggested that the follicles possess a rhythmical activity in regard to their function of concentrating iodine a conclusion similar to the one at which R G Williams (1937) earlier arrived through his observations on living transplants of thyroid tissue

4 The intensity of function as measured by the concentration of radioactivity appears to be related to the degree of differentiation of adenomas To this rule there are some exceptions but by and large the more embryonal the cells of the tumor masses the less the concentration of radioiodine within them Conversely the more fully differentiated the cells the greater their avidity for I^{131} This is shown graphically in Figs 21-28 inclusive

5 Some hyperplastic adenomas show considerable function, while others similar in histological appearance are not associated with toxicity and do not take up ingested radioiodine (Figs 21 28)

6 Hyperfunctioning adenomas may suppress and cause atrophy of previously normal surrounding thyroid tissue (Fig 27)

7 Radioautographs have explained why some carcinomas respond to the administration of radioiodine and others do not

8 Of the carcinomas those with some degree of follicle formation best concentrated the radioactive isotope but in no instance did any

carcinomatous tissue exhibit activity comparable to that of the normal glandular structure. Even in the carcinomas there was a tendency for *greater concentration in one area of follicular formation than in another* of histologically identical structure. Papillary and solid carcinomas showed very little tendency to concentrate the radioactive iodine except in those areas where follicles were present. Hurthle cell tumors rarely showed any capacity for absorbing the radioactive isotope. The most malignant of the thyroid carcinomas, the spindle and giant cell varieties, have failed to take up any of the radioiodine delivered to them.

9. The ability of the metastatic carcinomatous nodules to pick up and concentrate radioiodine depends upon their degree of differentiation as shown by microscopic section autoradiographic technics. In general the activity of the primary and secondary lesions is similar just so long as the primary growth remains in situ. There are however notable exceptions to this statement. After removal of the primary growth there is a tendency for the metastases to develop some degree of thyroid function which can be enhanced as already mentioned by the use of antithyroid compounds or by the withholding of iodine. It should be emphasized that in any given patient the activity attained by the metastatic lesions may vary from location to location sometimes dramatically (Ball, Keating, Power and Bennett, 1949).

RADIOIODINE IN THERAPY

Both I^{131} and I^{130} as well as mixtures of the two have been used in the therapy of *thyrotoxicosis*. The indications, contraindications, results to be expected and complications are discussed in Chapter XXXVIII on the Treatment of Hyperthyroidism. There are those enthusiastic enough to believe that the method will supplant other forms of therapy in the Graves type of the disease where a diffuse hyperplasia of the whole gland exists (Mergoni and Orlandini, 1948). In selected cases it may be the method of choice. However, technics of determining dosages and factors related to individual reactions seem to warrant much more consideration before a dogmatic position is justified.

Doses selected for the purpose of treating the diffusely hyperplastic toxic gland of Graves disease have varied from those which will allow the thyroid to collect 50 microcuries to those which will allow it to pick up 500 microcuries of I^{131} per estimated gram of tissue (Haines, Kelsey, Williams and Keating, 1948; Miller and Soley, 1948; Soley and Miller, 1948; Crile, McCullagh and Glasser, 1949; Chapman and Evans, 1949). These have represented total doses ranging from 0.8 to 20 millicuries. With the higher doses between 200 and 250 microcuries of radioiodine (I^{131}) per estimated gram of thyroid tissue, myxedema is frequently encountered having occurred in eight out of 10 patients in one series of cases (Haines, Keating, Power, Williams and Kelsey, 1948). However in some instances even such amounts are not successful in bringing

the condition under control Wide individual variations in the effects of radiation therapy must therefore be recognized in which many factors may be concerned such as the state of the adrenal medulla the presence of bacterial toxins variations in food and environment and so forth (Williams et al 1918 Williams 1919 b) It has been observed that from 20 to 70 millicuries of I^{*} are necessary to produce myxedema in a person with a normal thyroid (Rawson 1950) but that 3 to 4 millicuries may prove sufficient for the same purpose in the subject with Graves disease (Crile McCullagh and Glasser 1949) In the present state of our knowledge it seems best to give the smaller doses—from 100 to 150 microcuries per gram of estimated tissue—and to repeat them as necessary until euthyroidism has been attained

In the therapy of carcinoma of the thyroid and its metastases results from the administration of radioactive isotopes of iodine have been largely disappointing despite careful selection of cases and unusually large doses of I While the application of radioiodine to therapy of all types of thyroid lesions is still in its infancy some conclusions can be drawn from the recently reported work of three groups of investigators covering an intensive study of over 60 subjects and tracer studies in more than 200 subjects with thyroid carcinoma (Rawson Marinelli Skanse Trunnell and Flaherty 1948 Trunnell Marinelli Duffy Hull Peacock and Rawson 1949 Seidlin Rossman Oshry and Siegel 1949 Fitzgerald and Foote 1949) A little less than half of the patients with carcinoma gave radioautographic evidence of concentration of the isotope in the carcinomatous tissue About three fourths of the alveolar and follicular carcinomas one fourth of the papillary group and nearly half of the solid carcinomas (chiefly those with colloid present) showed significant concentration of the radioactive material Occasional adenocarcinomas with Hurthle cell change picked up identifiable amounts of the isotope but for the most part were unresponsive No evidence of radioactivity was observed in cancers of the giant cell spindle cell and anaplastic types

In no case has there been a concentration of I in the tissue of thyroid carcinoma greater than or even equal to that attained in the surrounding normal thyroid Furthermore when considerable normally functioning follicular structure is present the tendency for the radioactive isotope to concentrate in the tumor is small It is obvious therefore that the destruction of a primary carcinomatous lesion in the thyroid necessitates the use of doses so large that complete destruction of normally functioning tissue is inevitable Frequently following such radioactive therapy the cancerous growth is not simultaneously destroyed On the contrary it may be actually stimulated to grow and to assume some thyroidal function thus partially or completely defeating the purpose for which it was given

For the above reasons it seems advisable to deal surgically with all primary malignant growths in the thyroid and to reserve isotopic therapy and I for the metastatic lesions Just as the primary lesion in the thyroid can be caused to assume some thyroidal function after all normal tissue is destroyed by the use of radioiodine metastases tend to concentrate iodine better after thyroidectomy than they did before and *therefore become more or less amenable to isotopic therapy*

In addition to thyroidectomy other measures which tend to increase affinity of metastatic thyroid cancer for iodine are a restriction of iodine ingestion the administration of antithyroid compounds and the injection of thyrotrophic hormone If iodine intake is low for several weeks prior to the administration of a carrier free dose of radioiodine all thyroid tissue with *any* function will avidly take up the radioactive *material* (Marinelli Trunnell Hill and Foote 1948) As a rule satisfactory depletion can be attained by having the patient eliminate from the diet for a few days all seafood and leafy vegetables and if in the habit of using iodized salt substitute the uniodized preparation

Antithyroid compounds cause a discharge of iodine from thyroid tissue and if continued for several weeks or months, will within two to several days following their withdrawal markedly increase the capacity of thyroid tissue for picking up and storing iodine (Marinelli Trunnell Hill and Foote 1948 Seidlin Oshry and Yalow 1948 Trunnell Marinelli Duffy Hill Peacock and Rawson 1949) If the thyroid and primary growth have been removed this effect upon the metastatic lesions is all the *more dramatic and useful in the localization of radioactive* material However in employing such compounds it must be kept in mind that prolonged periods of administration may be disadvantageous for two reasons In the first place valuable time may be lost In the second place as thyroid hormone production is suppressed activity of thyrotrophin is increased thereby stimulating the growth of the metastatic lesions to be treated Therefore it seems logical to utilize the antithyroid compounds no longer than is necessary to produce an early functional change For this purpose a preparation such as 1 methyl 2 mercaptoimidazole which shows clinically demonstrable effects in thyrotoxicosis within three days (McGavack 1950) should be ideal

Injections of thyrotrophin produce an activation of metastatic thyroid lesions similar to that above described for the antithyroid compounds thus improving their capacity for concentrating iodine (Seidlin Oshry and Yalow 1948 Frantz Quimby and Evans 1948 Marinelli Trunnell Hill and Foote 1948 Rawson Skanse Marinelli and Fluharty 1949 *Trunnell Marinelli Duffy Hill* Peacock and Rawson 1949) The last mentioned workers injected intramuscularly 30 mg (3 8 Evans chick units/mg) daily for several days Forty eight hours after

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present lesions capable of picking up and concentrating iodine. Large multiple doses of radioiodine such as are necessary in the therapy of cancer have not been used a very long time so that neither the full extent of their suppressive influence upon the cancer nor their toxic side effects are fully known.

Among the untoward reactions encountered to date are all of those observed in the management of hyperthyroidism (Chapter XXXVIII) plus the following (Trunnell, Marinelli, Duffy, Hill, Peacock, and Rawson) which appear as the radioactivity is increased to relatively tremendous proportions: (1) hyperthyroidism arising as a result of activity within the primary tumor tissue following the destruction of all of the *adjacent normal gland by* I^{131}; *(2) amenorrhea, three instances* which were attributed to damage to ovarian tissue from circulating radioactive iodine; and (3) a depression of hematopoiesis in all of the patients that we have *subjected to intensive treatment with* radioiodine. One patient who received 315 millicuries at a single dose developed an irreversible pancytopenia. However, the subject who to date has received the largest total dose, 1700 millicuries over a period of three years and a maximum single dose of 117 millicuries, has failed to show any significant disturbance of the bone marrow (Seidlin, 1950). This individual has had large functionally highly active metastases and it is believed that the rapid uptake of iodine by these metastatic areas has appreciably spared other tissues from excessive irradiation.

CONCLUSIONS

Radioiodine, now used almost entirely in the form of I^{131}, has proved to be a useful tool in the study of thyroid function. It has added particularly to our knowledge of the manner of synthesis of thyroid hormone, its storage by the thyroid, and its discharge therefrom. Furthermore, the role of thyrotrophin, of iodine, of antithyroid compounds, of foods, and of other environmental influences has been illuminated by following the behavior of administered radioiodine in laboratory animals and man.

Therapeutically, radioiodine seems to have a place in the management of selected cases of Graves' disease. Its therapeutic effectiveness against toxic nodular goiters and malignancies of all kinds is highly questionable, although isolated instances of positive results are well authenticated.

discontinuing the injections there was a marked increase in the uptake of radioiodine by the metastatic lesions followed some two weeks later by a refractory period in which their capacity for storing iodine was greatly depressed

The possibility of depositing radioactive iodine electively in a selected tissue by attaching it to an organ or tissue specific antibody must not be ignored as a future means of radiation therapy of malignant tumors and their metastases It has long been known that a wide variety of chemical agents can be coupled with an antibody without destroying their specific activities Pressman and Keighley (1948) and Pressman (1949) made use of this fact to study the tissue distribution of a radioactively iodinated antikidney serum Injection of this antiserum into the species to which the antigen donor belongs resulted in a long sustained and high concentration of radioactivity in the kidneys of such animals but showed slight to no detectable radiation effects in any other tissue This phenomenon opens up a potentially wide field of therapeutic interest for it has already been possible to prepare highly specific antibodies against certain strains of experimentally produced mouse mammary carcinoma (Imagawa Green and Halvorson 1948) May it be possible to prevent and cure recurrences and metastases from thyroid carcinomas by using the surgically removed gland as a source of antigen for the production of a specific antiserum to which radioiodine can be attached? Such an idea may be more than a fantasy

Because of the limited functional capacity of all thyroid carcinomas the doses of radioiodine to be effective must be relatively large Total doses employed have ranged from 111 to 1 700 millicuries and the patient who received the last mentioned dose appears to have had the progress of her lesions checked during a six year period of observation and a three year period of intensive therapy (Seidlin Rossman Oshry and Siegel 1949 Seidlin 1950) By means of radioautography Fitzgerald and Foote (1949) have shown an uneven variable concentration of radioactive iodine in normal as well as in neoplastic thyroid tissue They believe a phasic activity of the thyroid follicle is thus suggested so that multiple dose rather than a single dose therapy will be necessary to ensure irradiation of all parts of either normal or cancerous tissue With this in mind the majority of observers are employing multiple doses in the treatment of the metastases from primary carcinoma of the thyroid the largest single dose to date having been 315 millicuries (Trunnell 1949 Rawson 1949b Trunnell Marinelli Duffy Hill Penrod and Rawson 1949)

It is hazardous at the present time to make dogmatic statements regarding the final results to be obtained by the use of radioiodine in the management of cancer of the thyroid If the reported cases are viewed statistically then it appears that in about one fourth some benefit has been derived from the therapy while in nearly one half there have been

secretory activity To meet the growth and energy requirements of the fetus as well as the increasing caloric needs of the mother a rise in the secretion of thyroid hormone occurs accompanied by an increment in the amount of colloid stored The degree and extent of the histological changes and of the gross enlargement of the thyroid are altered by a number of factors such as age number of pregnancies previous goiter habitat and so forth

As a rule the older the person and the greater the number of pregnancies the more likely is the subject to have a goitrous enlargement with gestation (Wegelin 1926 Eugster 1934 Szendi 1939 Hiilesmaa 1948) This has been spoken of as the stepladder effect of pregnancy on simple or colloid goiter In other words after the work hypertrophy and hyperplasia of pregnancy involution of the thyroid is incomplete leaving a successively larger gland following each period of gestation

By far the most important factor in the development of a permanent enlargement of the thyroid or goiter as a result of pregnancy is the environment and its relation to the availability of iodine In a nongoitrous district Portis and Roth (1939) report physiological enlargement of the thyroid gland in 31 per cent of their parturient women the percentage increasing with succeeding pregnancies while in a highly goitrous belt approximately 90 per cent of the subjects developed or showed further enlargement of an already developed goiter during pregnancy (Rubsamen 1912)

Marine (1917) early called attention to the work hypertrophy and hyperplasia which occur in the thyroid when its iodine content drops to 0 1 per cent or below In pregnancy the increased need for thyroid hormone causes not only an increase in its manufacture but an increase in its discharge from the thyroid with a concomitant decrease in its concentration of iodine When only a minimum amount of iodine is available as in goitrous belts the result is a lowering of the levels beyond the point at which the thyroid can function efficiently in such instances goiter is inevitable Several years ago Mussey (1938) commented that the amount of iodine normally ingested was frequently insufficient to meet the requirements of the pregnant woman If there is doubt about a sufficient intake of iodine then it seems wise to administer small amounts e g 1 minim of Lugol s solution from one to several times weekly throughout the period of gestation Thus the incidence of concurrently appearing or subsequently developing colloid goiter nodular goiter and thyrotoxicosis may be strikingly diminished (Enright Cole and Hitchcock 1935 Marine 1935 Mussey 1938 Zener David and Phatak 1947 Heinemann Johnson and Man 1948)

It has already been mentioned that the physiological hyperactivity and enlargement of the thyroid during pregnancy normally subside or involute so completely that no perceptible change can be detected grossly

Chapter XVIII

PREGNANCY AND THE THYROID

Hyperthyroidism complicating pregnancy has always posed a difficult therapeutic problem for the obstetrician and the endocrinologist for which until recently surgical intervention under not too favorable conditions or prolonged tedious and often not too successful roentgen radiation afforded the best available solutions In either event once the presence of the condition was recognized and a course of action reached the internist usually played no further direct role in the management of the case With the recent advent of potent antithyroid compounds and the applicability of radioiodine at the bedside this has changed and the internist or endocrinologist must share with the obstetrician the day to day care of the pregnant patient with thyrotoxicosis Although the confines of space exclude other important subjects this change in our approach to hyperthyroidism if nothing else justifies the inclusion here of a brief consideration of the thyroid gland as influenced by physiological and abnormal conditions which may arise during gestation

PHYSIOLOGICAL ALTERATIONS IN THE ACTIVITY OF THE THYROID DURING PREGNANCY

The thyroid gland undergoes a work hypertrophy and hyperplasia during pregnancy as a result of the altered energy and growth requirements of that period Where health and environmental conditions are normal this is accomplished without any symptoms or signs noticeable by friends or family and the postpartum restitution to a normal albeit not pristine state is accomplished as an integrated completely unrecorded part of the intricate delicately poised glandular adjustments which Nature imposes at that time Behind this remarkable adaptation for procreation lie a veritable panorama of alterations in which the changing of the basal metabolic rate the blood and tissue levels for protein bound iodine the redistribution of calcium the heightened adrenal activity and the enlarging neck all point toward the dramatic functional and histological variations taking place in the thyroid

(1) **The Enlargement of the Thyroid During Pregnancy**—In 50 to 90 per cent of pregnancies the thyroid becomes enlarged The added work of the gland first induces an increased vascularity which may in itself cause sufficient active congestion to enlarge the gland In addition the epithelial cells usually increase in number height over all size and

disturbances age of subjects and so forth Under average conditions it seems safe to conclude that a moderate increase (up to plus 25 per cent) in basal metabolism is to be expected in the latter months of pregnancy and that such an elevation does not call for any specific therapy unless the thyroid gland is noticeably enlarged or an absolute or relative deficiency for iodine is proved or believed to exist If there is doubt regarding the latter prophylactic doses of iodine should be used

This moderate elevation of the basal metabolism during normal pregnancy is of further practical importance in relation to the management of thyrotoxicosis in the pregnant woman by the use of thiouracil In order to avoid damage to mother and fetus from this or any of the antithyroid compounds the above mentioned moderate degree of elevation in the metabolism should be maintained

3 The Behavior of Blood Iodine in Pregnancy —There is very little if any evidence which contradicts the observation made some years ago that blood iodine is elevated in pregnancy (Mamer 1927) Nearly all observers have confirmed this finding (Bokelmann and Scheringer, 1931 Phatak Zener and David 1940 Zener David and Phatak 1917 Hemenann Johnson and Man 1918 Peters Man and Hemenann 1918) and recent analyses suggest that this elevation occurs chiefly if not solely in the protein bound fraction of the blood iodine (Hemenann Johnson and Man 1918 Peters Man and Hemenann 1918) These latter workers note that there is a sharp rise in the precipitable iodine of the serum at the very onset of pregnancy which is maintained until after delivery when it returns rather promptly to normal

In some individuals the expected rise in serum precipitable iodine fails to occur and in a few an decrease during the first months of gestation To Peters and other workers (1948) this signifies a thyroid deficiency often results in abortion but when promptly recognized may be overcome by the administration of iodine and desiccated thyroid substance Peters well summarizes the status of the serum iodine in pregnancy It does seem certain that for some reason the precipitable iodine of the serum rises during normal pregnancy The evidence to date suggests also that if the serum iodine does not rise abortion is likely to occur in the early months of pregnancy

4 The Probable Role of the Thyroid in the Redistribution of Calcium That Occurs in Pregnancy — With the heightened activity of the thyroid gland there is always an increase in the mobilization of calcium from the bony structures without a concomitant alteration in the blood levels unless hyperthyroidism occurs (see the discussion on diagnosis of hyperthyroidism Chapter XXVI) The growing skeleton of the fetus requires large amounts of calcium which the mother will supply from her own tissues chiefly the bones if sufficient amounts of that element are not furnished in the diet The thyroid probably plays a leading role in making such

in the appearance or feel of the gland post partum However, should a simple colloid goiter be left this may become the breeding ground for nodular goiter particularly provided that the thyroid is subjected to an additional period of stress or succession of stresses such as further pregnancies Thus the incidence of nodular goiter in pregnancy is greater in those who have had a preceding simple or colloid goiter (Hulesmaa 1948) Furthermore particularly in goitrous belts pregnancy may cause the development of nodular goiters even though no preceding evidence of a simple goiter may have been apparent (Schleussing 1931)

In conclusion the presence of slight enlargement of the thyroid gland may be a normal finding during pregnancy the result of a work hypertrophy and hyperplasia which will involute satisfactorily during the puerperium Its presence however should always raise the question of a relative or absolute deficiency of iodine and is a fully sufficient reason for the empirical use of iodine prophylactically In regions where iodine deficiency is known to exist enlargement of the gland may occur in 100 per cent of all pregnant women and involution post partum be incomplete or fail entirely Thus both simple colloid and nodular goiters may be formed To avoid them iodine should be employed prophylactically in all pregnant women living in an endemic goiter belt, and in all those in whose families goiter is a common occurrence

2 **The Behavior of the Basal Metabolic Rate in Pregnancy** — Normal variations in the basal metabolism increases in which were first noted by Magnus-Levy in 1897 have been rather intensively studied during pregnancy (Zuntz 1910 Bier 1921 Root and Root 1923 Sandiford and Wheeler 1924 Rowe Alcott and Mortimer 1925 Daly and Strouse 1925 Mussey, Plummer and Boothby 1926 Davis 1926 1932 1935 Falls 1929, Plass and Yorkum 1929 Kimball 1931 Niederwieser 1932 Hughes 1934 1940 Enright Cole, and Hitchcock 1935 Dietel 1935 Pohl 1936 Hanna, 1938 Wahlberg 1938 1946 Krogh um 1947 Zeher David and Phatak 1947 Hememann Johnson and Man 1948 Peters Man and Hememann 1948) There is considerable disagreement regarding details of variation in the basal metabolism during pregnancy but the majority of the data point to a normal basal metabolism during the first four to five months of gestation with an increase up to plus 25 per cent during the last trimester Zeher and his associates (1947) working in the Pacific Northwest found an elevation throughout the entire period of pregnancy and during at least six weeks of the puerperium Rowe Alcott and Mortimer (1925) in Boston noted a continuous decrease in the basal metabolism until the twelfth week of gestation following which it increased steadily to plus 20 to 25 per cent a figure rapidly superseded following delivery by a sharp drop to subnormal values From these and the experiences of others it seems that variations in individual studies must be analyzed in the light of environment (goitrous as compared with nongoitrous belts) pre existing thyroid

further believe that a decrease of such values early in pregnancy is unequivocal proof of underfunction of the thyroid warranting the administration of iodine which if not done effective should be supplemented by the ingestion of thyroid hormone These workers have been unusually fortunate in establishing reproducible data for the values of serum precipitable iodine under a wide variety of conditions Unfortunately such laboratory technics are available in only a few places throughout the country and in many instances where available have not yielded results as uniformly satisfactory as those reported by the Yale group Therefore the majority of clinicians must content themselves at least for the present with diagnoses established on the basis of their appraisal of all other data

Unrecognized hypothyroidism in the pregnant woman may result in irreparable damage to the patient s thyroid abortion miscarriage or stillbirth congenital goiter with or without other abnormality and a wide variety of disturbances in the somatic development of the fetus

a Thyroid Disease in the Patient —Simple colloid goiter nodular goiter and myxedema may occur as a result of the overstrain imposed by pregnancy upon a woman whose thyroid gland for one reason or another is unable to meet such increased demands The goiters thus produced have already been discussed above Hypothyroidism with or without myxedema represents an exhaustion atrophy and may persist often unrecognized following delivery (Roberton 1948)

b Spontaneous Interruption of Pregnancy as a Result of Hypothyroidism —The influence of frank myxedema on pregnancy seems to be well established and generally recognized A number of workers have called attention to the more insidious nature and behavior of subclinical hypothyroidism (Litzenberg 1926 Litzenberg and Carey 1929 Haines and Mussey 1935 Kemp 1939 1947 Delfs and Jones 1948 Buxton and Yann 1948) which the clinician must recognize and treat if he is to do justice to both the patient and her unborn child Emphasis has always been placed on the history of a decrease in menstrual activity in these subjects (Buxton and Yann 1948) but it must not be forgotten that any type of irregularity may exist (Haines and Mussey 1935 Buxton and Yann 1948)

There will usually be corroborative evidence of the underfunction of the thyroid in these subjects Common manifestations are a tendency to gain weight lassitude dryness of the skin coarseness of the hair brittleness of the fingernails and some degree of mental or emotional unrest In such patients habitual abortion is frequent indeed Delfs and Jones (1948) found it to be the commonest etiological factor in their series of patients developing that condition In goitrous areas the iodine deficiency with its secondary lowering of thyroid function has been and remains a potent factor in influencing the incidence of miscarriage and

material preferentially available to the developing embryo In managing the calcium problem clinically Lozeau (1950) has found the administration of a nontoxic vitamin D more satisfactory than the ingestion of additional calcium In his opinion the average pregnant woman tolerates the latter poorly and maintains satisfactory calcium balance without it by virtue of the better absorption obtained from the use of the vitamin D preparation

5 **Miscellaneous Effects of the Increased Thyroidal Activity of Pregnancy**—With present improved technics it might be well to repeat Anselmino and Hoffmann's studies (1930 1931) in which there was demonstrated an increase in the capacity of serum of pregnant women to mobilize glycogen from the liver and to increase the formation of acetone bodies and lactic acid While their results have already been partly supported (Soule 1932 Thiessen 1934) they have also been questioned (Neuweiler, 1933 1935) However these earlier results are in keeping with the hypertrophy of the adrenal cortex which is known to occur in all states of hyperfunction of the thyroid (see Thyroid Adrenal Relationship Chapter XIV) and may be due at least in part to the change in adrenal function which occurs during pregnancy

THE INFLUENCE OF ABNORMAL THYROID FUNCTION ON PREGNANCY AND THE FETUS

Physiological changes in thyroidal function during normal pregnancy are extremely important to the welfare of the mother and child The failure of the thyroid to respond satisfactorily or the appearance of an unrecognized abnormally vigorous response may be fraught with tragic consequences for both the host and her developing embryo

1 **The Effects of Hypothyroidism**—Underfunction of the thyroid in pregnancy may be brought about by a deficiency in the ingestion of iodine by previous damage to the thyroid or by inability of the gland to respond to the added burden of gestation The clinician should suspect the condition if during the first two or three months of pregnancy the patient persistently complains of lassitude and inability to accomplish simple routine duties If prior to pregnancy there has been menstrual abnormality (Buxton and Mann 1918 Krigbaum 1917 Roberton 1918) then the suspicion should be all the greater These findings should warrant more complete historical as well as other investigational procedures directed toward uncovering a hypothyroidism

Such underfunction of the thyroid is usually not associated with myxedema nor with any sharply defined reduction in the basal metabolic rate (see hypothyroidism without myxedema Chapter XXV) One group of investigators (Peters Man and Hememann 1948 Hememann Johnson and Man 1948) emphasize the importance of the values for serum precipitable iodine in the diagnosis of borderline cases They

of bringing gestation to term are decreased if the mother is not treated Of Stockl's cases 21 per cent were delivered prematurely (1918)

On the other hand should the nervousness emotional instability altered appetite and vegetative nervous system symptoms sometimes observed in pregnancy be mistaken for hyperthyroidism when taken in conjunction with a moderately elevated basal metabolism a poorly conceived medical regime employing some one of the antithyroid compounds could do untold harm to mother and baby alike Contrariwise if the diagnosis is carefully made and medication accurately applied there is today no need to add the burden of thyroidectomy to the already considerable physiological task entailed in going through the gestational period

The treatment of the pregnant patient who has hyperthyroidism is like that of any other patient with the disease a matter for individualization Nevertheless in some fundamentals pregnancy itself creates a difference In the first place pregnancy alters metabolism so that the full extent of the hyperthyroidism is often difficult to evaluate Furthermore hyperthyroidism first occurring during pregnancy not infrequently disappears shortly following its termination never to recur Garcia Gallego (1947) observed this type in 10 per cent of all pregnant women

Readjustment to radical measures such as surgery during pregnancy *may entail periods of abnormal thyroid activity resulting in an* unrecognized stress upon the thyroid of the child which normally begins to function between the fourteenth and sixteenth weeks of intrauterine life (Chapman Corner Robinson and Evans 1948) For these reasons we favor the most conservative course possible in managing the subject with hyperthyroidism complicating pregnancy Irrespective of how the condition is treated it cannot be overemphasized that the control of the *thyrotoxicosis is of prime importance There is no need to interrupt the* pregnancy if necessary thyroidectomy may be done at any time during the period of gestation There are those who favor a standard method of preparation with an antithyroid compound of iodine followed by subtotal thyroidectomy (see treatment of hyperthyroidism Chapter XXXVIII)

In view of the discovery of the antithyroid compounds we now see *no need to subject our thyrotoxic pregnant patients to surgery at least* not until the period of gestation is completed

A number of cases of hyperthyroidism with pregnancy have now been treated with thiouracil or one of its closely allied derivatives (Astwood 1944 McGavack et al 1944 Rose and McConnell 1944 Davis 1944 Palmer 1945 Davis and Forbes 1945 Eaton 1945 Astwood and VanderLaan 1946a Carns and Poser 1946 Sexton 1946 Vogt 1946 Williams 1946 Stepto 1946 Whitelaw 1947 Mussey Haines and Ward 1948 Acton and Cottrell 1949 Caren 1949 Ryan and Kooperstein 1949 McGavack 1949a Sislaw and Kraff 1950)

stillbirths (Kemp 1909 1917) He very pertinently observes that supplementation of the diet with iodine especially during pregnancy and lactation is indicated in the interests of both the mother and her offspring

c *Fetal Abnormalities*—In goitrous districts a majority of the children may be born with a thyroid enlargement This can be completely prevented by the prophylactic use of iodine If the mother is goitrous the chances of finding an enlarged thyroid in the fetus are increased as much as twofold (Hulesman 1918) Gestation is unduly prolonged in the thyroid deficient or goitrous subject so that the babies of such mothers are heavier than others at birth This per se may give rise to certain forms of dystocia thus further increasing morbidity and mortality for mother and child If the thyroid deficiency in the mother is severe and the iodine lack uncompensated then various congenital abnormalities particularly pertaining to bony growth and somatic development occur in the child These have been detailed under cretinism (Chapter XXIX)

2 The Effects of Hyperthyroidism – In a section devoted primarily to a discussion of physiological relationships of the thyroid to the pregnant state we feel that no apology is needed at the present time for introducing certain questions relating to hyperthyroidism in the pregnant woman Errors regarding the diagnosis and treatment of hyperthyroidism in pregnancy seem to be based upon some physiological and pharmacological misconceptions that may be best discussed apart from our general consideration of thyrotoxicosis (q v)

Because severe thyrotoxicosis itself often causes sterility it is a relatively rare complication of pregnancy (Mussey Plummer and Boothby 1926 Wallace 1933 Portis and Roth 1939 Stepto 1916 Whitelaw 1917 Hulesman 1918 Mussey Haines and Ward 1918) The incidence of hyperthyroidism in pregnancy has been reported as varying from 0 008 to 3 7 per cent of all pregnancies (Javert 1940) with an average figure of about 0 2 per cent (Mussey Haines and Ward 1918)

Thyrotoxicosis in the pregnant individual does not differ from that in the nonpregnant but it is important before establishing treatment to be sure that we are dealing with a true hyperthyroidism Mussey Plummer and Boothby (1926) made the matter clear We believe the metabolism must be elevated well above normal and probably above plus 30 per cent and a hyperplastic thyroid gland with tachycardia and definite activation should be present before a final diagnosis of hyperthyroidism in pregnancy can be safely established Untreated thyrotoxicosis in pregnancy may cause considerable damage to the mother of a kind described in discussing the subject in general (see thyrotoxicosis complications Chapter XXVII) and the added burden of pregnancy tends to increase the possibility of such complications Untreated thyrotoxicosis in the parent does no apparent harm to the child although the chances

ism of the fetus The gestational period has been prolonged by the use of antithyroid compounds (Grossowicz 1946)

Thiouracil compounds are readily diffusible and have been found in high concentration in the milk of lactating women (Williams Kay and Jandorff 1944) Similarly retarded growth has been produced in the sucklings by feeding thiouracil to lactating rats (Williams Weinglass Bissell and Peters 1944)

In the work with animals as a general rule the doses of the antithyroid compounds have been comparatively large often as much as 100 times the amount that would be given to a human being on a proportionate weight basis Even under such conditions the fetus suffers little as its thyroid appears to bear the brunt of and to compensate for the untoward effects

Care must be taken to avoid three things in administering thiouracil and its derivatives to pregnant women with thyrotoxicosis

1 The basal metabolism must not be brought below the normal figure for pregnancy we like to maintain it between +20 and +30 preferably nearer the upper figure

2 A mother who during pregnancy has taken or during the puerperium continues to take a thiouracil derivative must not nurse her child The drug may be carried in effective quantities via the milk

3 An enlarged thyroid gland may occur in the child of a woman who has used an antithyroid compound during pregnancy The full significance of this finding will have to await further observation and analysis It is certainly an undesirable feature of the use of thiouracil derivatives even in the present state of our knowledge for it affords unequivocal evidence that the child s pituitothyroid mechanism can be directly affected by the compound administered to control its mother s thyrotoxicosis It is now established that the thyroid of the fetus begins to function between the fourteenth and sixteenth weeks of intrauterine life (Chapman Corner Robinson and Evans 1948) and while capable of acting in part in conjunction with the thyroid of the mother seems also capable of an autonomous function of considerable degree

In the pregnant woman advantages of the treatment of thyrotoxicosis with antithyroid compounds are the simplicity of administration and the lack of any need for interfering in any way with her usual routine of living Thus far the results seem to indicate that such therapy can be carried out safely and that the thyroid enlargement in the offspring if and when occurring disappears spontaneously within several weeks after birth

In applying antithyroid compounds to the thyrotoxicosis of pregnant women several points must be stressed and a routine scrupulously followed

1 Observations of the patient including laboratory examinations shall be made as for nonpregnant patients (see hyperthyroidism Chapter XXXVIII)

Of Eaton's (1915) two patients one delivered a child with a large thyroid which receded to normal in several months The child of the other patient was normal Vogt's (1916) patient delivered a normal child although the mother developed a large thyroid—rather definite evidence of overtreatment

The patient of Davis and Forbes (1915) *died suddenly without* explained cause during the sixth month of pregnancy The fetus's thyroid was large and hyperplastic Freiesleben and Kjerulf-Jensen (1917) successfully controlled hyperthyroidism in their patient, but interrupted pregnancy in the fifth month because of complicating heart disease The fetal thyroid was hyperplastic

In Stepto's patient (1946) thiouracil was stopped because of a granulocytopenia a normal baby was later delivered

Palmer (1945) treated three pregnant women two of whom delivered normal children the outcome in the third instance was not stated

Normal babies were delivered of the mothers whose pregnancies were reported as follows by Astwood (1944) four cases McGavack Gerl Vogel and Schwimmer (1944) one case Rose and McConnell (1944) one case Davis (1944) one case Williams (1946) five cases Carns and Poser (1946) one case Astwood and Vanderlaan (1946a) three cases Sexton 1946) two cases, Vogt (1946) one case, Mussey, Haines and Ward (1948) one case treated for the first two months only Acton and Cottrell (1949) one case treated for the first three months only, Caren (1949) one case McGavack (1949a) five cases, Saslaw and Kraff (1950) one case Undoubtedly many other patients have been followed during pregnancy while under treatment with antithyroid compounds but if one summarizes only those here reported excluding that of Stepto (1946) it is noted that of 34 babies the condition of one was not reported three had large hyperplastic glands while 30 appeared normal in all respects In two of the three with large glands gestation was not brought to term because of maternal complications the fetuses appeared healthy except for the hyperplastic thyroids The third baby with a large gland was delivered normally and showed normal progression in all regards with a recession to normal in the size of the thyroid by the end of the third month of extrauterine life

The young or small laboratory animals fed an antithyroid compound during gestation have been found to have large thyroids (Andrews and Schnetzler 1945 Goldsmith Gordon and Charipper 1944 1945 Webster and Young 1948 Goldsmith 1949) but subsequent growth and development have not been disturbed This thyroid enlargement has been shown to take place fairly early in embryonic life at least in the case of the guinea pig (Mitskevich 1948) thus suggesting that the effect of the antithyroid compound is exerted directly on the pituitothyroid mechan

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2 Toxicity shall be watched for and treated as in the nonpregnant individual

3 A level for the basal metabolism shall be maintained at or slightly above the normal for a patient who is pregnant, that is between +20 and +30 per cent It shall under no circumstances be brought down to 'normal i e +5 to +10 per cent

4 Administration of iodine shall be begun as soon as the manifestations of the thyrotoxicosis are controlled and shall be continued throughout the pregnancy Small doses that is, not exceeding one minim of Lugol s solution daily, are best

5 The baby shall not be allowed to suckle the mother

6 No treatment shall be given to the baby who shows a large thyroid at least not until four to six months have elapsed As a general rule, such enlargement disappears spontaneously Furthermore there is reason to believe that this complication of the treatment will not arise if the patient is properly treated with *small* doses of iodine during the period of antithyroid compound administration

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of the classifications now in use including his own His arrangement is derived from a combination of functional pathological and anatomical terminology It is obvious therefore that overlapping must occur and that in some instances the terms themselves may be misleading Nevertheless his scheme brings some degree of clarity into a chaotic field and has with modifications been used by us for several years

The term simple goiter is faulty a point Means has already emphasized Nevertheless it still affords the clinician a useful concept of a certain group of thyroid disturbances without employing some descriptive adjective such as colloid which necessarily excludes certain cases that should remain together While objection may be raised to the term hyperthyroidism our reasons for using it are described in detail under that subject (Chapter XXXIV) It seemed preferable to thyrotoxicosis which infers that some nonphysiological substance of a toxic nature is present We have avoided the term *toxic goiter* which *carries the implication of an enlargement of the* gland

In view of its probably unique etiology and simply defined clinical picture (Maher and Sittler 1936 Brain and Turnbull 1938 Marine 1938 Means Hertz and Williams 1941 Mulvany 1941 Schall and Reagon 1945 Soley 1942 1941) malignant exophthalmos has been treated separately as the ophthalmopathic form of Graves disease

The term nontoxic nodular goiter has been returned in a restricted sense because it offers the simplest method of categorizing a clinically recognizable group of conditions

It is realized that some conditions might have been placed as easily in one category as in another for instance athyroidism is mentioned under the congenital anomalies it might also be added under thyroid insufficiencies Moreover by redefinition the term might be made to include an etiology in surgery or in disease Such duplications and ramifications seem hardly justified in the interests of simplicity and brevity Questionable categories such as the sarcomas have been completely and purposely omitted

Many purely descriptive terms have crept into the codification of thyroid disease There is nothing in the present classification which precludes their use in the particular cases to which they may be applicable For instance it is perfectly proper and helpful clinically to speak of nodular colloid goiter multiple adenomata diffuse multiple adenomata colloid goiter with cystic degeneration and calcification *adenoma or adenocarcinoma with Hurthle cell change* and so forth

A simple flexible and easily taught classification of thyroid diseases is detailed in Table VIII However it is far from perfect

SECTION III

Morbid States

Thomas Hodge McGavack

Chapter XIV

CLASSIFICATION OF THYROID DISEASE

The classification of thyroid disease should afford a veritable field day to lexicographers despite the likelihood of confusion in programming the events and in establishing the criteria and rules governing entry into each. An etiological arrangement would undoubtedly be most satisfactory from the clinician's viewpoint. However in spite of our increasing knowledge of the biochemistry physiology and pathological physiology of the thyroid the cause of many of the disorders which commonly require the clinician's attention are as yet unknown. Any attempt at a purely anatomical classification seems to be meaningless in view of the kaleidoscopic alterations in living thyroid follicles (Williams 1937) which occur in normal glands. Moreover the histopathological changes associated with morbific processes within the thyroid have been summarized (Graham 1911) and shown to bear no specific relationship to the problems with which the clinician must cope.

In view of the above the major objective of any classification is simplification with a view to facilitating our mutual understanding of the diseases which may affect the thyroid. The ultimate goal is the establishment of reliable criteria for the recognition and management of disturbances within that gland. Judged in the light of this goal every classification thus far made has been a compromise unsatisfactory in some particular to biochemist physiologist anatomist pathologist and internist. Means (1937) has critically discussed a number

of the classifications now in use including his own His arrangement is derived from a combination of functional pathological and anatomical terminology It is obvious therefore that overlapping must occur and that in some instances the terms themselves may be misleading Nevertheless, his scheme brings some degree of clarity into a chaotic field and has with modifications been used by us for several years

The term simple goiter is faulty a point Means has already emphasized Nevertheless it still affords the clinician a useful concept of a certain group of thyroid disturbances without employing some descriptive adjective such as colloid which necessarily excludes certain cases that should remain together While objection may be raised to the term hyperthyroidism our reasons for using it are described in detail under that subject (Chapter XXXIV) It seemed preferable to thyrotoxicosis which infers that some nonphysiological substance of a toxic nature is present We have avoided the term toxic goiter which carries the implication of an enlargement of the gland

In view of its probably unique etiology and sharply defined clinical picture (Maher and Sittler 1936 Brain and Turnbull 1938 Marine 1938 Means Hertz and Williams 1941 Mulvany 1941 Schall and Reagon 1945 Soley 1942 1944) malignant exophthalmos has been treated separately as the ophthalmopathic form of Graves disease

The term nontoxic nodular goiter has been retained in a restricted sense because it offers the simplest method of categorizing a clinically recognizable group of conditions

It is realized that some conditions might have been placed as easily in one category as in another for instance athyroidism is mentioned under the congenital anomalies it might also be added under thyroid insufficiencies Moreover by redefinition the term might be made to include an etiology in surgery or in disease Such duplications and ramifications seem hardly justified in the interests of simplicity and brevity Questionable categories such as the sarcomas have been completely and purposely omitted

Many purely descriptive terms have crept into the codification of thyroid disease There is nothing in the present classification which precludes their use in the particular cases to which they may be applicable For instance it is perfectly proper and helpful clinically to speak of nodular colloid goiter multiple adenomata diffuse multiple adenomata colloid goiter with cystic degeneration and calcification adenoma or adenocarcinoma with Hurthle cell change and so forth

A simple flexible and easily taught classification of thyroid diseases is detailed in Table VIII However it is far from perfect

TABLE VIII

CLASSIFICATION OF THYROID DISEASE

(Modified From Thyroid Committee of the New York Medical College)

I	Congenital anomalies
	A Heterotopic thyroid tissue—lingual and sublingual thyroid tracheal thyroid intrathoracic goiter (congenital) ovarian struma lateral aberrant thyroid athyreosis rarer forms of heterotopia
	B Thyroglossal duct cysts sinuses and fistulae
II	Intrathoracic goiter (acquired)
III	Thyroiditis
	A Acute—nonsuppurative suppurative
	B (1) Subacute (2) pseudotuberculous (3) giant cell
	C Chronic simple Riedel's Hashimoto's specific infectious (actinomycosis syphilis and tuberculosis)
IV	Iodine deficiency goiter (subiodic goiter simple goiter colloid goiter iodine want goiter)—pubertal adolescent gestational menopausal endemic sporadic
V	Hypothyroidism—adult with and without myxedema cretinism infantile myxedema juvenile myxedema
VI	Nontoxic nodular goiter (thyroiditis and carcinoma treated separately)—arising from (a) preexisting subiodic goiter (b) preexisting Graves disease and (c) fetal adenoma
VII	Carcinoma—epidermoid papillary adenocarcinoma fetal type of adenocarcinoma small round cell carcinoma large round cell carcinoma epidermoid carcinoma adenocarcinoma with Hurthle cell change
VIII	Hyperthyroidism
	A Graves disease (exophthalmic goiter)—with exophthalmos without exophthalmos intermediate forms forme fruste
	B Plummer's disease (toxic adenoma)—arising from (1) the normal gland (2) simple goiter (3) preexisting simple goiter (4) preexisting Graves disease (5) preexisting thyroiditis and (6) fetal adenoma
IX	Malignant exophthalmos (ophthalmopathic Graves disease)
X	Amyloid disease
XI	Hodgkin's disease
XII	Sclero lympho lipomatosis
XIII	Sarcoidosis

Undoubtedly a major fault is its failure to indicate the transitions which may take place from one form of goiter to another or from one functional state to another For instance Graves disease may terminate spontaneously as a hypothyroidism or as a myxedema Simple goiter and thyroiditis may end in hypothyroidism Nodular goiters may become toxic or undergo malignant degeneration and so forth

Chapter XX

DISTURBANCES OF THE THYROID GLAND DUE TO OR CLOSELY ASSOCIATED WITH CONGENITAL ANOMALIES I EMBRYOLOGY AND ANATOMY

The thyroid gland is derived from one median and two lateral primordial structures (Weller 1933) The main mass of the gland de velops from the median anlage This arises from the floor of the primitive pharynx between the first and second pharyngeal pouches where the tuberculum impar and the two lateral anlagen of the tongue join This evagination is first seen as an entodermal pocket in the 2 0 mm embryo that is at about the middle of the third week of gestation and rapidly grows into a pyriform body occupying the midline well in front of the lower end of the primitive larynx By the end of the fourth week of intra uterine life (about 3 mm embryo) this spherical body has become bilobed but remains attached to its original point of origin in the pharynx by a pedicle or narrow neck the thyroglossal duct Normally this duct atrophies toward the end of the fifth week of intra uterine life but the point at which it was attached to the pharynx remains permanently as a depression in the tongue the fora men cecum which lies behind the apex of the V shaped row of the circumvallate papillae

As the median thyroid anlage descends into the neck it retains a connection superiorly with the tongue by means of the long thyro glossal duct Toward the latter half of the second month of embryonic life the developing hyoid bone divides the thyroglossal duct into an upper and a lower portion Under normal conditions each section of the divided duct completely atrophies by the end of the eighth week However rests of cells may remain anywhere along this tract In post natal life these may give rise to cysts sinuses fistulas or accessory thyroids

Should the lower end of the thyroglossal duct fail to atrophy a pyramidal lobe pointing upward from the fully developed thyroid may be formed

During the seventh week of intra uterine life the median anlage of the thyroid assumes a transverse position Each of its two lobes grows laterally until its outer edges encounter the carotid artery Further development is directed cephalodorsally along this vessel thus form

ing in conjunction with its fellow of the opposite side the U shape which the adult thyroid gland possesses At this time, the median thyroid plate has come to intervene between the laterally placed third branchial complex and the more medially situated complex from the fourth branchial pouch

Shortly after the median anlage of the thyroid can be identified the lateral thyroid components appear in connection with the fourth entodermal pouch and its evaginations on each side

From a study of 139 human embryos varying in crown rump length from 1 to 300 mm Norris (1937) has described six somewhat overlapping stages in the development of the lateral anlagen of the thyroid beginning with their first appearance as the fourth entodermal pouches about the middle of the third week until their differentiation into parathyroid and thyroid tissue and the complete incorporation of the latter into the main mass of the thyroid toward the end of the sixteenth week It is clinically important to remember that at first these lateral thyroid components lie laterally and inferiorly with regard to the median anlage However by the end of the seventh week they have migrated forward and upward to contact the posterior and lateral surfaces of the median thyroid They finally become completely fused with it in such a manner that they are surrounded by and fully incorporated into the main thyroid mass In conjunction with this migration and fusion the cells in the lateral anlagen contributed by the fourth branchial cleft come to resemble those arising from the median thyroid Thus the lateral thyroid components contribute from one fourth to one third the total mass of follicular tissue found in the thyroid of the human fetus (Norris 1937)

By the end of the eighth week of gestation discontinuous cavities representing the follicular structure begin to form throughout the fetal thyroid This evolutionary process is completed by the sixteenth week of intrauterine life Shortly after the follicles begin to appear colloid may be seen within them thus suggesting that the gland has at this early stage developed an ability to store iodine (Gorbman and Evans 1943) a fact now proved through the use of tracer doses of radioactive iodine (Chapman Corner Robinson and Evans 1948) This follicular differentiation begins with the periphery of the thyroid and gradually extends to the deeper portions

Interference with the development of the embryonic thyroid at any one of the stages mentioned above may result in the production of one or more anomalies of clinical interest and importance

Chapter XXI

DISTURBANCES OF THE THYROID GLAND DUE TO OR CLOSELY ASSOCIATED WITH CONGENITAL ANOMALIES II HETEROTOPIC THYROID TISSUE

It is clear from what has been said in the preceding chapter that an arrest in the descent of the median anlage of the thyroid or in the upward and forward migration of the lateral anlagen may leave in its wake abnormally placed islands of functioning thyroid tissue

The mildest and most common anomaly associated with the development and descent of the median anlage is the presence of a so called pyramidal process or median lobe This pyramidal process is a nonabsorbed portion of the thyroglossal tract which has been most commonly observed clinically in districts of endemic goiter It probably develops in response to an increased functional need for thyroid tissue at a period of intra uterine life when absorption of this portion of the gland should normally take place At the other extreme of embryonic maladjustment we may find complete absence or agenesis of the median thyroid anlage or of the entire thyroid gland Such agenesis however is usually associated with other serious congenital defects which are rarely compatible with life

1 LINGUAL, SUBLINGUAL, AND PRELARYNGEAL THYROIDS

Of clinical significance in connection with the descent of the median anlage of the thyroid gland are the masses of aberrant thyroid tissue which may be discovered at the base of the tongue (lingual thyroid) below the tongue (sublingual thyroid) or in front of the larynx (prelaryngeal thyroid) In the order named these forms of aberrant thyroid represent decreasing degrees of interference with the descent of the median anlage during intra uterine life Two brief but satisfactory summaries of the condition have been made recently (Recio and Yambao 1948 Dorenbusch 1949)

Incidence—The lingual thyroid located at the base of the tongue around the foramen cecum is much more common than the sublingual variety Both types are noted about three times as frequently in women as in men They usually pass unnoticed until the time of puberty when the increased functional demand upon the thyroid causes en

ing in conjunction with its fellow of the opposite side the U shape which the adult thyroid gland possesses At this time the median thyroid plate has come to intervene between the laterally placed third branchial complex and the more medially situated complex from the fourth branchial pouch

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Interference with the development of the embryonic thyroid at any one of the stages mentioned above may result in the production of one or more anomalies of clinical interest and importance

hemorrhage into the abnormally situated gland It must be emphasized that the ability to produce symptoms depends directly upon the size of the mass Therefore many instances of thyroid masses along the remnants of the thyroglossal duct are completely asymptomatic and are discovered only at the time of postmortem examination

These tumors particularly the lingual variety may be large enough to be seen by direct vision but the smaller ones must be visualized through the laryngoscope They appear as rounded or lobulated highly vascular pinkish to brownish tumors Those above the hyoid bone can rarely be seen or felt externally In the rare instances in which the masses occur below the hyoid it may be possible to palpate them Ulceration occasionally associated with hemorrhages of alarming proportions may occur when the tumor mass is large

Despite the long recognized functional capacity of these heterotopic thyroid masses which can be readily demonstrated by the use of radioactive iodine (Nachman Crawford and Bigger 1949 Schilling Karn and Hursh 1950) it was not until recently that hyperthyroidism has been reported as a result of their activity (Buck and Guthrie 1949) On the other hand cretinism is a relatively common association believed to occur in approximately 10 per cent of subjects with a lingual or a sublingual thyroid gland

A syndrome has been described in which a lingual thyroid has been associated with complete absence of normal thyroid tissue cystic changes in the pituitary and dwarfism This has been called the syndrome of Wells (1935) who believes that the dwarfism is secondary to a deficiency of the internal secretion of the thyroid

Treatment—No treatment is indicated unless the abnormally placed thyroid produces definite symptoms of a mechanical nature Surgical removal is then necessary In undertaking this however it must be kept in mind that this abnormally placed gland may be the only functioning thyroid tissue the individual has Even though this is so the aberrant tissue should be removed as completely as possible and thyroid deficiency compensated by the feeding of thyroid hormone While the initial operation is difficult due to the relative inaccessibility of the area reoperation in the face of distortion due to scar is well nigh impossible

In conjunction with the rather formidable surgical procedures which have in the past been necessary for dealing with lingual thyroids the recent report of Schilling Karn and Hursh (1950) relative to the therapeutic use of I^{131} is of importance Such therapy may be quite logically applied to a majority of lingual thyroids as most of them possess normally functioning thyroid tissue They may indeed be the only source of such tissue as in the case just cited Therefore they should be treated only when distressing symptoms arise A total of 11.4 millicuries of I^{131} was given the above mentioned patient with a calculated radiation

lugement However Witte Meils and Frusler (1916) have reported the case of an 8 year old girl in whom enlargement of the abnormally placed thyroid began following infection and progressed to produce serious mechanical symptoms This response was probably the more marked as the lingual growth represented the only thyroid tissue which the patient possessed One of Goetsch's (1918) three patients also was only 8 years old In that case the mass was discovered in the course of routine physical examination but had been the cause of slowness in mastication and swallowing for at least two months previously In from 5 to 10 per cent of the subjects with a lingual or sublingual thyroid there is no normally located thyroid tissue a point to be kept in mind in treating the condition In any event the mechanical symptoms and signs must be dealt with first and no remnant of the aberrant tissue left even though such a course results in hypothyroidism or myxedema

Pathological Anatomy — In normal individuals a few thyroid follicles are found at the base of the tongue about the foramen cecum These are in sharp contrast to the single centrally placed tumor mass in the same region to which we give the name lingual thyroid This mass is smooth or slightly lobulated and is usually covered by a perfectly normal mucosa Its gross appearance varies from pink to brown depending upon the degree of vascularity It may vary in size from that of a pea to that of a pullet's egg (0 7 to 7 5 cm) It rarely causes symptoms until it reaches the size of a marble (about 1 5 cm) Histologically its appearance is that of normal thyroid tissue about 85 per cent of Montgomery's (1935 1936) collection of cases showing no abnormal types of cells Occasionally however cystic degeneration may occur when the commonly firm but elastic consistency may give way to fluctuation Carcinomatous degeneration has also been described but must be exceedingly rare At least one case histologically malignant and clinically benign has been described (Wipshaw 1942) Montgomery (1935 1936) found five cases in the literature between 1910 and 1935 in which carcinoma was present and ran a usually fatal course Dwarfism and cystic changes in the pituitary are associated pathological conditions which have been noted occasionally Sometimes more than one mass is present and occasionally one of such aberrant growths may not be in the midline (Kidd 1945)

Clinical Picture —The most common symptom encountered in lingual and sublingual thyroids is difficulty in swallowing which varies in severity with the size of the tumor mass Later spells of coughing and dyspnea occur In the prelaryngeal variety of aberrant thyroid the onset of symptoms is somewhat in the reverse order with coughing and extreme dyspnea prominent Hoarseness and other disturbances of speech often attract attention A rapid enlargement and sudden intensification of symptoms particularly the dyspnea may follow

descent differentiation and incorporation of the ultimobranchial bodies of the two sides a difference which could readily account for aberrant tissue more commonly on the left On inspection the intratracheal thyroid mass appears as a lobulated smooth surfaced ovoid or rounded tumor about 0 5 to 2 0 cm in diameter, which is usually surmounted by normal mucous membrane that may or may not show some tendency toward transformation to an epithelium of squamous type As a rule, the cut surface reveals a simple type of colloid goiter and in two thirds of the cases a coexistent extratracheal goiter has been described Both hyperthyroidism and cancer have been observed in conjunction with intratracheal goiter when there have been no changes in the normally placed thyroid pointing to either condition However both are rare complications

Clinical Course and Diagnosis —The manifestations of intratracheal goiter vary directly with the size of the mass and are due to pressure upon surrounding structures or to stenosis of the respiratory passages The mass may therefore give no symptoms and be found only in the course of autoptic examination As a rule the progression of symptoms is gradual and the relative anoxia accompanying the stenosis may be compensated by polyglobulia and eosinophilia for considerable periods of time prior to the appearance of subjective complaints Thoren (1947) believes that symptoms have been present in the average case for from four to five years prior to operation or exitus By far the most common and earliest appearing symptom is dyspnea which may be accompanied by a feeling of a lump or foreign body in the throat that gives rise to an irritating cough Later hoarseness occurs as a result of mucosal catarrh or involvement of the recurrent laryngeal nerve Then the dyspnea may give way to laryngeal stridor worse in the expiratory phase As a rule the intralaryngeal or intratracheal tissue preserves its thyroidal function a fact of some importance in diagnosis and differential diagnosis Physiological periods of stress such as puberty pregnancy marriage and so forth give rise to a hyperplasia of the aberrantly located thyroid tissue with an increase in its size that aggravates the dyspnea and hoarseness

On laryngoscopic examination the mass usually appears as a rounded smooth incurving in the lateral subglottic space At times a rounded delimited shadow without dislocation of the trachea can be made out by soft tissue roentgenography of the cervical region Such a shadow is in sharp contrast to the elongated somewhat spool shaped construction which an extratracheal goiter will produce when it grows about the trachea This differentiation is often important as the two conditions may coexist in such instances should thyroidectomy fail to relieve the stenotic manifestations thorough search must be made to exclude an intratracheal goiter the secondary hyperplasia of which may

to the aberrant thyroid of approximately 11 000 roentgen equivalents physical As a result the mass, originally 4 cm in diameter, decreased to 1 5 cm Pressure phenomena disappeared and extensive atrophy and fibrosis occurred The subsequent hypothyroidism has been satisfactorily controlled by desiccated thyroid substance 1 5 grains daily As far as we know this is the first recorded case to have such therapy It is fair to suggest that the procedure here employed may prove to be a method of election in the future

2 INTRATRACHEAL THYROID AND GOITER

Definition —The collective term intratracheal goiter has been used to include normal or diseased thyroid tissue situated within the lumen of trachea While some of these tumors are the result of failure in embryonic development and others represent local invasion from the main body of the thyroid it seems best to consider them all together as the clinical course and management are the same for both types

Incidence Age, and Sex —Thoren (1917) has recently added a case of his own to 79 he was able to call from the world literature since 187 Therefore although rare intratracheal goiter comprises between 6 and 7 per cent of all intratracheal tumors It causes symptoms most frequently between the ages of 15 and 40 years but suffocation of the newborn has been attributed to it and stenotic tracheal manifestations have first been seen in subjects above 65 years of age The condition has been observed three times as frequently in women as in men The left side of the trachea is involved four times as often as the right

Pathogenesis and Pathology —The various theories of the origin of intratracheal thyroid tissue masses have been critically reviewed by Thoren who divides them into two main categories

I Malformation theories which we may also call the v Brun Falk Hulten concepts as these three workers have advanced data that emphasize the primordial faults capable of giving rise to aberrant intratracheally located thyroid tissue

II *Ingrowth theories* or Pfaff Wegelin concepts which are supported by clinical observations and Wegelin's experimental work with rats treated with goiter producing diets

Clinically it makes very little difference to which of these major theories one subscribes and the evidence is rather convincing that the intratracheal condition may arise in some instances in the first and in others in the second way

While these aberrant tumors may be found all the way from the level of the vocal cords to the tracheal bifurcation the majority occur posterolaterally in the caudal portion of the larynx four times as frequently on the left as on the right side This predilection for the left side led Hulten (1937) to emphasize the differences in the embryonic

descent differentiation and incorporation of the ultimobranchial bodies of the two sides a difference which could readily account for aberrant tissue more commonly on the left On inspection the intratracheal thyroid mass appears as a broad based smooth surfaced ovoid or rounded tumor about 0 5 to 2 0 cm in diameter which is usually surmounted by normal mucous membrane that may or may not show some tendency toward transformation to an epithelium of squamous type As a rule the cut surface reveals a simple type of colloid goiter and in two thirds of the cases a coexistent extratracheal goiter has been described Both hyperthyroidism and cancer have been observed in conjunction with intratracheal goiter when there have been no changes in the normally placed thyroid pointing to either condition However both are rare complications

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actually increase the troublesome symptoms and lead to death by asphyxia.

Several other forms of laryngeal and intratracheal tumefaction must be distinguished from a misplaced goiter. It may be impossible to differentiate adenoma, lipoma, and lymphoma without histologic examination. Papillomas and fibromas usually have a narrow constricted base, and the former appear at an earlier age than does the aberrant thyroid. Rare tumors such as endochondroma and osteoma are much firmer than thyroid tissue, a fact which can be confirmed by probing. Moreover, calcium deposits will be seen in roentgen ray shadows of the latter. Tuberculous and syphilitic infections and carcinoma will usually present a different laryngoscopic appearance as well as clinical findings of a confirmatory nature. Bronchial asthma should not be confused with intratracheal goiter, as inspiration is not disturbed, and the expiratory wheeze is free of laryngeal stridor.

Prognosis.—The mortality due to intratracheal goiter is low, provided the patient is operated upon before the lungs and heart are damaged. *The most frequent cause of postoperative death* has been pneumonia, but intratracheal obstruction must be reckoned with, particularly where an endoscopic removal of the mass has been carried out.

Treatment.—Although two cases have been described in which the administration of iodine relieved the distressing symptoms, it seems to us that surgical removal of the aberrant thyroid mass affords the only satisfactory method of treatment. The surgical approach should be through the anterior tracheal wall or via the laryngeal fissure. Endoscopic removal is fraught with considerable difficulty because the lesion is highly vascular and usually broad based; therefore, in most, if not all, instances this therapeutic approach should be avoided. Aggravation of the condition during pregnancy constitutes an additional indication for immediate surgical intervention, as the physiological swelling of the mass due to gestation may in itself be sufficient to precipitate a fatal outcome.

3. ABERRANT INTRATHORACIC THYROID

From the standpoint of embryology, it would appear possible for the median anlage of the thyroid to descend to an abnormal position just above the aortic arch. The presence of such tissue at postmortem examination has been described. However, in no instances have such embryonic rests ever been shown to produce symptoms (Lahey, 1915). Clinically recognizable intrathoracic goiters (Chapter XXIV) have an entirely different origin and are always acquired (Lahey, 1915).

Chapter XXII

DISTURBANCES OF THE THYROID GLAND DUE TO OR CLOSELY ASSOCIATED WITH CONGENITAL ANOMALIES III HETEROTOPIC THYROID TISSUE (CONTINUED)

4 OVARIAN THYROID

Synonyms—Struma ovarii dermo thyroid of the ovary

Definition—Ovarian thyroid is an ovarian teratoid in which thyroid tissue is the predominant and sometimes the only tissue

Incidence Nature, and Pathology—Since 1889 when the presence of thyroid tissue was described in an ovarian dermoid not less than 150 cases of struma ovarii have found their way into the literature according to Emge (1940) and Smith (1946) Of these 40 have been reported within the confines of the United States Struma ovarii represents about 3 per cent of all ovarian teratomata Nevertheless small thyroid glandlike inclusions occur in about 10 per cent of ovarian embryomas About 6 per cent of all struma ovarii have produced metastases which are of a superficial rather than of an invasive character and are entirely confined to surrounding abdominal structures (Emge 1940) These metastases are not incompatible with good general health for long periods of time but eventually account for death in about 50 per cent of the patients in whom they are demonstrable

While much of a controversial character has been written about the nature of ovarian struma it is now generally believed that it is teratomatous in origin It occurs with relative frequency in teratomas of the ovary and very rarely in teratomas of the testis In those instances in which thyroid tissue alone is found in the tumor it is believed that the entodermal elements of the thyroid anlage have undergone excessive development within the teratoma They have thereby crowded out the other tissues either partially or completely (Sanders 1935 Emge 1940)

Grossly the growth appears as an irregularly shaped nodular brownish mass the cut surface of which presents a honeycombed appearance with many small follicles and frequent large even cystic areas filled with colloid Microscopically and in their staining reac-

actually increase the troublesome symptoms and lead to death by asphyxia

Several other forms of laryngeal and intratracheal tumefaction must be distinguished from a misplaced goiter. It may be impossible to differentiate adenoma, lipoma and lymphoma without histologic examination. Papilloma and fibroma usually have a narrow constricted base and the former appear at an earlier age than does the aberrant thyroid. Rare tumors such as endochondroma and osteoma are much firmer than thyroid tissue, a fact which can be confirmed by probing. Moreover, calcium deposits will be seen in roentgen ray shadows of the latter. Tuberculous and syphilitic infections and carcinoma will usually present a different laryngoscopic appearance as well as clinical findings of a confirmatory nature. Bronchial asthma should not be confused with intratracheal goiter, as inspiration is not disturbed and the expiratory wheeze is free of laryngeal stridor.

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only the first group should be considered here but since the clinical considerations are similar both types will be treated together

Definition—By aberrant thyroid tissue of the lateral component we mean any collection of thyroid cells in the neck not in the median line and usually lying laterally to the main thyroid mass and lacking any evidence of any anatomical connection with it

Origin—Speculation regarding the origin of aberrant lateral cervical thyroid masses has been rampant since the turn of the present century Two main theories regarding their formation have been advanced The earlier school of thought suggested that they arose as a result of some abnormality in the development of the lateral anlage of the thyroid More recently the concept has been vigorously championed that lateral aberrant thyroids are actually metastatic carcinomas in the cervical lymph nodes secondary to a primary lesion in the homolateral lobe of the thyroid proper These theories regarding the etiology and histogenesis of lateral aberrant thyroids are largely based upon the observations of embryologists and upon the clinical course and morphology of such tumors in human beings

Many variations of these general concepts have been expounded Schrager (1906) and later Dunhill (1931) expressed the belief that embryological remnants or rests were left in the descent of the lateral anlagen of the thyroid which became hyperplastic under the stimulation of ordinary physiological demands

Attention was first called to the predominantly papillary nature of these growths by Low (1903) who observed the fact now repeatedly confirmed that they grow slowly show a mild local invasive character along lymph channels with little or no tendency to distant metastases

Dunhill (1931) championed the idea that the lateral anlagen are constitutionally inferior to the median anlage and concluded that any excessive physiological demand upon them was followed by papillary change Cohn and Stewart (1940) in an analysis of 20 cases have further amplified this concept by expressing the opinion that the location of a papillary tumor within or without a lobe of the main body of the thyroid was dependent upon whether or not the embryonic cellular rests were separated from the lateral component before or after fusion with the main mass of the thyroid In those cases in which similar tumors existed in the lateral component and in the homolateral lobe of the thyroid simultaneously they postulated that splitting off must have occurred both before and after fusion of the lateral component with the main body of the thyroid

The later school of thought now widely accepted to the nearly complete exclusion of the earlier concept is that lateral aberrant thyroids represent either thyroid tumors which have been split off the main thyroid mass by mechanical means or metastatic lesions from

tions these tumors usually resemble simple colloid goiter but may simulate the normal gland or various other types of goiter In the malignant forms the picture is usually that of a cystadenocarcinoma of thyroid tissue

It is not uncommon to find an asymptomatic normally placed nodular goiter in persons who have an ovarian thyroid

Clinical Picture—An ovarian struma has been shown to behave like other thyroid tissue when tested chemically pharmacologically and biologically (Plaut 1933 Smith 1916) It is not surprising therefore that hyperthyroidism has been reported in connection with such tumors (Plaut 1933) and probably occurs in one out of every fifteen to twenty cases (Emge 1910 McGarrity and Dodson 1918) Nevertheless the presence of thyroid tissue in an ovarian dermoid or teratoma has usually been discovered quite incidentally Some local pelvic symptoms have brought the patient to the physician who discovers on bimanual examination a mass which usually varies in size from 5 to 10 cm but has been known to be much larger Sanders (1935) recorded a case in which the tumor measured 18 by 11 by 11 cm and weighed $3\frac{3}{4}$ pounds

Treatment—Inasmuch as symptoms of ovarian struma are usually mechanical surgical removal is the only logical approach to its management Furthermore the dangers of thyrotoxicosis and of malignant change preclude the use of conservative measures

5 "ABERRANT THYROID TISSUE OF THE LATERAL COMPONENT"

There is at the present so much discussion regarding laterally placed nodules of thyroid tissue which show no discernible gross connection with the main body of the thyroid gland that one hesitates to use the above caption even with quotation marks However it is of such paramount importance to recognize and treat isolated thyroid nodules within the neck whatever their origin that theoretical discussions regarding their manner of development and probably associated pathology are of secondary concern While we might have reserved the present discussion for the section on Nodular Goiter (Chapter XXXII) or that on Carcinoma of the Thyroid Gland (Chapter XXXIII) it has been felt that such a course might have served to minimize its importance and perhaps be construed as ignoring the entire question of their origin

It may be wise to recognize the possibility that some of the laterally placed thyroid tumors of the neck which show no gross connection with the thyroid arise as the result of an arrest in normal embryological processes while others are secondary to abnormal cellular activity within the main body of the thyroid gland Logically

are wholly right or wholly wrong Indeed it seems probable that while the large majority of these tumors arise as metastases from neoplasms of the homolateral *lobe of the thyroid* (Warfield Foote and Farwell 1948) a few may be the result of failure in the normal development migration and incorporation of the lateral anlagen of the thyroid (Cohen and Stewart 1940) Certainly the views of one group cannot at this juncture be accepted to the complete exclusion of the observations of the other

Pathology—The difficulties surrounding the interpretation of thyroid *histology in general (Graham 1924 1941)* are present in connection with the classification of lateral aberrant thyroid masses so that any overall appraisal of the group as a whole may be faulty

TABLE IX

CLASSIFICATION OF TUMORS OF THE LATERAL ABERRANT COMPONENT

	CONDITION	PER CENT
I	Benign lesions	
	a Normally appearing thyroid tissue in lateral cervical location	0.5 - 2.0
	b Nontoxic nodular goiter of the lateral aberrant thyroid	3 4
	c Simple adenoma of the lateral aberrant thyroid	3 4
	d Papillary cystadenoma of the lateral aberrant thyroid	10
II	Malignant tumors	
	a Papillary adenocarcinoma of the lateral aberrant thyroid—*associated thyroid lesions often not found*	65 70
	b Nonpapillary adenocarcinoma of the lateral aberrant thyroid—similar thyroid tumor almost always demonstrable	15 20

The pathological changes seen in tumors of the lateral thyroid components are summarized in the accompanying table (Table IX)

Tumors of the lateral thyroid component containing only normal thyroid glandular tissue appear to be rare Frantz et al (1942) described two cases in which there was simple thyroid tissue without abnormality other than site In other reports representing comparable material and equally careful analysis tumefactions on such a basis have not been recorded The involutional changes of nontoxic nodular goiter represent the commonly reported nonneoplastic lesions of the lateral component Adenoma and papillary cystadenoma are the only

primary growths within the thyroid proper (King and Pemberton 1942 Wolfenbarger Foote and Frizzell 1948 Howard 1949 Warren and Feldman 1949) Several facts support their thesis

1 Papillary change while more frequent in laterally placed tumors does occur in connection with disturbances of medially placed thyroid tissue (Probstein and Agress 1936)

2 The majority of so called lateral aberrant thyroids occupy positions in the neck anatomically identical with the cervical lymph nodes (Figs 29 and 30) If they were connected with the lateral anlagen they should be found along the course of their descent into the neck which is between the carotid sheath and the thyroid lobe laterally and the trachea and esophagus medially At the Mayo Clinic the majority of lateral aberrant thyroid tumors' have been found outside and usually superficial to the carotid sheath (King and Pemberton 1942) Moreover in the same clinic there is no record of the finding of normal thyroid tissue elements lateral to the thyroid gland during the course of routine microscopic examination of material removed in several thousand radical dissections of the neck performed for conditions other than cancer of the thyroid gland

3 More than half of the lateral aberrant thyroid tumors contain tissue of lymph node type i e capsule lymph follicles and peripheral sinuses In the opinion of Ward (1940) and Crile Jr (1939) however the presence of lymphoid tissue in aberrant thyroid tissue is far from bona fide evidence that a metastatic lymph nodal lesion exists for as Graham (1924 1925) pointed out some years ago capsular and lymphatic invasion is common in the purely papillary forms of thyroid carcinoma

4 The frequent occurrence of papillary growth in the main body of the thyroid in conjunction with an aberrant tumor is suggestive of the fact that the primary lesion is in the normally placed thyroid This conclusion is based on the fact that the flow of lymph is outward from the thyroid to the deep cervical lymph nodes Since papillary thyroid growths spread predominantly if not exclusively by lymph channel invasion primary involvement of the lateral tissues of the neck with secondary disturbances in the medially placed thyroid seems unlikely In this conclusion the possibility suggested by Cohn and Stewart (1940) is ignored namely that primary tumors may simultaneously appear in the thyroid and the side of the neck resulting from the presence of lateral embryonic rests in each area

5 The benign thyroid tumors which are found laterally in the neck are believed to be adenomatous masses pinched off mechanically from large goiters by surrounding structures particularly the long neck muscles (Pemberton 1921 Pemberton and Mahorner 1931)

In the last analysis there is no unequivocal evidence that the proponents of either theory of origin of lateral aberrant thyroid tumors

In making this division it may be well to emphasize that all of these lesions should be accepted as potentially malignant irrespective of their histological and clinical benignity The second or *malignant* group of tumors may be further subdivided into those in which the lateral mass or masses were the first noted and major problem of the patient with or without grossly recognizable lesions in the thyroid proper and those in which the lateral masses gave every evidence of being clinically secondary to the lesion within the main body of the thyroid gland

a Incidence Age and Sex—In 1940 Cohn and Stewart were able to collect from the literature 156 cases of tumor of the lateral thyroid component two years later Frantz and his associates (1942) found reports of 251 to which they added 30 of their own Ward (1940) noted that one in 285 thyroid operations was performed for a tumor or tumors of the lateral component In one of the larger clinics the condition has been encountered in approximately one out of each 500 patients with goiter (Cattell 1940 Lahey and Ficarra 1946) There is no uniformity of opinion about the distribution according to sex the condition having been found five times as often in women as in men by one group of observers (Lahey and Ficarra 1946) and with approximately equal frequency in the two sexes by another (King and Pemberton 1942)

While lateral cervical tumors of thyroid origin have been observed at all ages they are most common under the age of 40 (Lahey and Ficarra 1946) The average age of Ward's (1940) twelve patients with a malignant tumor was 34 years of whom three were 51 or more when they came under observation Cohn and Stewart's subjects with papillary types of growth averaged 35 years of age Of Frantz's (1942) 23 patients with a malignancy 14 were 40 years old or less Seven of the remainder had a lesion in the thyroid proper to which the lateral masses were believed to be secondary King and Pemberton (1942) found the highest incidence for women in the fourth decade of life and for men in the third decade In general it appears that when the lateral nodules are predominantly papillary in type and the main or only tumors grossly detectable the age is below 40 whereas when the lateral masses represent lesions clinically secondary in appearance to a tumefaction in the normally located thyroid the subject is older

b Symptomatology—There are no pathognomonic symptoms or signs of tumors of the lateral thyroid component A swelling in some portion of the neck is the manifestation which usually prompts the patient to seek the advice of a physician The average duration of noticeable swelling prior to seeking medical aid is from 1½ (Ward 1940) to 5 (King and Pemberton 1942) years and has varied from 8 months to 15 years Ward (1940) believes the malignant changes in such nodules may have occurred as much as two years before the patient consulted his physician The tumors have been single in from

recorded types of benign neoplasm However in this connection it should be stated that most observers recognize the potential malignancy of these processes King and Pemberton (1942) were unable to classify any of 51 neoplasms of the lateral component as benign and Krantz and his associates (1942) found that 50 per cent of those they had so recognized later behaved in a malignant fashion The question of benignity or malignancy is no more easily solved than it is for thyroid tumors in general (see Carcinoma of the Thyroid Gland Chapter XXVIII)

By far the greater percentage of laterally aberrant thyroid tumors is composed of papillary adenocarcinomas and of these more than 50 per cent represent grade 1 malignancy (grading on the basis of 1 to 4 in which 1 is the least and 4 the most malignant) Histological changes corresponding to grades 3 and 4 are rarely if ever seen In many of the grade 2 tumors of this class the papillary tissue may be mixed with nonpapillary solid carcinomatous tissue In the grade 1 papillary growths long branched fingerlike processes with a lining epithelium one layer thick project into large cystic spaces In grade 2 cases these processes are shorter thicker and tend to be surrounded or interspersed with areas of less well differentiated cells Mitoses are difficult to find in tumors of grade 1 and vascular invasion is rarely if ever encountered Vascular capsular and lymphatic invasion is common when the malignancy is of grade 2

Fortunately nonpapillary adenocarcinoma is less commonly seen than the papillary form In this any degree of malignant degeneration from grades 1 to 4 may be observed with a correspondingly poor prognosis In all or nearly all the cases an associated lesion is demonstrable in the body of the normally placed thyroid Histologically mitoses are abundant in the grade 4 tumors of this type but often very difficult to find in grades 1 to 3 Invasion of the blood vessels occurs more frequently than in the papillary growths but capsular and lymphatic invasions are less prominent features Tumors of grade 4 are wholly undifferentiated and invade all surrounding structures

More than half of the malignant tumors of the lateral component of the thyroid contain lymphoid tissue whereas lymphoid elements appear rarely in the associated lesion of the homolateral lobe

Clinical Course—In sharp contrast to the wide divergence of opinion surrounding the origin of lateral aberrant thyroids is the uniformity of agreement regarding their incidence clinical course and management It seems rather clear from the several exhaustive surveys and reports which have been made recently (Crile Jr 1939b Ward 1940 Cohn and Stewart 1940 King and Pemberton 1942 Krantz et al 1942 Fahey and Lierman 1946) that we may distinguish benign and malignant types of lateral aberrant thyroids

decade is common A more rapid course is observed when the thyroid shows clinically demonstrable involvement

The large majority of all aberrant thyroid tumors lie beneath the sternocleidomastoid muscle and may protrude from beneath it The data of Ward (1940) and of Frantz and his associates (1942) which concern 45 cases and a total of 161 nodules may be readily combined to illustrate the localization of such masses (Fig 29) Eighty-seven per cent of the nodules described lay in direct approximation to the sternocleidomastoid muscle Of these 27 per cent protruded from beneath

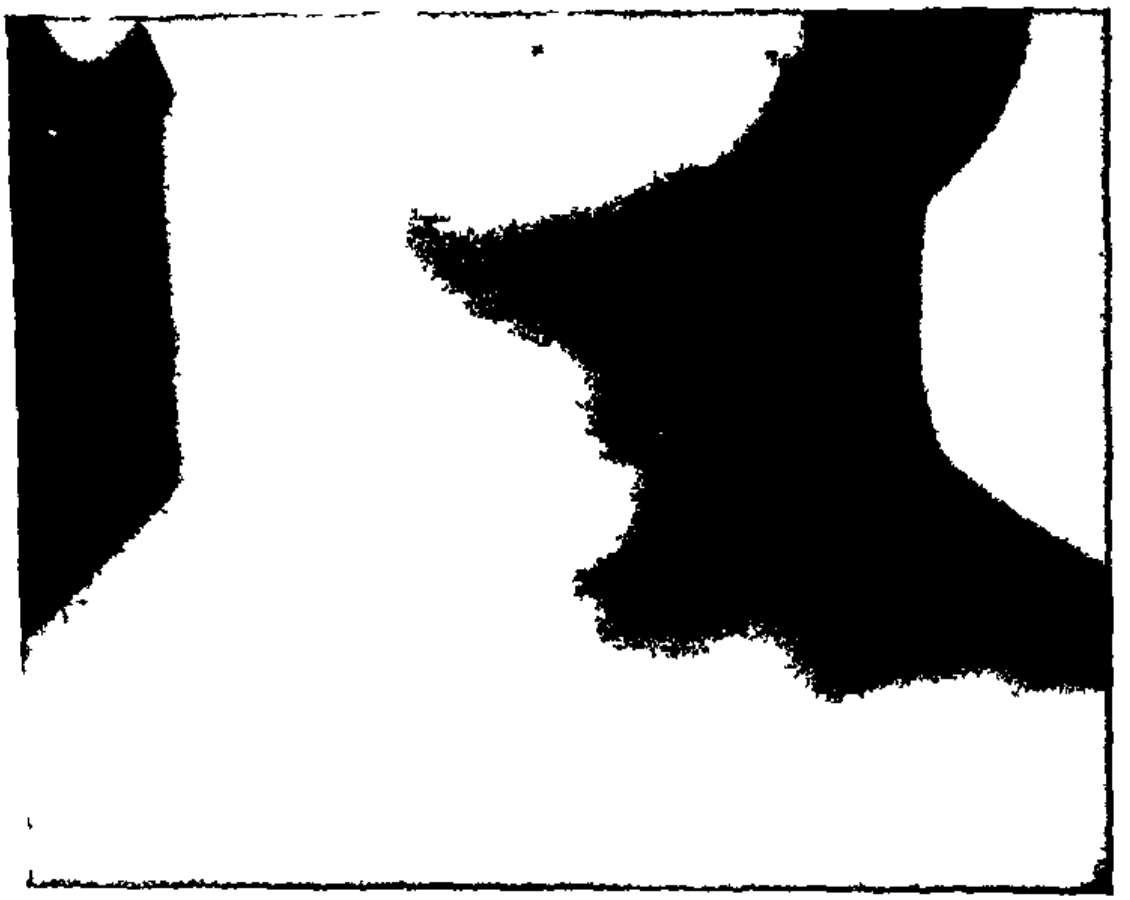


Fig 30—Lateral aberrant thyroid tumor (Case JB 1948) This 23 year-old man had first noticed a swelling in the right submaxillary triangle approximately five months prior to seeking medical advice The had been little change in size during that time A apparently benign papillary cystic tumor and a small right lobe of the thyroid were removed at the time of operation While direct extension of the thyroid proper might have caused a primary tumor of microscopic size no such lesions were found in the multiple sections made

this muscle into the posterior triangle and 34 per cent from under its mid portion toward the superior carotid and submaxillary triangles (Fig 30) Twenty six per cent were noted in relation to the lower third of the sternocleidomastoid muscle some lying deep thereto with the majority palpable in the inferior carotid triangle Rarer sites of aberrant thyroid nodules of the neck have included the suprasternal and supraclavicular fossae King and Pemberton (1942) placed the lesion

one fourth (Ward 1910) to one third (King and Pemberton 1912) of the reported cases and multiple in the remainder As many as 16 nodules have been found in a single patient at operation (Ward, 1910) in 12 patients with malignant lesions of lateral thyroid tissue a total of 86 tumors have been noted (Ward 1910)

Commonly these tumors of the neck are completely asymptomatic Occasionally they are tender and less frequently painful Some of the patients develop pressure symptoms, in such instances a thyroid mass is usually demonstrable which is histologically identical with the aberrant tumor Sometimes the pressure phenomena are quite marked or bizarre Ward (1910) observed the development of a Horner's syndrome in one of his patients with a papillary type of adenocarcinoma in which the largest mass was aberrant Hyperthyroidism has been reported due to lateral aberrant thyroid tissue but such functional activity is extremely rare Indeed, following the removal of the median thyroid, hypothyroidism usually occurs although lateral thyroid tissue is present

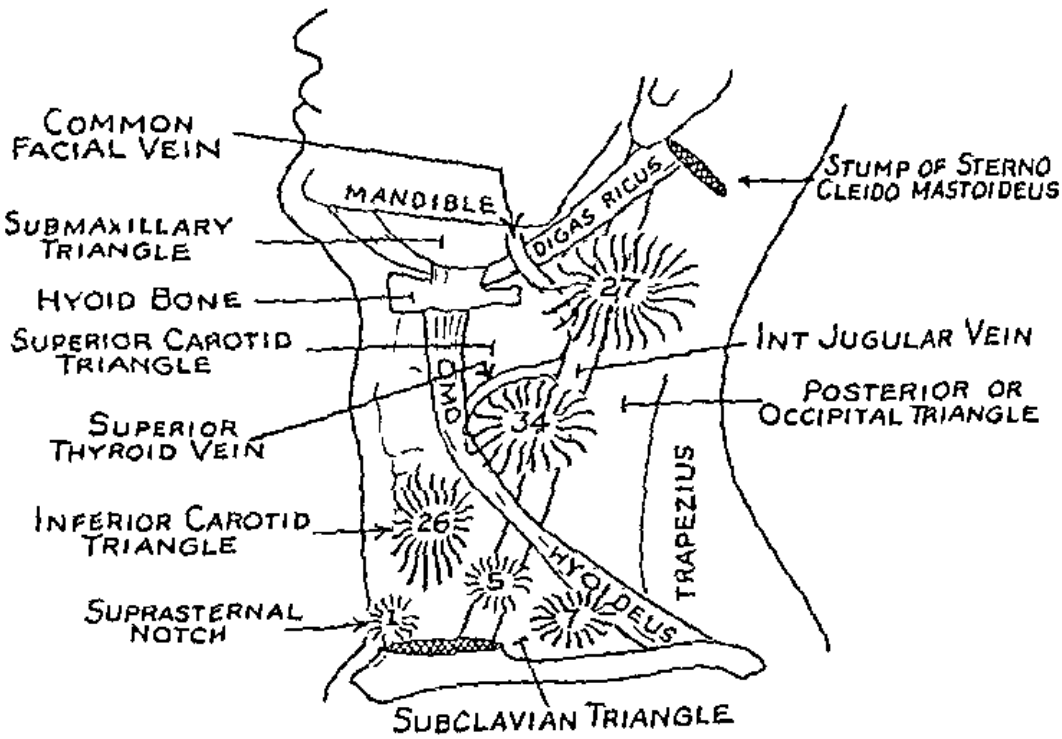


Fig 3—Location of lateral aberrant thyroid tumors as charted by a combination of the data of Ward (1910) and Heintz and Sachs (1932)

All lateral aberrant thyroid tumors whether benign or malignant, are characterized by their very slow but progressive growth and their tendency to be firm discreet and freely movable even when histologically malignant

There is a tendency for the tumors to recur in more than 50 per cent of all cases However even in the patients with histologically malignant lesions the growth is very slow and survival for more than a

2 *Hodgkin's Disease and Lymphosarcoma*—The enlargement of the glands in both these conditions usually takes place much more rapidly than in lateral aberrant thyroid tumors In both the entire chain of anterior cervical lymph glands may be involved thus simulating the location of tumors of the lateral thyroid component However there is a great tendency for coalescence and fixation of the gland to surrounding tissues in lymphosarcoma Matting to each other of the individual glands of a chain may occur late in Hodgkin's disease but a discrete line of demarcation from surrounding tissues is usually maintained Like aberrant thyroid tumors Hodgkin's disease is predominantly unilateral until very late whereas the involvement is more or less symmetrically bilateral in lymphosarcoma and an enlarged spleen may be present

3 *Lymphatic Leukemia*—The involvement of the cervical lymph nodes is usually bilaterally symmetrical in lymphatic leukemia Superficial nodes are commonly palpable in other parts of the body A very large firm spleen is so consistently present as to be of great diagnostic value Some anemia is usually encountered and the blood count and bone marrow findings are pathognomonic

4 *Branchial Cysts*—The location and long duration of branchial cysts always necessitate their differentiation from tumors of lateral aberrant thyroid origin While they usually occur singly they may be multiple They are perfectly smooth globular masses situated in the midcervical region just anterior to the sternocleidomastoid muscle As a rule their cystic character may be made out on palpation and variations in size from time to time are noted by the patient features which aberrant thyroid tissue invariably lacks

5 *Tuberculous Adenitis*—This unilateral disturbance differs from an aberrant thyroid tumor in its more rapid evolution the signs of inflammation about it its fixation to surrounding structures and the occasional presence of fluctuation over it When suppuration does not occur there is a tendency for enlargement of the lymph nodes when the patient has an acute infection such as a cold After this has been controlled and his resistance is improved the lymph nodes decrease in size

6 *Lipomas and Fibromas*—As a rule these lesions are solitary and more anterior to the sternocleidomastoid muscle than beneath or posterior to it They have usually been present for many years without material change in size shape or consistency Lipomas are rather soft with poorly defined borders

7 *Fungus Infections*—Actinomycosis and blastomycosis usually affect the submaxillary group of glands Signs of inflammation of the overlying structures occur early and eventually the skin breaks down with the formation of sinus tracts

deep to one or the other sternocleidomastoid muscle in 50 per cent in the posterior triangle of the neck in 27 per cent in the submaxillary triangle in 19 per cent and in the carotid triangle in the remainder of their cases Thus they emphasize the close anatomical relationship of these masses to the big muscles

The left side of the neck is involved more frequently than the right in the approximate ratio of 1.5 1

There is some divergence of opinion as to the frequency with which a tumor of the main body of the thyroid is present in conjunction with aberrant lateral masses Those who hold to the view that all aberrant thyroids arise from the main body of the thyroid believe that the primary site for all malignant forms of aberrant thyroid may be found in the homolateral lobe if search is sufficiently painstaking Such a lesion may be microscopic in size and yet associated with a cervical metastasis of mechanically disturbing proportions Readily demonstrable tumors in the thyroid gland similar histologically to the aberrant tissue have been demonstrated in from two thirds to three fourths of the reportedly malignant cases The incidence of coexisting thyroid lesions is higher in subjects with nonpapillary adenocarcinomas than in those with papillary types of growth In fact King and Pemberton (1942) noted that all the former group were associated with a thyroid tumor to which they believed the "aberrant" mass was invariably metastatic

Differential Diagnosis —Cervical aberrant laterally placed thyroid tumors must be distinguished from

1 Metastases in the Cervical Lymph Nodes Secondary to Carcinoma of the Mouth Pharynx Stomach and Nearby Structures—As a general rule metastatic lymph nodes due to lesions in the tissues mentioned enlarge more rapidly are firmer and show a greater tendency for fixation to underlying and overlying structures than do the tumors of the lateral thyroid component' Demonstration of a primary lesion will affirm the secondary nature of the cervical involvement When the tumor is in the submaxillary region it is probably due to carcinoma of the lower lip cheek or lower jaw Should the primary cancer be in the tongue hypopharynx or tonsillar region then the lymph nodes deep in the carotid triangle of the neck are the ones most likely to be affected In cases of carcinoma of the nasopharynx these same nodes or those under the upper third of the sternocleidomastoid muscle are involved When carcinoma of the larynx metastasizes by way of lymph channels the nodes overlying the bifurcation of the carotid artery are enlarged When the primary malignant lesion is in the esophagus stomach or breast cervical metastases are usually found in the supraclavicular region

6 RARER LOCATIONS OF ABERRANT THYROID TISSUE

Thyroid tissue may be observed in teratomas of the branchial cleft but the presence of such tissue is confirmed only by histological examination Aberrant thyroid tissue has even been described in the vertebral column producing pressure symptoms upon the spinal cord (Denker and Osborne 1943) and in the region of the maxilla destruction by pressure upon its bony wall (Nambiar 1949)

Other anomalies of the development of the thyroid include an absence of the isthmus the absence of one lobe commonly the left (seven out of every eight instances of the anomaly—Livingstone and Garven 1949) and the presence of a pyramidal lobe usually in response to functional strain during the developmental period of the thyroid in utero

5 *Carotid Body Tumor*—This is a rare cause of swelling about the bifurcation of the carotid artery. A tumor deep in this area that moves readily from side to side but not up and down should make the physician think of this condition. When malignant, the growth may be confused with a tumor of the main body of the thyroid gland as well as with an aberrant thyroid mass.

Prognosis—The prognosis of aberrant cervical tumors containing thyroid tissue should be guarded even though the lesion appears grossly and microscopically benign. Factors which affect the prognosis include:

1 *The Type of Malignancy*—Recurrence of the tumefaction in the neck after surgery is about twice as common in the nonpapillary as in the papillary type of growth. However, the percentage of deaths due to the lesions in the two groups of cases contrary to earlier conceptions is approximately the same.

2 *Involvement of the Thyroid Gland*—The clinical course of all cases with involvement of the thyroid gland is more rapid and more severe than in those without it. When the major or earlier disturbance is in the thyroid, this difference in behavior is accentuated.

3 *The Type of Therapy*—Recurrence is difficult to prevent even when there is ablation of all grossly involved structures, block dissection of the lymph nodes, and complete removal of the homolateral lobe of the thyroid. However, such procedures reduce the incidence of recurrence more than 50 per cent with a corresponding decrease in the mortality due to the malignancy or its metastases.

The place of radiation therapy in the treatment of tumors of the lateral component is not very clear at the present time, but from the available evidence roentgen ray and radium therapy have had little influence upon the prognosis. This might be expected in view of the low grade of the malignancy usually present and the relative insensitivity of papillary growths to radioactivity.

Treatment—Inasmuch as all tumors of lateral aberrant thyroid origin are potentially malignant, they should be dealt with surgically. If the lesion appears histologically benign, complete removal of the affected area offers a fair chance of cure. However, if there is any doubt as to the benignity at the time of operation, a block dissection of the lymph nodes, complete removal of involved tissues, and a homolateral hemithyroidectomy should be performed. Some workers believe that postoperative radiation is helpful (Lahey and Figari, 1946; Cattell, 1940, 1946), while others hesitate to commit themselves (Ward, 1940; Krantz et al., 1942; King and Pemberton, 1942).

highest incidence of clinical onset in the decade between 11 and 20 years (17.4 per cent) with a total of 68.1 per cent making their appearance before the age of 30 years. These workers emphasize that no age is exempt as 15 of their subjects were 61 years or older when the lesion was first noted.

From 70 to 80 per cent of all vestigial thyroglossal duct lesions are cysts and the remainder are either sinuses or fistulas. Girls are more commonly affected than boys in the ratio of from 1.2-2.0 to 1.0 (Gross and Connerley 1940, Pemberton and Stalker 1940, Baumgartner 1947, Marshall and Becker 1949), although one group of workers reporting upon patients of all ages found the incidence about equal in the two sexes (Ward, Hendrick and Chambers 1949).

Symptoms and Signs.—Corresponding to the path of descent of the median anlage of the thyroid, thyroglossal duct cysts may be found in or very close to (Ward, Hendrick and Chambers 1949) the midline of the neck anywhere from the base of the tongue to the suprasternal notch. Sixty-one of a series of 348 were found above the hyoid bone (Marshall and Becker 1949). They should be looked for (a) at the foramen cecum, (b) between the folds of the tongue muscles anterior to the foramen cecum, (c) immediately above the hyoid bone, (d) just below the hyoid bone, and (e) near the isthmus of the thyroid gland. The most commonly seen are those about the hyoid bone, while rarely is a cyst observed at the foramen cecum. The discovery of a cyst in any one of these locations is indicative of the presence of a thyroglossal duct tract which is potentially open throughout its entire length. This must be remembered in dealing with the cyst.

These cysts may vary in size from that of a pea to that of a somewhat flattened golf ball. Usually they are from 1 to 2 cm. in diameter, have a well-defined border and are smoothly rounded. However, the larger the cyst, the more likely it is to be compressed and misshapen by the overlying skin or fascia.

The smaller cysts are freely movable, usually rise on swallowing and are not painful or tender unless secondarily infected. The larger the cyst, the less freedom of movement there is. Unless a sinus or fistulous tract has been established, there is no attachment of the cyst to the overlying skin. If a sinus tract exists between the cyst and the mouth, a small amount of fluid may be discharged spontaneously from time to time.

The dermal openings of spontaneously occurring sinuses vary from 1 to 3 mm. in diameter and appear in the midline of the neck anywhere from the suprasternal notch upward to a position just in front of the hyoid bone. If the neck is carefully palpated, the examiner may detect a cord of tissue running upward in the deep structures to an attachment in the hyoid bone. The sinus tract may become inflamed and from time to time discharge droplets of fluid which vary from a

Chapter XXIII

DISTURBANCES OF THE THYROID GLAND DUE TO OR CLOSELY ASSOCIATED WITH CONGENITAL ANOMALIES IV THYROGLOSSAL DUCT CYSTS, SINUSES, AND FISTULAS

Definitions —A thyroglossal duct cyst is a retention cyst which has its origin in a patent or unabsorbed portion of the vestigial thyroglossal tract A thyroglossal duct sinus is an intermittently or continuously draining channel from such a cyst the buried end of which stops blindly in the tissues Such a sinus results from the spontaneous rupture or incision of a thyroglossal duct cyst Should the sinus tract run uninterruptedly from skin surface into the mouth by way of the foramen cecum then the term fistula' is applicable The origin of these conditions in embryological maldevelopment has already been discussed in connection with the chapters on heterotopic thyroid tissue (Chapters XVI and XVII)

Pathology —Thyroglossal cysts sinuses and fistulas are lined by either endodermal cells of columnar or ciliated columnar type or by squamous (ectodermal) epithelium Occasionally both ectodermal and endodermal elements are present suggesting that a communication has existed in embryonic life between the pharyngeal pouch and the branchial cleft Ramifications of the sinuses may penetrate several millimeters into the surrounding tissues The irregularly shaped epithelium lined tract may pierce the hyoid bone or its periosteum without being discernible even at the time of operation This emphasizes the necessity for removing a portion of the hyoid bone in all operated cases

Acute and chronic inflammation is occasionally observed in the walls of cysts but is frequently encountered in the histological examination of sinuses and fistulas

Clinical Picture —

Incidence —In a children's hospital slightly less than one third of a large series of cases had a lesion noted at birth and in from 75 to 80 per cent symptoms were observed before the sixth year (Gross and Connerley 1940) In reviewing the entire experience of one large clinic which included 348 cases of thyroglossal duct cysts and sinuses of *all* age groups Marshall and Becker (1949) found the

or not any remnants of the thyroglossal duct in this area can be palpated. On the other hand, Pemberton and Stalker (1940) feel that dissection above the hyoid is unnecessary in those cases where no traces of the tract can be visualized or palpated at the time of operation. Recurrences are rare if the dissection is carefully carried out.

clear glairy mucus to a cloudy usually thin, sometimes yellowish discharge The nature of the drainage depends upon whether the epithelial lining is of a squamous (yellow discharge) or columnar (very clear discharge) type A mucopurulent type of secretion may also accompany secondary infection Carcinoma has been known to develop from the epithelial lining of these structures

Diagnosis and Differential Diagnosis—A soft sometimes *fluctuant* tumefaction in the midline of the neck unattached to the skin and usually freely moveable which appeared during the first two decades of life is suggestive of a thyroglossal duct cyst The softness of the mass will usually distinguish it from aberrant thyroid tissue arising from the median anlage of the thyroid and the presence of a midline sinus confirms the diagnosis

Branchiogenic cysts appear laterally along the anterior border of the sternocleidomastoid muscle Midline *sebaceous cysts* lie above the muscular structures and are always attached to the skin whereas thyroglossal cysts and sinuses originate beneath the deep fascia and the muscles and move easily *Lipomas* are less spherical more superficial and usually softer than thyroglossal cysts The lesions of both suppurative and nonsuppurative *acute submental adenitis* lie more anteriorly than any vestigium of the thyroglossal duct system a primary focus of infection should be looked for in the teeth chin or lower lip

Other suppurative lesions may have to be considered in the rare instances in which the opening of a thyroglossal duct sinus lies below the level of the isthmus of the thyroid Roentgenograms of the cervical spine and thorax will be helpful in differentiating *tuberculosis* *Dermoid cysts* in the midline of the neck are extremely rare and attach themselves to the overlying skin rather than to the deep muscular and fascial structures

Treatment—No active treatment was advised in approximately 15 per cent of a representative series of cases (Gross and Connerley 1940) If the cysts are small not disfiguring and show no palpable signs of growth the patient should be made acquainted with the nature of the lesion and no treatment should be instituted

A radical surgical approach should be made in all other cases including *all* sinuses and *all* fistulas However if the patient is first seen with a sinus or fistula in which secondary infection with abscess formation is present simple drainage of the abscess and conservative treatment are necessary until all inflammation has subsided Following this the entire sinus tract should be removed as well as the cystic area A majority of workers (Gross and Connerley, 1940 McClintock and Maffey, 1930) believes that the dissection should always be carried upward through the hyoid bone to the foramen cecum whether

or not any remnants of the thyroglossal duct in this area can be palpated. On the other hand, Pemberton and Stalker (1940) feel that dissection above the hyoid is unnecessary in those cases where no traces of the tract can be visualized or palpated at the time of operation. Recurrences are rare if the dissection is carefully carried out.

Chapter XXIV

INTRATHORACIC GOITER

Definition—For symptomatologic diagnostic prognostic anesthetic, and surgical reasons it seems wise to restrict the term intrathoracic goiter to those cases in which the entire goiter is within the bony thoracic cage. An intrathoracic goiter is no longer able to escape upward from its deep position in the mediastinum because under the above definition, its greatest diameter is well below the upper aperture of the thoracic cage made by the vertebral bodies first ribs and sternum. We may use the term substernal or partial intrathoracic goiter to include those tumors that still move in and out of the upper thoracic aperture on swallowing while a complete intrathoracic or true intrathoracic goiter is too large to do this.

Pathogenesis—It is generally agreed as expressed by Lahey (1915) that all intrathoracic goiters start either as discrete adenomas of the thyroid or as multiple adenomatous goiters. In other words with rare exceptions intrathoracic goiters are migrating adenomas which were originally located about the level of the thyroid and gradually descended to their intrathoracic positions. Such adenomas usually arise in the isthmus or one of the lower poles of the thyroid. A pedicle which carries their blood supply maintains their connection with the main body of the thyroid gland. Their descent into the thorax is furthered by the following factors: (1) individual variations in the upper bony aperture of the thoracic cage; (2) the arrangement of fascial planes of the neck; and (3) the position of the thyroid between the prevertebral fascia in front and the pretracheal fascia behind. Both of these fascial planes enter directly into the superior mediastinum and therefore create a potential space with no bottom. As a result of these anatomical relationships the following forces aided by gravity drag the goiter into the chest: (a) flexion of the neck which crowds the adenoma downward and (b) ascent and descent of the adenoma with swallowing. While it is still small the goiter tends to move in and out of the thoracic cage during deglutition. Later as it grows neither swallowing forced holding of the breath coughing nor other violent effort can drag or force it upward into the neck.

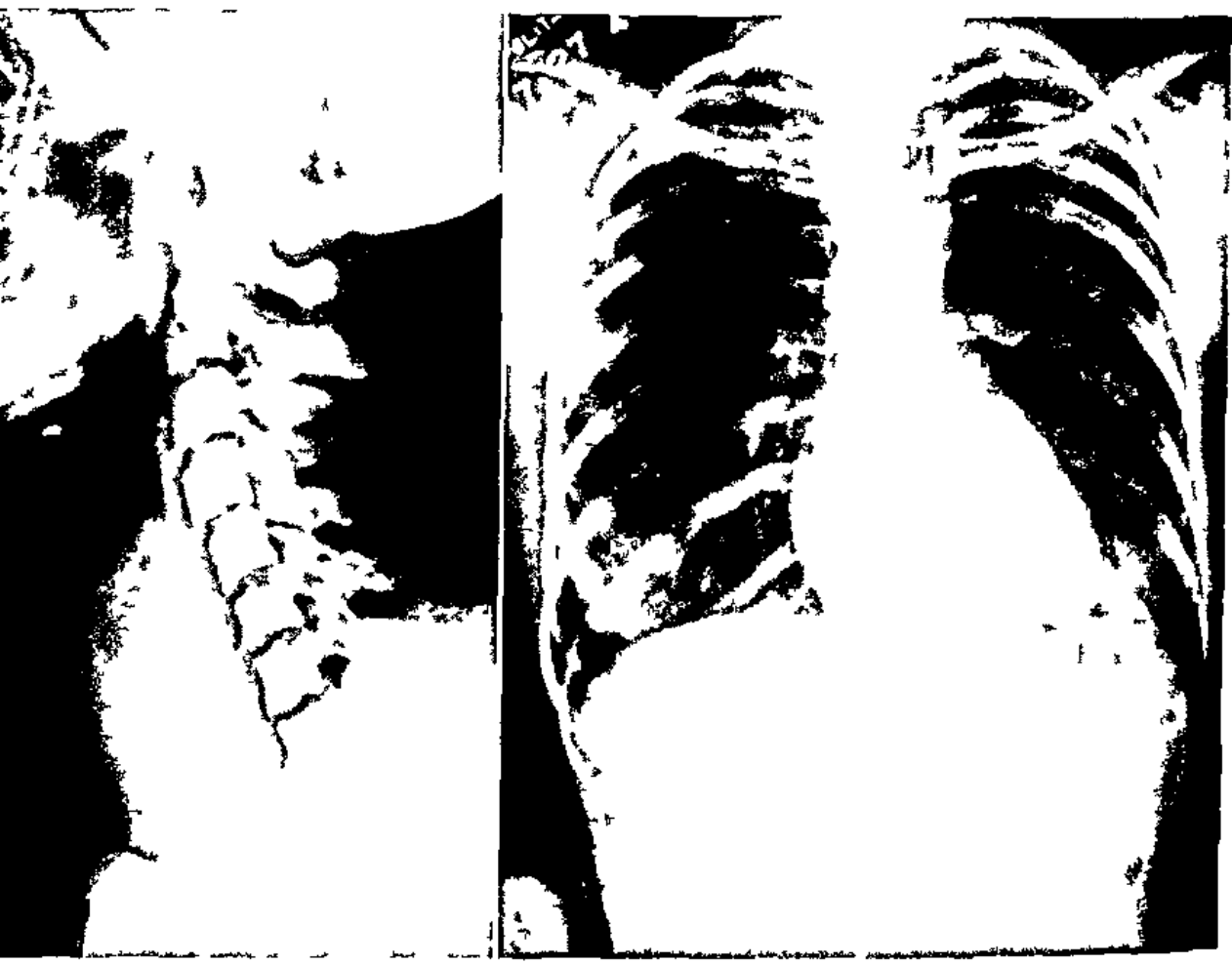
In addition to the *intrathoracic goiters*, originating as described above two other groups of mediastinal thyroids must be considered *Embryonic follicular rests* have been found post mortem near the arch of the aorta but as they have no clinical *significance they may* be dismissed without further comment Not less than nineteen cases of congenitally mediastinal aberrant goiter have been reported (Mora et al 1944 Rives 1947 Bradford et al 1947 Negre and Balmes 1950) in seventeen of which the clinical findings were sufficient to justify surgical intervention These lesions are believed not to belong in Lahey's groupings of adenomas that arise in the thyroid proper and slide into the chest because of the nature and origin of their pedicles the sources of their blood supply and/or their location Indeed Rives (1947) is probably correct in expressing the view that such aberrant lesions are much more frequent than commonly recognized Of the nineteen reported cases seventeen required surgery *because of size or obstructive phenomena two were discovered* at autopsy Seven were in the posterior mediastinum four were behind *the esophagus two were in the inferior mediastinum resting upon the* diaphragm and the remaining six were found in the anterior mediastinum The location of thirteen of these tumors makes it unlikely that they arose from the main body of the thyroid in extrauterine life Moreover in some of them a blood supply from an intrathoracic vessel rather than from a thyroid artery was identified Of the six aberrant thyroids in the anterior mediastinum five showed no connection whatsoever with the neck In the one connected to the trachea by a fibrous band as well as in the other five without any such attachment a blood supply from other sources was identified

It seems important to keep this small group of congenitally aberrant mediastinal goiters in mind in connection with the surgery of all intrathoracic goiters for it may not be possible to deal with them at all by way of the cervical approach as their blood supply cannot be thus controlled before evacuation and dissection are begun

Incidence—Partially intrathoracic goiters are relatively common and represent from one eighth to one fifth of all thyroid tissue enlargements in areas of endemic goiter (Clute and Lawrence 1941) (Fig 31) As might be expected completely intrathoracic goiters are much less frequently observed and account for about 0 5 per cent of all goiters (Pemberton 1921 Crile 1939a Wakeley and Mulvany 1940) With the *exception of seven cases (Mora et al 1944) all* completely intrathoracic goiters have been found in the anterior mediastinum These seven were in the upper posterior mediastinum *and were believed to have an* origin similar to that of the goiters in the anterior area However Mason (1942) states that his case which incidentally was not reviewed by Mora showed no connection whatsoever between the tumor and

the main body of the thyroid gland He therefore considered it a true instance of heterotopia of the thyroid

The majority of completely intrathoracic goiters are first noted in the fifth decade of life but have been seen at any age from early adolescence onward As might be expected the sex incidence is the same as for adenomatous goiters in general i e , female to male as five to one This ratio, however varies in relation to the endemicity of the area and approaches one in the most goitrous areas



A *B*

Fig 31 *A B C* and *D*—Roentgenograms (*A* and *B*) of a symptomless adenoma of the thyroid with substernal extension (S W MH # 8 31 49) The thyroid enlargement was first noted at the age of 11 two years before puberty Now at the age of 29 years there is a multinodular cystic soft asymptomatic goiter with a substernal extension which is not causing any tracheal deviation It is of extreme interest that an homologous twin *(C)* has no thyroid difficulty although the menarche was established at the same age and both the subject *(D)* and sister have as far as can be ascertained lived in the same environment up to the present moment

Pathology—Pathologically intrathoracic goiters behave in a fashion similar to adenomatous goiters elsewhere A small number about 2 per cent undergo malignant degeneration Cystic calcareous and hemorrhagic changes frequently occur The symptoms and signs of



C D

Fig. 31. C and D. (From Lyerly and Pilcher.)

thyrotoxicosis appear as often as they do in association with nodular lesions of the normally placed thyroid gland Among patients operated upon at the Cleveland Clinic for intrathoracic goiter 50 per cent showed hyperthyroidism (Crile 1939a) Diffuse goiters (exophthalmic goiter primary hyperplastic hyperthyroidism) never become intrathoracic (Thiey 1936 1939 Thiey and Swinton 1934, Crile, 1939a)



Fig 32—Roentgenogram of asymptomatic intrathoracic goiter (Case of MH #14 64) Despite its large size this was a completely asymptomatic intrathoracic goiter occurring in a 3 year-old Negro with luetic aortitis

Clinical Picture—Intrathoracic goiter may be asymptomatic (Fig 32) or it may give rise to pressure phenomena due to its size and to thyrotoxicosis as a result of increased physiological activity

The relatively large group of intrathoracic goiters that cause neither symptoms nor signs usually expand into the lung field in such a manner that the trachea is little if at all disturbed

When thyrotoxicosis results from intrathoracic goiter the general picture is identical with that produced by toxic adenomata of the normally placed thyroid gland Thyrotoxicosis occurs with equal frequency in those intrathoracic goiters which do and those which do not

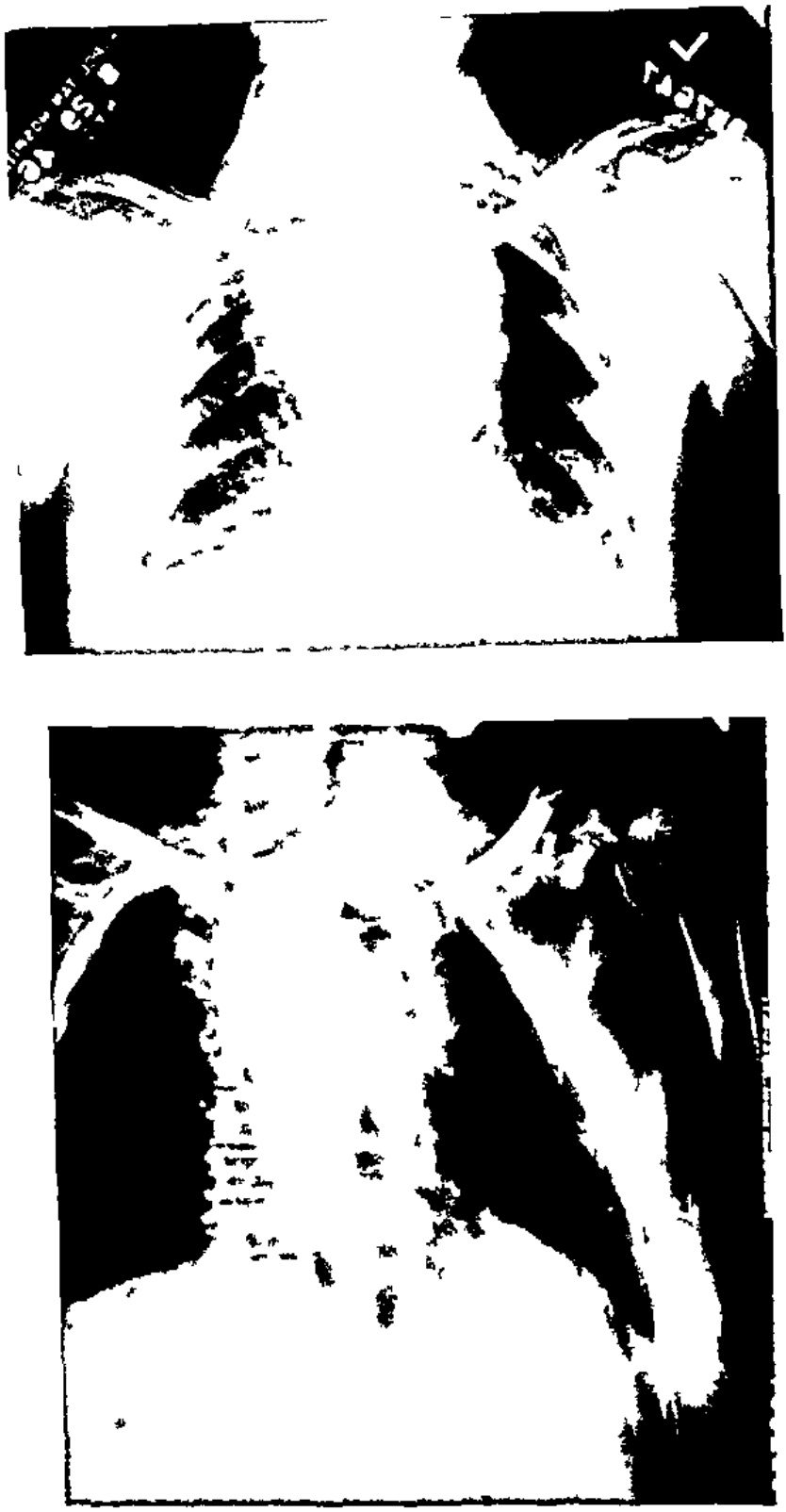


Fig. 33.4.—*A* and *B*—Roentgenograms of thyrotoxicosis with cardiac pre-eminent symptoms and extensive thoracic goiter (Case CA MH # 38 46). This 55-year-old woman had had goiter since the age of 18 years and frequently had to undergo for 20 years. She had had buts of rapid failure of recently. There was extensive dilatation involving both lateral and extending into the neck and downward over the chest and anterior abdominal wall. The transhatched markedly dilated the right innominate vein which could not be distinguished with the aid of contrast medium—pulmonary hypertrophy of the heart and fine bruits over the thyroid and basal metabolic rate +80 a serum protein of 5.1 per cent and total serum cholesterol of 100 mg per 100 c. At autopsy a multinodular thyroid gland weighing 30 grams was removed this contained many highly hyperplastic and other degenerating portions with hemorrhagic fibrosis and infiltration. The roentgenograms show the transmediastinal shadow in the diminished and filling defect as well as the dilatation and impairment of the tracheal

give rise to local pressure symptoms (Fig 33) The location and size of the growth and the nature of the degenerative processes through which it has passed are important factors in determining the nature and severity of the local manifestations If the recurrent laryngeal nerve is involved one should suspect a malignant lesion A small retrotracheal adenoma may cause more respiratory embarrassment than a much larger laterally placed tumor In large growths which extend bilaterally the walls of the trachea may be sufficiently compressed to produce inspiratory stridor The characteristic raspy cough associated with the stridor indicates that there is deviation angulation or compression of the trachea

The diversity of the clinical picture (Figs 31 32 33 53 54 55 56 and 57) that accompanies intrathoracic goiter may be readily understood when one considers the large number of important structures in the neck that may be displaced or compressed the pneumogastric phrenic sympathetic and recurrent laryngeal nerves the common carotid artery the innominate and subclavian vessels the internal jugular vein the trachea and the esophagus Difficulty in swallowing often worse in certain positions of the body may be encountered but usually suggests a very large goiter or one which is partially extrathoracic and extending backward to encircle the trachea and compress the esophagus Cardiac irregularities may arise as a result of intrathoracic pull or pressure upon the sympathetic nerves Disturbances in diaphragmatic excursion and interference with gastric and intestinal activity indicate interference with the vagal and phrenic nerves Hoarseness and aphonia accompany involvement of the recurrent laryngeal nerve Pressure on the jugular veins will interfere with the return flow of blood from the head to the heart Eventually this pressure will result in dilatation of the superficial veins of the chest wall more marked on the side toward which the goiter is expanding If such pressure is severe the neck veins may share in the dilatation and engorgement Finally edema of the face appears Similar disturbances in the arm may be expected to follow interference with the patency or position of the subclavian vessels

If part of the goiter is extrathoracic the larynx as well as the trachea may be deviated If the goiter becomes sufficiently large its position in the anterior mediastinum makes it rather easy to detect by percussion over the upper anterior chest wall

The cardiac load may be increased in at least two ways by intrathoracic goiter Pressure upon the great vessels often increases the work of the left ventricle with consequent chronic hypertrophy of that structure A narrowed compressed trachea admits less air or oxygen to the lungs thereby further adding to the work hypertrophy which the heart undergoes In some instances the dyspnea suggests asthma more than cardiac distress In either event removal of the space consuming mass gives complete relief

Diagnosis and Differential Diagnosis—A clinical diagnosis of intrathoracic goiter is made with reasonable certainty when an upper anterior mediastinal mass spherical or tonguelike in shape which ascends and descends during the act of swallowing is identified A mass with such characteristics will be most easily demonstrated by fluoroscopic examination (Fig 30) However it is often possible to make the diagnosis entirely by physical examination The examiner may be able to outline the mass by percussion sometimes however even goiters of considerable size may not alter the percussion note If goiter is suspected it may frequently be palpated in or above the suprasternal notch during the acts of swallowing and coughing This sign is nearly always positive in a partially intrathoracic goiter but may be entirely absent in the complete type *Occasionally when the patient reclines the* upper pole of the mass may appear in the thoracic aperture because of its tracheal attachment motion on swallowing may then be readily detected Pemberton (1946) has described a very useful sign have the patient elevate both arms until they touch the sides of the head In a few moments after this position is assumed congestion of the face some cyanosis and finally respiratory distress will appear He believes the phenomena are caused by a narrowing of the thoracic inlet and an obstruction of venous return from the head and neck resulting from the alteration in anatomical relationships produced by raising the arms

In the differential diagnosis of intrathoracic goiter the presence of a mass which moves on swallowing is the one nearly infallible sign However since an inflammatory process may partially fix the goiter *even this pathognomonic feature may be difficult or impossible to con* firm Several conditions must be distinguished from a completely intrathoracic goiter

1 Congenital Cysts—The three most common congenital cysts probably have a similar embryonic origin and may be considered together

(a) *Epidermoid cysts dermoid cysts and teratomas* These lesions are usually found in the upper anterior mediastinum and occur with sufficient frequency (approximately 250 in the literature—Lapply 1945) to justify their careful exclusion in all cases of suspected intrathoracic goiter The first two are usually asymptomatic and many of the teratomas present no symptoms unless they undergo malignant degeneration Such a clinically benign course for these three types of lesions is due mainly to the fact that they are not attached to the trachea Therefore they are free to migrate outwardly as they enlarge thus rarely causing tracheal deviation or other mediastinal evidences of pressure Since they are not connected with the trachea they do not move with deglutition or tussal effort They are rarely if ever palpable at the upper thoracic aperture In the case of dermoid cysts and teratomas

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5 *Thymic Tumors*—*Persistent thymus* and *benign thymoma* appear as flattened somewhat triangularly shaped masses in the upper anterior mediastinum. Local symptoms are frequently absent but a generalized *reaction closely simulating if not identical with* myasthenia gravis is often present. On roentgenographic examination the smaller of these tumors may be entirely missed because its shadow is hidden behind the sternum. If lateral pictures are taken the flattened outline sharply differentiates the lesion from an intrathoracic goiter. *Thymic cysts* which are extremely rare and *malignant thymomas* produce rounded anterior mediastinal shadows the midline position of which *may be helpful in differentiating them from an intrathoracic goiter* with its tendency to appear somewhat larger on one side than on the other. Pressure symptoms are common and appear early in the clinical course of these two thymic lesions. Supraclavicular and cervical glandular involvement and malignant cachexia accompany the malignant tumors and progress rather rapidly.

6 *Lymphosarcoma and Hodgkin's Disease Involving the Hilar Lymph Glands*—These lesions lack the mobility of intrathoracic goiters are usually lower in the mediastinum than the latter and as a rule cast a less discrete roentgenographic shadow. Cervical and supraclavicular lymph nodes are generally involved. Indeed among 90 cases of Hodgkin's disease Jackson and Parker (1915) found but one that did not have a peripheral lesion in addition to the mediastinal growth.

7 *Sacculated Aneurysms of the Arch of the Aorta*—When these tumors point upward and forward into the upper anterior mediastinum they may be mistaken for intrathoracic goiter. However they almost always have a transmitted pulsation which is sometimes expansile. They do not move during deglutition.

8 *Secondary Carcinomas*—Secondary carcinomas from the lung, breast, esophagus, or one of the abdominal viscera may occupy the mediastinum. Usually the primary site can be detected and even when that is difficult the configuration of the location of the mediastinal growth does not resemble that of intrathoracic goiter.

Prognosis—As a general rule the prognosis of intrathoracic goiter is good provided (1) the heart has not been damaged and (2) the tumor can be removed by way of the neck.

Treatment—Surgery affords the *only* satisfactory therapeutic approach to the problem of intrathoracic goiter. Inasmuch as the operative procedure is tedious and difficult at best surgery should be advised as soon as the mass is discovered and identified. Lahey and Swinton (1931) and Clute and Lawrence (1941) have shown that it is not necessary to remove any portion of the bony thorax, a procedure which has always greatly increased the operative risk. They

roentenographic shadows of calcified structures such as bones and teeth and materially in the differential diagnosis

(b) *Rare congenital cysts* *Pericardial celomic cysts* are commonly asymptomatic and are found low in the chest and usually occupy the cardiodiaphragmatic angles more commonly the right than the left *Bronchial cysts* may appear in nearly any portion of the mediastinum and are usually asymptomatic but may be accompanied by dull aching pain They often compress portions of the lung thus producing physical signs At times they become secondarily infected and simulate an intrapulmonary condition *Esophageal cysts* are usually low in the posterior mediastinum *Cystic lymphangiomas* are extremely rare and present multiloculated roentgenographic shadows

2 *Mediastinal Echinococcus Cysts*—These cysts are extremely rare their spherical contours and frequently calcified walls will usually differentiate them from intrathoracic goiter

3 *Connective Tissue Tumors*—Of these masses which include fibromas lipomas leiomyomas xanthomas chondromas myxomas and various combinations of them only those in the interior mediastinum are likely to be confused with acquired intrathoracic goiter These tumors do not move with deglutition As a rule they attain considerable size and in such instances usually produce rather severe pressure symptoms and signs From a therapeutic standpoint it is important to differentiate them preoperatively if possible from intrathoracic thyroids as they cannot be surgically approached by way of the neck Their size their failure to move with the act of swallowing and the inability of the examiner to palpate them in the suprasternal notch are among the important distinguishing features

Fibroma arising in the esophageal wall may be very difficult to differentiate from an intrathoracic goiter as like the latter it moves up and down during the act of swallowing Lahey (1915) has seen three instances of this condition These tumors are spherical in outline firm in character ascend and descend upon swallowing and may at times be partly within and partly without the thoracic cage If the esophagus is filled with thin barium a smooth spherical indentation of the esophageal wall will indicate the presence of a fibroma as such a filling defect is practically never seen in goiter

4 *Neurofibroma*—Of the neurogenic tumors neurofibroma is the one most likely to be confused with the intrathoracic goiter as it is the one most frequently seen in the anterior superior mediastinum Sometimes preoperative differentiation is impossible but the comments made in regard to connective tissue tumors apply equally here except that as a rule the neurogenic tumors of this type do not attain so great a size as their connective tissue counterparts

Chapter XXV

THYROIDITIS I ACUTE AND SUBACUTE

Definition—If inflammation is defined in its broadest sense as a condition into which tissues enter as a reaction to irritation then thyroiditis must be looked upon as a relatively commonplace event Frequently under physiological and pathological states of stress demonstrable morphological alterations in individual thyroid cells and even in groups of acini may indicate the presence of an acute or chronic inflammatory reaction (Womack and Cole 1931 Womack 1944) Variations in acinar size and shape vascular damage pooling of colloid in extra acinar stroma fibrosis and sometimes calcification are seen in varying degree in most nodular goiters and strictly speaking represent inflammation However the term thyroiditis is commonly used *to denote those inflammatory processes which are directly responsible* for the clinical manifestations observed In this latter sense the term will be used here

Classification—Within the limits above imposed inflammatory conditions of the thyroid gland may be divided into two main groups (1) specific thyroiditis occurring in the course of such diseases as tuberculosis syphilis echinococcic cysts actinomycosis and trypanosomiasis (Chagas) (2) nonspecific thyroiditis which may be acute subacute or chronic The acute and subacute varieties while sometimes suppurative in type commonly evolve without pus formation Of the chronic nonspecific forms two main types are well recognized Riedel s struma (ligneous thyroiditis) and Hashimotos disease (struma lymphomatosa) Some chronic cases cannot be placed in either one of these categories (Kearns 1940) but actually represent a mixture of the two

ACUTE AND SUBACUTE THYROIDITIS

Acute and subacute thyroiditis will be considered together as they possess a common etiology and sometimes merge imperceptibly one into the other Much that has been written about one applies equally to the other so that the acute variety will be described in detail and the differences between it and the subacute type pointed out when that may be necessary

stress the fact that with care even the largest masses can be removed without disturbing any bony tissue Surgery is usually contraindicated if the growth is malignant but where doubt exists operation should be attempted

ful enlargement of the thyroid gland with all the signs and symptoms of acute thyroiditis has been described as one of several manifestations of sensitivity to thiocyanate (Fahlund 1942)

Suppuration has been reported in one third of the cases of acute thyroiditis seen at the Mayo Clinic (Davis and Howell 1940) However other workers believe the condition is extremely *uncommon* (*Clute* and Smith 1927 Womack 1944 Lahey 1944 Stock 1944) In the thyroid clinic of a general hospital it seems likely that 10 per cent or less of the cases of *acute thyroiditis* will be associated with *abscess formation* Womack (1944) observed that acute suppurations of bacterial origin are extremely uncommon when compared to the frequency of metastatic abscesses in many other organs of the body He found that abscess formation rarely followed the injection of pure cultures of streptococci and staphylococci directly into the superior thyroid artery of dogs Among the organisms obtained from suppurative processes within the thyroid gland are streptococci staphylococci pneumococci typhoid bacilli and colon bacilli (Candel 1946) Usually bacterial invasion of the gland takes place by way of the blood stream occasionally there is a direct extension of an infection from other structures within the neck itself

Pathology —The nature and course of the inflammatory processes which occur within the thyroid gland are in part predetermined by its unique anatomical relationships The gland is extremely vulnerable to injury by accident because of its superficial location beneath the thin platysma sternohyoid and sternothyroid muscles On the other hand it is well protected against the direct spread of infections by a firm well developed capsule Further protection is afforded by the split fascial planes which completely envelop this capsule The lymph and blood vessels are highly anastomatic the supply of both of these fluids is greater per unit of weight than for any other organ of the body *Therefore the blood and lymph vessels offer the only portals by which* infectious material enters the gland

In view of the above inflammatory processes within the thyroid involve first the interfollicular vascular structures and later the perivascular spaces Indeed the intensity of the reaction seems to vary directly as the blood and lymph vessel distribution At first there is an intense vascular small round cell infiltration then edema and later thickening of the vascular walls with perivascular fibrosis and widening of the interfollicular spaces Acute thyroiditis is accompanied by the earliest of these changes If the process goes on sufficiently long these interacinar disturbances interfere with the blood and lymph supply of the follicles and therefore with both their nutrition and their function In the subacute forms of thyroiditis this secondary reaction *in the follicle is evidenced by the degeneration* of the acinar epithelium the loss of colloid to the interfollicular spaces and the formation of

Synonyms—For acute thyroiditis acute nonspecific thyroiditis, acute perithyroiditis For subacute thyroiditis pseudotuberculous thyroiditis giant cell thyroiditis deQuervain's thyroiditis (1936) *struma fibrosa*—giant cell variant

Incidence, Age and Sex Distribution—Acute thyroiditis is generally believed to be an extremely rare condition Lahey (1911) found 19 instances among 22 100 thyroidectomies Candel (1916) observed the condition only once in 11 151 admissions to a Naval Medical Center In 1911 Robertson collected 93 cases from the literature and added three of his own Hagenbuch (1921) reported 13 cases among 16 000 admissions to the Basle Clinic in Switzerland for a ten year period 1911 to 1921 These statistics indicate the infrequency with which the condition is observed However, we believe it is much more common than is suggested by the evidence, as it is often not recognized and still less frequently reported (Nordland 1937 Thompson 1941 DeCourcy 1943 Candel 1916)

Suppuration of the thyroid gland very rarely occurs Crile (1932) observed it 71 times in 10 000 operations

Acute thyroiditis affects females about twice as frequently as it does males The age incidence varies from extremes of 18 months to 77 years (Higbee 1913) but the condition is most commonly seen between the ages of 20 and 40 In only 26 per cent of the cases reviewed by Higbee (1913) was the thyroid gland believed to be previously normal

Etiology—An upper respiratory tract infection has preceded *acute nonsuppurative thyroiditis* in most of the patients we have observed Womack (1941) found such an infection in 50 per cent of the cases he studied The condition has accompanied or followed other infections pneumonia typhoid fever rheumatic fever influenza tonsillitis (Davis and Howell 1940) infections near the mouth and jaw (Davis and Howell 1940 Young 1940 Higbee 1913 Lahey 1911, Kist and Dannenberg 1915) measles (Candel 1916) scarlet fever (Jensen 1943) mumps and diphtheria (Clute and Smith 1927) pelvic cellulitis complicating the puerperium (Wahrsinger 1931) and malaria (Sem, 1938) In an analysis of 130 cases collected from the literature Higbee (1913) found the exciting cause to be pneumonia in 30 patients inflammations about the mouth and throat such as Vincent's angina in 30 influenza in 26 puerperal fever in 19 typhoid fever in 11, erysipelas in 7 rheumatic fever in 7 malaria in 6 diphtheria in 4 arthritis in 2 mastoiditis in 2 genitourinary tract infection in 2 empyema in 1 otitis media in 1 carcinoma in 1 and bronchitis in 1

Acute thyroiditis usually follows some local or generalized infection it often arises without any demonstrable antecedent condition (Clute and Smith 1927) Unusual causes also exist For instance pain

In *summary* acute thyroiditis is pathologically characterized by an inflammatory process involving interfollicular vascular and perivascular structures with secondary disturbances in the function of the thyroid follicles The condition usually subsides without complications but may go on to abscess formation or to chronic changes represented by either ligneous thyroiditis or Hashimoto s disease

Clinical Picture —The clinical course of acute and subacute thyroiditis varies considerably It is often mild and afebrile in the uncomplicated nonsuppurative and subacute cases and fulminant and severe in those which become purulent

The acute nonsuppurative form runs a self limited course of from 5 to 15 days which in its mildest forms may infrequently be afebrile Pain in the neck of rapid onset diffuse throughout the cervical regions and sometimes referred to the ear jaw or occiput may be the only complaint The patient may continue his usual routine of living (The gland is only slightly swollen sometimes unilaterally) The subacute variety commonly follows the above pattern except that a persistent low grade fever is frequently present and the condition may last for from one to several months indeed even a year (Schilling 1945) (Hyperthyroidism sometimes occurs) (Villafane and Rosenblit 1949)

(In the more severe cases of acute thyroiditis fever usually is present associated with enlargement and tenderness of the thyroid) The swelling of the soft tissues of the neck may be sufficient at times to obliterate completely the hollow formed by the junction of the two sternocleidomastoid muscles

The pain and exquisite tenderness of acute thyroiditis is due to the rapid swelling of the gland and the resultant increase in intrafascial tension Hence the patient holds his head slightly forward in order to relax the subhyoid muscles For the same reason he avoids swallowing even to the point of drooling saliva from the mouth He keeps the head perfectly still and may voluntarily splint it with pillows

Tension within fascial and muscular planes likewise explains the dyspnea and dysphagia which are sometimes seen in acute thyroiditis When a nodular goiter has developed prior to the thyroiditis hemorrhage is common and may materially increase the above symptoms sometimes indeed to alarming proportions

In thyroiditis associated with abscess formation the onset is abrupt Fever and the cardinal local signs of inflammation are always present but in rare instances systemic manifestations are absent (Stock 1944) Spasm of the ribbon muscles of the neck is extreme with correspondingly intense pain aggravated by the slightest motion even swallowing Hoarseness may occur

The abscess is confined to one lobe or to the isthmus The surrounding edema of the thyroid masks its outline and together with exquisite tenderness makes a satisfactory physical examination very dif-

giant cells and pseudogiant cells (pseudotuberculous thyroiditis—Lasser and Grayzel 1919) The special nature of these alterations occurring in thyroiditis has prompted DeCourcy (1943) to speak of perithyroiditis rather than thyroiditis He recognizes in the acute phases of perithyroiditis the condition more commonly called acute thyroditis Its chronic analogue is found in the changes that may be seen in Riedel's or Hashimoto's struma Crile Jr (1938b 1939) has described the intermediate stages involved in the evolution of chronic from acute stages of nonspecific inflammation of the thyroid under the term subacute thyroiditis but believes this condition represents a sharply defined entity which is neither etiologically nor clinically connected with struma ligneosa or lymphomatosa There is little doubt however that Crile is describing the condition of which Schilling (1915) speaks under the name of struma fibrosa—giant cell variant and to which DeCourcy (1943) refers as the subacute phase of his perithyroiditis The present state of our knowledge hardly justifies dogmatic assertions regarding the interrelationship or lack of such association between the acute and chronic forms of thyroiditis However it certainly seems likely and well supported by carefully and tediously detailed study that in many instances the various forms of thyroiditis are related and that the transition from the acute to the chronic types is at least in some instances a continuous rather than a discontinuous process

In other words the pathological status parallels the clinical findings The vascular and perivascular changes of acute thyroiditis give rise to the secondary functional and mechanical disturbances already described In the majority of instances these changes completely recede as the infectious process comes under control In a small percentage, abscess formation occurs In still another group the condition may become chronic when the predominant reaction is periarterial and lymphangitic fibrosis (Goetsch 1940a DeCourcy 1943) This fibrotic process is responsible for the development of ligneous thyroiditis In other words the widespread degeneration of acinar structures in Riedel's struma represents the end results of an interference with follocular blood supply It has been suggested that the condition is in every way analogous to the disturbances produced experimentally by Goldblatt in the kidney following a partial blockage of blood supply to the functioning units of that structure (Graham 1940 DeCourcy 1943, Womack, 1944) In keeping with this concept DeCourcy (1943) has been able to follow five cases of thyroiditis through acute subacute and chronic stages which finally ended in Riedel's struma

Should the lymphatic reaction supersede or outdistance the fibrotic changes in chronic thyroiditis it seems possible that in a certain percentage of cases a cellular rather than a sclerotic picture may ensue resulting in the condition described by Hashimoto (struma lymphomatosa)

as unreleased tension within the abscessed area may result in serious complications such as laryngeal or esophageal fistulas or severe mediastinitis Subacute thyroiditis rarely threatens life but may pursue a prolonged course with final complete remission or progression to a chronic thyroiditis and some of its late sequelae especially myxedema

Treatment —The majority of cases of acute thyroiditis will resolve without specific treatment if the patient is placed at bed rest with the head immobilized Penicillin and sulfonamides are important in the management of patients in whom an antecedent bacterial infection is known to exist Therapy with the roentgen ray has been used little or not at all in the most acute cases In the subacute varieties the reports with roentgen radiation are extremely favorable (DeCourcy 1943 Crile Jr 1948a) Crile has observed complete remission with divided doses totaling from 300 to 1 050 roentgens (r) with an average recommended dose of from 600 to 800 r We have seen the condition equally well controlled with a similar amount of radiation In some instances DeCourcy has utilized high voltage roentgen therapy with remission of all acute and subacute manifestations However he noted that the thyroid was still in a hard swollen condition and was eventually removed and histologically identified as a Riedel s struma

Harvill (1948) and King and Rosellini (1945) have seen rapid and dramatic improvement following the administration of thiouracil in the manner commonly employed in hyperthyroidism to patients with acute thyroiditis Not only have all associated symptoms suggesting hyperthyroidism been relieved but the course of the inflammatory process appears to have been shortened This drug or one of its closely allied and safer derivatives such as propylthiouracil or methylthiouracil may warrant a place in the routine management of acute and subacute forms of thyroiditis

ficult Spontaneous rupture of an abscess is relatively common, but fortunately occurs externally in a majority of instances Should the abscess break into the esophagus the trachea or the mediastinum sudden death may ensue

The thyroid gland rarely returns to normal following an acute inflammation although patients with no clinically demonstrable sequelae have been described In some instances hypothyroidism and even myxedema follow extensive involvement In many patients degenerative changes take place which eventually lead to a chronic thyroiditis As above mentioned in at least five patients DeCourcy (1913) has been able to demonstrate the gradual progression of acute thyroiditis through subacute and chronic stages with the ultimate development of a ligneous thyroiditis (Riedel's struma) Schilling (1915) emphasizes the tendency for subacute thyroiditis (struma fibrosa—giant cell variant) to assume slowly all the attributes of a Riedel's struma

Differential Diagnosis —

a Acute Nonsuppurative Forms —When the cardinal signs of inflammation are observed in the region of the thyroid gland and the inflammatory mass moves with deglutition there are very few conditions that may be confused with acute thyroiditis

It is necessary to differentiate

(1) Spontaneous hemorrhage into a cyst or adenoma of the thyroid gland Severe pain and tenderness often accompany hemorrhage into a cyst or adenoma of the thyroid Chills fever and the other constitutional symptoms commonly associated with acute thyroiditis usually do not occur

(2) Perichondritis of the thyroid cartilage In perichondritis of the thyroid cartilage palpation reveals a swelling which obscures the normally sharp edges of the thyroid cartilage The entire area of the swelling is tender In contrast the outline of the thyroid gland is sharp and the gland itself is not involved

b Suppurative Forms —When cellulitis appears low in the midline of the neck and tends to obliterate the hollow between the sternocleidomastoid muscles and the upper end of the sternum an abscess of the thyroid gland is probably present Sometimes the condition may be confused with Ludwig's angina In this condition however the infection usually starts in or about the floor of the mouth The swelling begins high in the neck beneath the chin and spreads downward

Prognosis —In the nonsuppurative forms of acute thyroiditis the prognosis is usually good as under complete rest sedation and supportive treatment the inflammation subsides spontaneously in the majority of cases within 10 to 14 days When suppuration occurs prompt recognition and surgical drainage are essential to a favorable outcome

The nature of the changes in simple chronic thyroiditis is not incompatible with the concept that they represent variants of the two most commonly recognized forms of chronic thyroiditis—Riedel's and Hashimoto's strumata (Marshall Meissner and Smith 1948)

LIGNEOUS THYROIDITIS

Twelve years before Riedel (1896) described what he believed to be a cancriform inflammation of the thyroid gland Bowlby (1884) had observed the condition and called it an infiltrating fibroma of the thyroid The actively fibrosing nature of this chronic inflammatory process seems to warrant the use of the term ligneous thyroiditis to the exclusion of the other names commonly employed

Synonyms—Riedel's struma chronic fibrous thyroiditis infiltrating fibroma of the thyroid eisenharte strumitis primary cancriform inflammation of the thyroid

Incidence—After all doubtful cases had been excluded Goodman (1941) identified 141 cases of Riedel's struma in the literature up to and including 1939 Since the appearance of his exhaustive review not less than 85 additional cases have been presented and discussed (Goetsch 1940a Womack 1944 Bothe 1944 Schilling 1945 Latimer 1946 Crile Jr 1948b Marshall Meissner and Smith 1948 Oldfield 1948 Merrington 1948 Brayton 1948 Lasser and Grayzel 1949) While there still appear to be some differences of opinion regarding the criteria by which we shall recognize each of the types of chronic thyroiditis nevertheless the number of accepted cases now affords a basis for a reasonably accurate clinical analysis However the problem is complicated by the fact that some cases present classical characteristics of both Riedel's and Hashimoto's strumata (Oldfield 1948 Merrington 1948)

Riedel's struma accounts for approximately 0 2 per cent of all thyroidectomies The condition is most common between the ages of 30 and 50 but has been observed in a 4 year old girl and in a 68 year old man (Goodman 1941) Women are affected three times as frequently as men A pre existing goiter has been discovered in 30 per cent of the subjects one worker observed a much higher incidence of goiter having found a degenerating adenoma in seven of his eleven subjects (Crile Jr 1948b)

Pathology—In the earlier stages of struma ligneosa the thyroid gland may be pale pink normally confined and almost entirely free of adhesions to surrounding structures Eventually however the chronic inflammatory reaction and replacement of thyroid with fibrous tissue produce a gross appearance which is highly characteristic This fibrous tissue proliferation is so abundant as to form a bulky tumor

Chapter XXVI

THYROIDITIS II CHRONIC

There are several ways in which chronic thyroiditis may develop

1 *The factors producing acute and subacute thyroiditis may continue to act after the clinical condition has disappeared* Subacute and, later chronic inflammation ensues which, in some instances apparently gives rise to a ligneous type of the disease and in others to a lymphomatous form (Boyden Coller and Bugher 1935 DeCourcy 1913 DeCourcy and DeCourcy 1918)

2 *Toxic goiter may be associated with histological evidences of a chronic inflammatory process* In the course of involution of the hyperthyroid gland, hypothyroidism and sometimes myxedema may occur

3 *Hashimoto's and Riedel's strumata may arise de novo* Any connection between acute and chronic thyroiditis is flatly denied by some authorities, but there is certainly evidence that one may lead to the other Even if the chronic varieties of thyroiditis are clinically distinct from each other as would appear now to be true it has not been disproved that they may actually represent differences in individual responses to strikingly similar stimuli influenced by such things as age sex previous infections food habits and so forth

'SIMPLE" CHRONIC THYROIDITIS

As a rule, this type of chronic thyroiditis is associated with a goiter for which surgical resection has been carried out On histological examination such glands show unmistakable evidences of chronic inflammatory change which are usually diffuse and involve both lobes Lymphocytes dominate the histological picture and may occur in clumps with or without typical germ centers There is proliferation of the connective tissue stroma with an increase in plasma cells Degeneration of the epithelial elements depends upon the severity of the process Clinically this 'simple' chronic thyroiditis is important because it may give rise to myxedema spontaneously or following subtotal thyroidectomy If the nature and severity of the changes are recognized at operation, the surgeon may minimize the postoperative complications by leaving a higher percentage than usual of the thyroid tissue

a malignant growth especially in 30 per cent of the patients who had a previously existing nodular goiter However while Riedel's struma becomes attached to the muscles and other structures adjacent to the gland unlike malignant growths it is never fixed to the skin

When the mass is localized and unilateral it rarely becomes larger than a goose egg Bilateral involvement occurs in about half of the cases In extreme instances the fibrous tissue growth may extend from the bifurcation of the trachea to the base of the skull fusing the blood vessels and the ribbon muscles into one conglomerate mass

Tracheal deviation and compression may occur occasionally producing *unilateral laryngeal paralysis* that is associated with hoarseness There is never any involvement of the cervical lymph glands

Signs of hyperthyroidism are relatively common especially in the early stages While the basal metabolic rate may be elevated in such cases this is dependent more upon nervousness and an anxiety state than upon an increase in the activity of function of the thyroid follicles Late in the disease destruction of normal functioning tissue may be so markedly advanced as to produce hypothyroidism with or without myxedema

The most striking symptoms of ligneous thyroiditis and those for which the patient usually consults the physician are the result of pressure *Disturbances caused by pressure are more pronounced in this* than in any other known thyroid disorder Early there is an awareness of the thyroid gland Later dyspnea is the most striking feature and occurs in more than 50 per cent of all cases It is quite independent of the size of the gland which helps to differentiate it from dyspnea due to malignancy

The pressure symptoms are due to the invasive nature of the proliferative fibrous tissue process and in addition to dyspnea include dysphagia dry hacking cough hoarseness and finally respiratory stridor The dyspnea and dysphagia result from the encirclement and constriction of the trachea and esophagus respectively They are the foremost and commonest of the symptoms and are found in over 50 per cent of all cases Pain and tenderness are usually localized over the thyroid mass When they radiate to the ears shoulders or chest the condition is usually in a transitional stage similar to that described by Schilling (1945) as struma ligneosa giant cell variant

In struma ligneosa the general health of the patient is usually not impaired unless the constrictive phenomena are too long ignored In the latter instance the heart may undergo hypertrophy with secondary strain and failure or the nutritional status may be lowered as a result of the decreased intake of food and consequent loss of weight

Differential Diagnosis (Table X) —A smooth stony hard goiter fixed to underlying muscles and fascia and associated with pressure symptoms out of all proportion to its size is always suggestive of Riedel's

which is sometimes five or six times as large as the lobe of the thyroid from which it originated A degenerating adenoma may be found as its center One or both lobes may be partially or wholly involved The entire mass is stony hard and attached to all the surrounding structures of the neck with the exception of the skin Natural planes of cleavage are lost as the thyroid capsule the trachea the ribbon muscles the carotid sheath the recurrent laryngeal nerves and other vessels of the neck are gradually enveloped in the fibrotic invasive process As Crile (1918) has aptly said The disease is in reality a diffuse fibrosis of the neck with the thyroid at its center

The gland and surrounding structures are brittle and cut like cartilage Normal lobulation may be entirely lost Occasional yellowish islands of colloid containing tissue break the monotony of an otherwise dull white avascular surface

It has been difficult to follow histologically the entire course of this or any other of the chronic inflammations which may involve the thyroid gland Simple chronic thyroiditis ligneous thyroiditis and Hashimoto's disease can be rather sharply separated clinically However histological elements of all three may be seen in the thyroid of any individual case (Graham 1940) It is an attractive premise that all forms of thyroiditis are closely interrelated and that while chronic forms may frequently arise *de novo* they may at other times represent the continuation of an acute inflammatory process through subacute and chronic phases (Goetsch 1910 German 1940 Goodman 1941 De Courcy 1943 Schilling 1945) Such phases may be made out in connection with many cases of struma ligneosa where there is an early infiltration of perivascular spaces with lymphocytes plasma cells neutrophiles and eosinophiles The ensuing proliferation of adult fibrous tissue slowly strangles the functioning thyroid elements Degeneration and desquamation of the follicular structures follow with the development of granulomas containing pseudogiant cells (Goetsch 1940 German 1940 DeCourcy 1943 Schilling 1945) These giant cells are derived from coalesced masses of degenerative desquamating follicular cells and have nothing to do either cytologically or functionally with the giant cells characteristic of tuberculosis and other specific granulomas which are derived from the reticuloendothelial system (Goetsch 1940 German 1940 DeCourcy 1943) When the fibrosing process is extreme or of long duration nearly all the elements of functioning thyroid tissue disappear completely

Clinical Picture—Clinical manifestations of Riedel's struma have been present for from one to several years when the patient appears for treatment (Table X) Variations from patient to patient in the clinical syndrome that develops depend upon the presence of a goiter the alterations of thyroid function and the disturbances due to pressure The smooth stony hard gland is characteristic but may be mistaken for

Pathological characteristics in the thyroid	Congested hyperemic bleeding tendency increased perivascular round-cell infiltration	Smooth grayish white gland bleeding tendency decreased acinar epithelium degenerated in involved areas dense lymphocytic infiltration with plasma cells and histiocytes giant cells periarteriolar fibrosis and thickening adenoma may be present	White smooth hard surface bleeding tendency decreased dense adhesions epithelium destroyed marked fibrosis round cell infiltration and colloid spillage thickening of intima and media of blood vessels adenoma associated not infrequently acidophilia absent or slight	Pseudolobulated with a yellowish cast bleeding tendency variable occasional pretracheal adhesions epithelium low cuboidal with slow degeneration and marked acidophilia scanty to absent colloid diffuse lymphocytic infiltration with formation of germinal centers
Treatment Roentgen radiation	Effects unknown	Small doses relieve promptly hypothyroidism follows occasionally	No effect	Response excellent but not often used as diagnosis is hard to establish
Thoracic groups	Course materially shortened		Contraindicated	
Surgery	Contraindicated except for drainage of abscess or symptoms of tracheal compression		Resection of all involved areas or wedge shaped excision of isthmus	Subtotal thyroidectomy
Postoperative course			Myxedema occasionally fibrosis may cause parathyroid tetany or laryngeal paralysis	About 80% develop myxedema

TABLE X
FINDINGS IN VARIOUS TYPES OF NONSPECIFIC THYROIDITIS

	ACUTE	SUBACUTE	RIEDEL'S	HASHIMOTO'S
Age (years)	20–40	20–40	30–50	40–60
Sex (M:F)	1:9	1:7	1:3	1:9
Duration of symptoms	One to several days	Several days to several months	Several months to several years	Two to five years with recent aggravation
Outstanding complaints	Intense pain often radiating to ear, jaw or occiput, swelling of neck	Pain often radiating to ear, jaw or occiput, pressure	Pressure symptoms, marked nervousness secondary to anxiety state	Goiter, mild or no pressure symptoms
Tenderness of thyroid	Marked—100%	Moderate—100%	Mild—10%	Rarely present
Fever	Usual, abrupt onset, often high	Common, low-grade, long continued	None	None
Pulse rate	Disproportionately high	High	Usually normal although high if anxiety state appears	Normal or low
Degree of thyroid involvement	Always diffuse	Diffuse	Unilateral—50%	Unilateral—70%
Palpatory findings	Exquisitely tender, diffusely enlarged, fluctuant with abscess	Generalized tenderness, firm	Stony hard, smooth, fixed to deep structures	Hard
Leukocyte count	High, polymorphonucleocytosis	Normal to high	Normal	Normal, total, relative lymphocytosis
BMR	Elevation due to fever and restlessness		Normal	Low—30%

Incidence—Lymphadenoid goiter occurs about as frequently as Riedel's struma and approximately one fifth as often as the more acute forms of thyroiditis. Of 11 000 thyroidectomies between 0.5 and 1 per cent were performed upon patients with Hashimoto's disease (McSwain and Moore 1943). The disease occurs most frequently between the ages of 40 and 60 with an average of the data of several investigators given as 48 years (McSwain and Moore 1943, Crile Jr. 1948, Schilling 1945, Lasser and Grayzel 1949). Ninety one of 97 patients were females.

Pathology—The enlargement of the thyroid may be considerable. McSwain and Moore (1943) found its average weight in 86 subjects to be 87 grams with a variation in size from 7 to 340 grams. All parts of the gland are affected so that the thyroid is uniformly increased in size and is conspicuously free of adenomatous masses.

While no single clinical or pathological feature of Hashimoto's disease is pathognomonic (Graham 1940) the combined data point to the condition as a clinicopathological entity.

The diffuse enlargement of the thyroid involves all prolongations and extensions of the gland and frequently proceeds posteriorly to encircle the trachea. The gland is firm, smooth or pseudolobulated in shape, friable, variable in color from grayish through yellow and orange to brown and usually has a diminished vascularity. The cut surface is grayish to yellow as a rule with a bosselated or pseudolobulated appearance and shows little evidence of colloid.

Microscopically any active exudative inflammatory process within the acini or around the blood vessels is conspicuous by its absence. In striking contrast to Riedel's struma significant changes in the vascular wall other than those incidental to a coexisting arteriosclerosis are not seen. The diffuse lymphocytic infiltration of all portions of the gland is the most striking single feature of the microscopic picture. Many fully formed lymph follicles are present with their characteristic germinal centers comprised of larger lymphocytes and reticulum cells showing mitotic figures. Leucocytes and pseudogiant cells are extremely rare. Plasma cells and large monocytes are not uncommonly seen; one case of plasmocytoma of the thyroid has been reported to have its origin in a lymphadenoid goiter (Shaw and Smith 1940).

Throughout the thyroid gland there is a degeneration of acini with a flattened, very low cuboidal epithelium the cells of which show dark, eccentrically located nuclei. The shrunken, sometimes coalesced follicles contain little or no colloid. Trabeculation is usually well marked but the texture of the fibrous tissue infiltration is usually of a finer waving texture than that seen in struma ligneosa (Schilling 1945). It appears in whorls about the lobules and usually lacks the features of hard, dense, productive cicatrization seen in Riedel's thyroiditis. The connective tissue changes probably represent a late mani-

struma particularly if there has been little or no damage to the general health Foremost among the conditions with which it may be confused are

1 *Cancer of the Thyroid*—Cancer of the thyroid is commonly engrafted upon a previously adenomatous goiter and while stony hard is also irregular and nodular in outline The skin and cervical lymph glands are usually enlarged Pain occurs frequently and may be so severe that it alone prompts the patient to see his physician Involvement of the recurrent laryngeal nerve is common early and severe in carcinoma and usually infrequent late and mild in Riedel's struma

2 *Hashimoto's Disease*—Struma lymphomatosa rarely occurs in men it enlarges the thyroid uniformly but the gland is never stony hard Pressure effects are few and usually mild The condition responds promptly to roentgen radiation Myxedema is a common and often early complication

3 *Infections of the Thyroid Associated With Necrosis or Suppuration*—Such infections as tuberculosis syphilis actinomycosis and pyogenic conditions may occur rarely and require differentiation from struma ligneosa As a rule etiologically related lesions are present elsewhere in the body The lymph nodes are enlarged Except in syphilis suppuration occurs the gland becomes fluctuant subsequently breaking down with the formation of a sinus tract

Treatment—The treatment of Riedel's struma is entirely surgical If the involved area is confined to a single lobe it may be completely resected together with the isthmus When the entire gland and surrounding structures are affected all of the gland which can be safely freed may be removed Sometimes this is a tedious and dangerous procedure In such instances a wedge shaped resection of the isthmus over the trachea is advisable This will completely relieve the pressure symptoms and is commonly followed by subsidence of symptoms It may be necessary to operate in order to rule out the presence of cancer when the diagnosis is in doubt there should be no hesitancy in proceeding with the operation Myxedema may occasionally develop following operative intervention

STRUMA LYMPHOMATOSA

Synonyms—Hashimoto's disease lymphadenoid goiter

Definition—Struma lymphomatosa is a comparatively rare progressive disease of unknown etiology in which there is widespread acidophilic degeneration of epithelial elements of the thyroid with replacement by lymphoid and fibrous tissue Moderate enlargement of the thyroid occurs and interference with its function is commonly so great as to cause hypothyroidism or myxedema

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festation of the disease process (Graham 1910) while isolated hyperplastic areas may represent attempts at functional compensation (Massachusetts General Hospital 1919) Indeed it has been suggested that the lymphadenoid changes in Hashimoto's disease are due to a relative ischemia in a gland subjected to increased thyrotrophic stimulation (Goldberg and Dawson 1918)

Clinical Picture—The onset of Hashimoto's disease is insidious, with few if any subjective symptoms This is in sharp contrast to the early appearance of pressure symptoms in Riedel's struma As a rule the patient seeks advice for the swelling in her neck which has been present for from two to five years but shortly prior to her first visit to the physician has increased in size over a relatively short period of time One or more pressure symptoms may be present, and are mentioned somewhat in the order of the frequency with which they occur dyspnea pressure sensation or other vague discomfort in the neck cough hoarseness or other alteration in the voice choking sensation, and dysphagia As a rule, none of these appear with the same frequency or with the same severity as in Riedel's struma Moreover, when the age of the patient is considered and the local phenomena in the neck fully evaluated it seems likely that some of these manifestations may be traced to a coexisting disturbance in ovarian function

The gland is uniformly and diffusely enlarged and in two thirds or more of the subjects is fixed to some neighboring structure usually the trachea less frequently to the ribbon muscles or large vessels Immobilization of the thyroid to the extent commonly seen in Riedel's struma does not occur

The nutritional status of the patient is good indeed the majority are overweight Spontaneous hypothyroidism appears in one third or more of the unoperated patients (McSwain and Moore 1913) and is evidenced by nervousness easy fatigability loss of weight and less commonly the cardinal symptoms and signs of myxedema (Chapter XXX) Fever occasionally occurs but pain and tenderness over the thyroid are almost never observed The disease runs a progressive course in which remissions rarely if ever occur

Laboratory Data—No pathognomonic laboratory finding exists for confirming the diagnosis of Hashimoto's disease

a Basal Metabolic Rate—The basal metabolic rate is usually low and in some instances reaches the levels observed in myxedema However until very late in the disease there is usually sufficient functioning tissue present to maintain the value within normal range (−10 to +15) Postoperatively, 80 per cent show abnormally low basal metabolic rates

b The White Blood Cell Count—The total leucocyte count is usually normal but a relative and absolute lymphocytosis is the rule

c Gastric Acidity.—Anacidity has been reported and hypoacidity occurs in nearly half of the patients (Graham, 1940).

d Other Findings.—When either hypothyroidism or myxedema supervenes the laboratory data reflect the physiological disturbances accompanying those states.

Diagnosis and Differential Diagnosis (Table X).—A slowly and progressively enlarging goiter of diffuse type occurring in a woman between the ages of 40 and 60 and associated with symptoms of hypothyroidism should lead us to suspect the presence of Hashimoto's disease. The greatest difficulty is experienced in differentiating the condition from simple colloid goiter and carcinoma.

a Simple Colloid Goiter.—Simple colloid goiter appears earlier in life than Hashimoto's disease. Colloid goiters may attain much greater size than the goiters of struma lymphomatosa despite which they rarely cause pressure symptoms probably because they completely lack the invasive character of the latter. Thyroid function is usually maintained at normal levels in the presence of a simple colloid goiter.

b Carcinoma of the Thyroid.—A previously existing adenoma, nodularity of the thyroid surface, pain early in the disease, more rapid growth and involvement of cervical lymph nodes all point more toward a carcinoma of the gland than to struma lymphomatosa. However, it is never easy to make a differential diagnosis between these two conditions, and a majority of the patients with struma lymphomatosa are operated upon in the belief that they probably harbor a thyroid cancer.

c Specific Forms of Thyroiditis.—Specific thyroid infections may usually be distinguished rather easily from struma lymphomatosa, as noted under the differential diagnosis of Riedel's struma (q.v. below) and in the descriptions of the individual conditions (Chapter XXVII).

Prognosis.—Spontaneous remission of struma lymphomatosa is apparently unknown. Following subtotal or total thyroidectomy, there is little or no tendency for recurrence. Postoperatively, hypothyroidism and myxedema are expected complications which may usually, but not always, be controlled by the proper use of thyroid hormone.

Treatment.—The radiosensitivity of struma lymphomatosa immediately implies the existence of a simple, safe and effective treatment. However, many cases cannot be correctly diagnosed prior to surgery and are operated upon with the belief that carcinoma exists. In others the invasive character is sufficiently great to necessitate operative procedure for the relief of pressure phenomena. Therefore, the actual number of subjects who have been treated with radiation therapy only is very few. Now that needle biopsy is available for thyroid diagnosis it seems possible that the group upon which such treatment will be tried should increase. It may be possible with care to apply roentgen

festation of the disease process (Graham, 1940) while isolated hyperplastic areas may represent attempts at functional compensation (Massachusetts General Hospital 1919) Indeed it has been suggested that the lymphadenoid changes in Hashimoto's disease are due to a relative ischemia in a gland subjected to increased thyrotrophic stimulation (Goldberg and Dawson 1948)

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ray therapy in such a manner that myxedema occurs less frequently than after surgical intervention. The same statement may apply to the use of radioactive iodine, although we are not aware of any critical trial of such material in this disease.

At the present time operative procedure is the only therapeutic measure which has been used in a sufficient number of cases to warrant critical evaluation. Subtotal or total thyroidectomy usually controls the condition but is followed in 80 per cent or more by hypothyroidism or myxedema. Subtotal thyroidectomy or even lobectomy appears to be preferable to complete thyroidectomy from the standpoint of general health, as the response of these patients to thyroid hormone is not always associated with a complete disappearance of all of the symptoms, especially in regard to the weakness and easy fatigability (Crile Jr., 1948a).

In addition to its therapeutic value, roentgen radiation may be of use in differentiating cancer of the thyroid, as the latter lesion is not responsive to any great degree when treated roentgenologically.

THE NATURE OF RIEDEL'S AND HASHIMOTO'S STRUMATA

Inasmuch as mixed forms of chronic thyroiditis, showing elements common to both Riedel's and Hashimoto's strumata, occur not infrequently, it has been suggested that these lesions represent different phases of the same condition. Graham (1931, 1940), Graham and McCullagh (1931), and many other workers take the stand that the two conditions are distinct clinical syndromes, while still other observers are inclined to believe that each represents a different stage in the same fundamental process (Boyden, Collet, and Bugher, 1935; Womack, 1944). Several facts favor the former view:

1. Some differences in etiology and pathogenesis may be made out (*vide infra*).

2. Hashimoto's disease rarely occurs in men. Riedel's struma is seen in women only three times as frequently as in men.

3. Hashimoto's disease is rarely found in persons under 10 years old and usually appears at the menopause or thereafter. Riedel's struma is noted at any age but predominantly between 25 and 40 years.

4. Hashimoto's disease involves the thyroid diffusely from the onset; no part of the gland escapes. Riedel's struma is usually focal and only late in its course may extend widely.

5. Myxedema is a common sequela of Hashimoto's disease, whether surgically treated or not. It is seen infrequently in Riedel's struma even after operation.

6. Scar tissue formation in Hashimoto's disease is fine, wavy, and limited in amount until very late, while coarse, dense scar, sometimes resembling that of a keloid, is observed in Riedel's struma.

Heyd's (1929) case is suggestive of the fact that the thyroid may at one time show aspects of Riedel's struma and at another those of Hashimoto's disease On histological examination McCarrison (1929) saw elements of both conditions in his experimental animals In Oldfield's (1918) Merrington's (1918) and Latimer's (1946) patients both types of pathology were coexistent Iodine metabolism is not disturbed in either condition until sufficient follicular destruction has taken place to diminish the output of a normal amount of thyroid hormone Blood levels for iodine in the chronic types of thyroiditis have been reported as normal (Curtis and Leitman 1915)

At the present time the clinical and pathological differences between Riedel's and Hashimoto's struma outweigh the similarities and seem to justify thoroughly the acceptance of each as a distinct and separate clinicopathological entity

Very little is known regarding the origin or pathogenesis of any form of chronic thyroiditis However the origin of acute and subacute thyroiditis in the course of or following an acute infectious process seems to be well established The giant cell variant of Riedel's struma as described by de Quervain and Giordanengo (1936) corresponds closely to subacute thyroiditis ending in a Riedel's form of chronic thyroiditis The evidence for the origin of Riedel's struma in an acute or subacute thyroiditis at least in some cases seems to be overwhelming (Goetsch 1910 German 1910 Graham 1910 McSwain and Moore 1943 DeCourcy 1943) With those who doubt such a relationship rests the burden of disproving it

Any real knowledge of the origin of Hashimoto's disease seems to be completely lacking An effort has been made to connect it etiologically with ovarian deficiency (Cheney and Mezey 1946 Parmley and Hellwig 1946) and the repercussions of such deficiency upon the regulation of the thyroid by the pituitary Goldberg and Dixson (1948) adduce considerable evidence to show that the changes of lymphadenoid goiter are due to the development of relative ischemia in a gland subjected to increased thyrotrophic stimulation On the basis of experimentally induced thyroid enlargements in rats McCarrison (1929) believes that diets poor in green vegetables fresh fruits and vitamins are capable of producing a histological picture resembling Hashimoto's disease He fed potassium iodide in conjunction with such diets Inasmuch as Boyden and his associates (1935) believe that the ingestion of iodine in excessive quantities is capable of causing a condition simulating that described by Hashimoto it is difficult to evaluate the role of diet or of any other single factor in the pathogenesis of the disturbance seen by McCarrison Despite characteristic clinical and pathologic features the etiology of the condition remains as obscure as when it was first described by Hashimoto

ray therapy in such a manner that myxedema occurs less frequently than after surgical intervention The same statement may apply to the use of radioactive iodine although we are not aware of any critical trial of such material in this disease

At the present time operative procedure is the only therapeutic measure which has been used in sufficient number of cases to warrant critical evaluation Subtotal or total thyroidectomy usually controls the condition, but is followed in 80 per cent or more by hypothyroidism or myxedema Subtotal thyroidectomy or even lobectomy, appears to be preferable to complete thyroidectomy from the standpoint of general health, as the response of these patients to thyroid hormone is not always associated with a complete disappearance of all of the symptoms especially in regard to the weakness and easy fatigability (Crile, Jr 1918 a)

In addition to its therapeutic value roentgen radiation may be of use in differentiating cancer of the thyroid as the latter lesion is not responsive to any great degree when treated roentgenologically

THE NATURE OF RIEDEL'S AND HASHIMOTO'S STRUMATA

Inasmuch as mixed forms of chronic thyroiditis showing elements contained in both Riedel's and Hashimoto's strumata occur not infrequently it has been suggested that these lesions represent different phases of the same condition Graham (1931 1940) Graham and McCullagh (1931) and many other workers take the stand that the two conditions are distinct clinical syndromes while still other observers are inclined to believe that each represents a different stage in the same fundamental process (Boyden Coller and Bugher 1935 Womack 1944) Several facts favor the former view

1 Some differences in etiology and pathogenesis may be made out (*vide infra*)

2 Hashimoto's disease rarely occurs in men Riedel's struma is seen in women only three times as frequently as in men

3 Hashimoto's disease is rarely found in persons under 40 years old and usually appears at the menopause or thereafter *Riedel's struma* is noted at any age but predominantly between 25 and 40 years

4 Hashimoto's disease involves the thyroid diffusely from the onset no part of the gland escapes Riedel's struma is usually focal and only late in its course may extend widely

5 Myxedema is a common sequel of Hashimoto's disease whether surgically treated or not It is seen infrequently in Riedel's struma even after operation

6 Scar tissue formation in Hashimoto's disease is fine wavy and limited in amount until very late while coarse dense scar sometimes resembling that of a keloid is observed in Riedel's struma

Gumma of the thyroid is an extremely rare lesion which may be confused with malignant disease tuberculosis or Riedel's struma As a general rule the true nature of the lesion is not suspected unless clinical evidence of syphilis elsewhere or operation for a presumed cancer reveals the true character of the lesion

Treatment—The treatment for syphilis of the thyroid gland is the same as for syphilis in general In order to avoid permanent damage to the thyroid structures and also to escape the systemic ravages of the disease specific therapy should be instituted at as early a date as possible Moreover should the diagnosis be in doubt, the prompt disappearance of lesions under treatment will tend to confirm the presence of this condition Laird (1915) described the almost complete disappearance of a large gumma following a month of treatment with sodium iodide bismuth oxychloride and Mapharsen

III TUBERCULOSIS OF THE THYROID

The toxemia of an active tuberculous process anywhere in the body frequently causes readily recognizable morphological and functional changes in the thyroid gland (see Hyperthyroidism Chapter XXXIV) On the other hand tuberculous lesions within the gland itself are rare according to most authorities as quoted by Seed (1942) Other workers (McGregor and Peacock 1939) think the condition is frequently overlooked The divergence of opinion depends upon the difficulty encountered in arriving at a satisfactory diagnosis of tuberculous involvement of the thyroid tissue itself

In many instances clinicians have been satisfied to base their diagnosis wholly upon the pathologist's report that tubercles are present German (1940) has emphasized the fallacy of such a position According to him Most of these cases when studied do not bear up under critical analysis and fail to satisfy the criteria necessary for an indisputable diagnosis of tuberculosis The lesion certainly becomes a rare one if Seed's postulates are fulfilled (1) tubercle bacilli must be found in the lesions (2) definite caseation necrosis or abscess formation must be demonstrated histologically and (3) an etiological tuberculous focus must be demonstrated elsewhere in the body

Classification—Tuberculous infection of the thyroid may take one of the following forms (1) miliary tuberculosis in which the thyroid findings are incidental to the systemic process (2) caseation necrosis with abscess formation secondary to an advanced tuberculous process in some other part of the body usually the lung and (3) a diffuse fibrous noncaseous type of tuberculosis secondary to or associated with demonstrable tuberculosis in other tissues this condition resembles a ligneous thyroiditis both macroscopically and microscopically

Chapter XXVII

SPECIFIC CHRONIC INFECTIONS

I ACTINOMYCOSIS OF THE THYROID

Actinomycosis of the thyroid gland is a very rare condition usually due to a direct extension of the cervical lesions

II SYPHILIS OF THE THYROID

Classification—Syphilis of the thyroid gland may be congenital or acquired In the *congenital* variety which is very rare and asymptomatic a diffuse *interstitial fibrosis associated with lymphocytic* infiltration is characteristic Occasionally gumma is present

Acquired syphilis may take the form of a chronic diffuse inflammation *of the thyroid or of a localized gummatous lesion* Sloan (1936) believes that acquired syphilitic inflammation of the thyroid is more common than is generally supposed

Pathology—The lesions in syphilis of the thyroid resemble those of the disease in other localizations

Clinical Course—Syphilis of the thyroid gland produces both local and generalized manifestations due to the disturbance within the thyroid *Both the gummatous deposits and the diffuse sclerosing* lesions of an inflammatory nature may produce a hard resistant goiter frequently leading to an erroneous diagnosis of carcinoma Associated involvement of the larynx trachea and cervical lymph nodes is not uncommon Subjectively particularly with a syphilitic thyroiditis of a diffuse type the patient complains of vague pains *in the neck* which are aggravated by swallowing and are frequently referred upward to the angle of the jaw or to the ear Occasionally there is tenderness of the gland In untreated syphilitic thyroiditis diffuse hyperplastic goiter occurs at times associated with exophthalmos Barber (1917) has observed thyrotoxicosis secondary to a gumma *which also caused* tracheal obstruction

Diagnosis and Differential Diagnosis—A diffuse syphilitic process in the thyroid gland will usually go unrecognized until it produces *the* symptoms of a chronic thyroiditis when at the time of operation the true nature of the disease is discovered

The tumefaction causes pressure symptoms such as dysphonia dysphagia and dyspnea each of variable severity Pain may be present but is never a prominent symptom Alteration in the functional status of the thyroid gland is rarely if ever seen

The diagnosis cannot be made with certainty before operation is performed The condition may simulate nontoxic adenoma or Riedel's struma

Prognosis for the lesion itself is good following surgical drainage or complete removal of the involved area although healing may be slow The ultimate prognosis depends of course upon the severity of the primary lesion

Lobectomy represents ideal treatment if the condition is well localized and the gland is firm and freely movable If widespread inflammation with fluctuation is present incision and drainage alone should be attempted

3 *Tuberculosis Simulating Ligneous Thyroiditis*—Tuberculosis of the thyroid gland simulating ligneous thyroiditis is a hazardous diagnosis at best Attention has been called repeatedly to the association of the condition with the signs and symptoms of thyrotoxicosis (Comando 1912 Seed 1912 Klassen and Curtis 1945 McGregor and Peacock 1939 Storey 1911) In such instances the thyroid is usually enlarged and the entire picture clinically resembles that of nodular toxic goiter so much so in fact that the diagnosis of tuberculosis is almost never made until characteristic giant cells and tubercles are demonstrated in the tissues Even the presence of these structures does not settle the diagnosis for both Broders (1910) and German (1910) have stressed the fact that it is necessary not only to find giant cells and tubercles but also to demonstrate the tubercle bacillus itself in such lesions before they can be looked upon as tuberculous in origin

Of 205 thyroid glands studied German found four which presented granulomatous lesions indistinguishable from young tubercles seen in tuberculous infection When the entire picture was considered as a whole two of these four glands represented Graves disease of long standing in which degenerative phenomena and fibrosis had occurred while two were instances of fibrous thyroiditis or Riedel's struma There is therefore grave doubt despite reports to the contrary that primary tuberculosis of the thyroid gland ever exists

Summary of Tuberculosis of the Thyroid - The toxemia of tuberculosis alters the functional status of the thyroid gland usually producing overactivity associated with hyperplasia and sclerosis the degree of each varying with the activity of the tuberculous process The gland is probably never the site of primary tuberculosis It may be secondarily invaded as a part of a generalized miliary tuberculosis or as a caseation necrosis in connection with a primary focus elsewhere Thyroid function is rarely if ever disturbed as a result of the invasion of the gland by tubercle bacilli

Incidence and Pathogenesis—If all fictitious cases are excluded tuberculosis of the thyroid gland is a very rare condition having been reported in about 250 patients (Stubbins and Guthrie 1918). These authors found one case of tuberculous abscess of the thyroid gland among 561 thyroidectomies performed over a period of ten years. In this instance the diagnosis was not made until the time of operation.

The rarity of tuberculous involvement of the thyroid has been ascribed to its relative lack of reticuloendothelial cells (Stubbins and Guthrie 1918). As the organs of this system such as the spleen lymph nodes and bone marrow are readily attacked by tubercle bacilli. The remarkable blood supply of the thyroid may be another reason for the infrequency with which tuberculous invasion occurs. The bacillus thrives best when oxygen tensions are slightly lowered. Invasion of the thyroid by any infection may cause irritation and increased functional activity. The increased production of thyroxin which follows may tend further to prevent any permanent damage from the tubercle bacillus (Izzo and Ciccardo 1947).

Clinical Picture—The clinical picture of tuberculosis of the thyroid gland depends upon which of the three types of process is present.

1 Miliary Tuberculosis—In miliary tuberculosis where miliary tubercles are discovered in the thyroid gland no symptoms or signs whatsoever can be traced directly to the lesions within the thyroid.

2 Secondary Tuberculosis With Caseation Necrosis and Abscess Formation—For cases with caseation necrosis and abscess formation the clinical picture has been described recently by Postlethwait and Berg (1944), Klassen and Curtis (1945), and Stubbins and Guthrie (1948). If we add to the data these workers have summarized the cases reported by Coggi (1947) and by Soustelle and associates (1947) there appear to have been a total of 33 well authenticated cases of this type recorded in the literature. This form of tuberculosis is never primary in the thyroid itself. However the focus from which the thyroid lesion originates may be difficult to demonstrate (Klassen and Curtis 1945). By far the commonest site is the lung. Moreover the pulmonary lesions are usually far advanced when caseation necrosis of the thyroid occurs. The condition may complicate a tuberculous osteomyelitis. It has also been observed as a direct extension from the cervical lymph glands trachea and larynx.

The condition appears with equal frequency in the two sexes. It has been observed as early as the seventh year of life and as late as the seventy fourth year. Prior to the tuberculous involvement the thyroid gland has usually been normal.

The thyroid lesion makes itself manifest as a firm smooth sometimes cystic occasionally tender and less frequently fluctuant swelling of the thyroid usually noticed by the patient for several months prior to medical consultation. It is rarely fixed to surrounding structures.

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Chapter XXVIII

IODINE DEFICIENCY GOITER (SUBIODIC GOITER)

Synonyms —Simple goiter struma bronchocele Derbyshire neck Kropf goiter colloid goiter iodine want goiter endemic goiter subiodic goiter

Definition —By *iodine deficiency goiter* we mean a work hypertrophy and hyperplasia of the thyroid occurring endemically sporadically and possibly epidemically in which a variety of etiological factors may be concerned Irrespective of the predisposing factors which are present and active the immediate or exciting cause is relative or absolute nonavailability of iodine for the completion of the processes by which thyroid hormone is produced

Synonyms most frequently and widely applied to this type of goiter have been simple goiter endemic goiter and colloid goiter There is no name thus far devised including the one heading this chapter that is completely informative The word simple leads to the inference that its mode of production its pathologic physiology pathology clinical course and ultimate outcome are less complex than those relating to other disturbances of the thyroid In the present state of our knowledge nothing appears to be further from the truth The word endemic is clearly limited As an attempt at pathological classification the term colloid merely serves to stress one frequently observed feature to the complete exclusion of all others

In using the phrase iodine deficiency goiter or the shorter term subiodic goiter it is intended to call attention to one common feature of *all* cases of the disease without regard for the origin of the deficiency or its relative or absolute degree

Etiology and Pathogenesis — In view of the recent heated discussions on the subject of iodine want and endemic goiter clarification of many factors concerned in altering the physiological status of the thyroid demands our consideration

The importance of the iodine factor in so called simple or colloid goiter was early stressed by Marine and Lenhart (1909b) Marine's conclusions in 1921 concerning the fundamental role of iodine in the causation and prophylaxis of subiodic goiter have been repeatedly confirmed

To sum up the evidence at present available concerning the etiology of goiter I believe we may abandon the older views that it is due to a specific living virus or a specific chemical substance and conclude that simple goiter is a compensatory or work hypertrophy depending upon a variety of metabolic stimuli for functional activity of the thyroid which depletes its iodin store The immediate cause of thyroid enlargement is a relative or an absolute deficiency of iodin This deficiency may result from

(1) Any factors which increase the needs of the organism for the iodin containing hormone as occur during puberty pregnancy and lactation during the menopause during certain infections and intoxications following sufficient injuries to the interrenal gland or as a result of diets consisting mainly of fats and protein

(2) Any factors which interfere with the absorption or utilization of the normal intake of iodin We have no knowledge as yet of such factors although it is conceivable that the intestinal bacterial flora or intestinal parasites could utilize or divert part of the iodin intake

(3) Factors which bring about an abnormally low intake or actual deprivation of iodin either natural or experimental The normal source of iodin is from food and water though traces may be taken by breathing the air in the immediate vicinity of the sea In districts of endemic goiter both the food and water derived from such soils have been proven to be very low in iodin

Corresponding to these three types of deficiency of iodine three groups of patients may be recognized

Group 1 Those in whom there is a relative insufficiency of thyroid hormone due to a temporary increase in bodily needs Physiologically the amount of iodine in the thyroid increases steadily from birth to puberty A maximum concentration is observed about the age of 20 which is maintained until approximately the age of 50 after that it decreases slowly There is no sex difference in the iodine content of the gland (Kimball and Hamilton 1940)

Common conditions increasing the demand for thyroxin thus bringing about a relative iodine deficiency include (a) improper diets (Greer 1950—*in vitro*) particularly diets (i) high in fat or protein with a low iodine content (ii) low in vitamins A (Steidle 1949) and C (McCarrison 1920 1928 Abercrombie 1935) and (iii) low in thiamine (Sure 1938) (b) starvation (c) infectious diseases (d) exophthalmic goiter (e) administration of thyrotrophic hormone (f) anemia (g) high altitude and (h) periods of physiological stress particularly exposure to cold puberty marriage pregnancy lactation and the climacterium

All too little is known about the practical application of these recognized conditioning factors in the actual development of endemic and sporadic goiter For instance thyroid enlargements even in a goitrous belt are in part genetically and sexually determined (Ryle 1917) This may explain why Clements (1948) and Osmond and Clements (1948) were unable to establish a positive relationship between the dietary food pattern of families and the incidence or severity of goiter among children in three well known endemic foci of goiter All

these children had an inadequate intake of calories, protein, iron, thiamine and ascorbic acid but in many instances there was a deficiency of vitamin A and calcium

Obviously all the influences mentioned may be equally active in goitrous and nongoitrous regions Variations in their appearance and intensity readily explain why all persons in a *moderately goitrous belt* do not develop an enlarged gland

Group 2 Those patients in whom there is an interference with the absorption or utilization of otherwise adequate supplies of iodine It is not clear what all these factors are but thyroid disturbances set up by members of the Brassica group of vegetables the cyanides and thiocyanates inulin and its derivatives thiourea and its derivatives and a number of other chemical compounds all fall into this group At least as far as cabbage goiters are concerned they may play a predisposing role in the development of some of the endemic goitrous centers of the world

The prevalence of *goiter in limestone countries (Robertson 1912)* is related to factors in the water or food chiefly the increased amount of calcium ingested

Attention has recently been called to the fact that goiter is endemic in mountainous areas near oil fields where there are radioactive substances in the soil which originate from marine sapropel In such locations ekaiodine (alabamine) and radon are ingested displace stable iodine from the thyroid gland and cause irreversible injury to its tissues by alpha radiation (Romell 1948 Berenesi and Matthes 1948)

Hinton and his associates (1931) have been able to show experimentally that despite an adequate intake of iodine completely parathyreotomized dogs will develop goiters because insufficient quantities of tyrosine are present to form thyroid hormone

Lymphadenoid goiter may be a variant of simple goiter usually occurring in or past the menopause and is believed to be a disturbance of cyclic thyroid activity due to a loss of ovarian function in which slitlike acini and strands of large oxyphilic cells resembling *hepatic or* adrenal cells constitute the predominant histological changes within the *thyroid (Parmley and Hellwig 1946)*

Greenwald (1915 1916 1919 1950) has again called attention to goiter epidemics long ago mentioned by Hirsch (1883) His findings indicate one factor in the production of goiters is a biological agent possibly a virus He bases this conclusion on the fact that such outbreaks of goiter have occurred in areas previously completely free and that in many instances endemic areas of goiter have almost completely disappeared *without any known change in water supply or iodine* ingestion The most striking example he uses is the disappearance of goiter in Derbyshire where goiter was first noted in England Later the condition became more widespread and is now most common in the south

western corner of the island This subject is further discussed in relation to the third group of patients in whom we believe the goiter is due to an insufficient quantity of iodine ingested (*vide infra*)

That the above and a number of other factors concerned with the activity of the thyroid gland may be potent influences in the production of subiodic goiter there is little doubt That their action uniformly results in an incapacity of the thyroid gland to synthesize its specific metabolic hormone we will all agree That this failure is ultimately due in *all* instances to nonavailability of iodine may be open to question Experimentally at least the failure may be a lack of tyrosine (Hinton et al 1931) However in medical practice it is difficult ever to implicate an inadequate supply of this raw material needed for thyroid hormone synthesis and comparatively easy to ascribe the disturbance to an absolute or relative lack of the other essential raw material iodine Therefore in the current state of knowledge it seems best to advocate the most widely accepted tenet that while many factors predispose to the development of simple goiter clinically the immediate exciting or precipitating cause is a relative or absolute lack of iodine as a raw material upon which enzyme and hormonal factors act to effect their manufacture of thyroid hormone

Group 3 Patients with an abnormally low intake of iodine Patients with an abnormally low intake of iodine as for instance the 12 to 15 micrograms recently found in Tipperary school children (O Donovan 1950) represent the endemic cases of goiter and some of the sporadic cases Both food and water contain insufficient quantities of iodine The two statements just made have been seriously challenged and not without reason However when qualified by recognizing that the incidence degree and severity of the goiters will depend not only upon the inadequate supply of iodine but also upon all the predisposing factors above mentioned then no exception of which I am aware can be taken to them

Greenwald (1945 1946 1949 1950) has vigorously championed the point that iodine deficiency is not the cause of simple colloid goiter In so far as we are aware no one has adopted the obverse viewpoint that iodine lack is the only and sole cause of such thyroid disturbance That iodine represents satisfactory prophylaxis against simple goiter and is helpful but less adequate therapy for the already established condition does not constitute a priori evidence that a deficiency of iodine is the cause of the condition However conclusive evidence of the ability of a low intake of iodine to produce colloid goiter is now available Crucial experiments on rats have been carried out by McClendon and Foster (1917 b) in which all conceivable sources of goiter noxa were excluded from a dietary normal in all respects except for the complete absence of iodine Without exception these animals developed goitrous thyroids approximately four times the size of the normal thyroids

found in the litter mates which were used as controls and twice as large as goiters produced in a goitrous region in rats of goitrous mothers.' Until these experiments were performed Greenwald (1915, 1916) had claimed that in areas of endemic goiter not the iodine deficiency but some goiter nova possibly a virus was responsible for the thyroid enlargement. While the possibility that some goiters do so arise has not been disproved it has been shown beyond all reasonable doubt that iodine want *alone* is capable of producing the full blown picture of simple or colloid goiter.

On the converse side of this argument, is there evidence that certain conditioning factors are capable of producing simple or colloid goiter in the absence of a lack of iodine? If we confine this question to a consideration of the amount of iodine ingested, then the evidence appears to be clear cut that colloid or simple goiter can and does occur in the presence of an abundant ingestion of iodine. (1) goiter occurs endemically in regions known to be rich in iodine (Adlercreutz 1928, Hojer 1935 Lunde 1933 McCarrison 1929 Ucko 1947 Mahorner 1941 Cole 1941) and in endemic regions after the addition of abundant supplies of this element (Kimball 1939 1946), (2) the severity of endemic goiter does not always vary quantitatively in inverse ratio with the iodine content of the water and soil (Ucko 1947). (3) factors mentioned in a discussion of patients of groups 1 and 2 (*vide supra*) are capable of causing goiter even though the alimentation of iodine is sufficient.

In so far as critical analysis and experiment have gone, it appears that each of the factors which influences the development of goiter has simultaneously interfered with the delivery of iodine to the thyroid gland or with its utilization after such delivery. Several examples may be illuminative. (1) Calcium in excess alters absorption and uptake of iodine. (2) Plants of the Brassica family and thiocyanates decrease or prevent the uptake of iodine from the blood. (3) Thiourea sulfa and closely allied compounds interfere with the enzymic processes concerned in incorporating iodine into the tyrosine and thyronine molecules to produce thyroxin. (4) Halides other than iodine have enhanced the goitrogenic effect of thiouracil and its dericatives in rats the intensity of their activity being in the order named—fluoride bromide and chloride (Williams and Solomon 1950). Their entire effect in this regard is probably predicated upon their ability to induce an increased excretion of iodide (Williams Jaffe and Taylor 1950).

The causation of goiter through an increase in the needs of the body which the thyroid is incapable of meeting has already been considered in our discussion of the first group of patients who may develop a simple colloid or subiodic goiter (q.v.).

If we summarize all the available evidence it seems that there should really be very little conflict of opinion today regarding the path

ogenesis of subiodic goiter The facts point to the conclusion that anything which decreases the production of thyroid hormone to a point where the output no longer meets the needs of the organism will cause a work hypertrophy and hyperplasia which results in the clinical and pathological picture found in simple colloid goiter Fundamental to such a process is a relative or absolute lack of iodine to which a wide variety of factors may be predisposing

Incidence and Distribution—Subiodic or simple colloid goiter is known all over the world It has been observed in each race in every climate and at all altitudes where life exists

There is an increase in the occurrence of goiter during the late winter and early spring months which corresponds to variations in the storage of iodine by the thyroid gland

While notable exceptions exist a partial or complete lack of iodine in the soil and water predetermines the areas of greatest endemicity Since the salts of iodine are readily soluble in water such areas will correspond to those in which natural causes have leeched iodine out of the soil and carried it away This process has occurred most strikingly in the highest mountain ranges—Alps Himalayas Andes and so forth—and in portions of the earth covered by water during the last ice age—as for instance the Great Lakes region In addition to the scarcity of iodine at higher altitudes the lowered oxygen tension becomes a factor in producing endemic goiter so that without exception the highest mountain ranges harbor the foci of greatest endemicity

Of major importance in the incidence and distribution of goiter are

1 Iodine Deficiency—If for any reason the iodine content of the thyroid gland falls below 0 1 per cent goiter invariably develops This degree of thyroid storage is not possible in areas of goiter endemicity In general the percentage of the population affected with goiter in such districts varies directly as the severity of the iodine want For instance in certain portions of the Himalayas and the Alps everyone has a goiter while in an area of very low endemicity such as certain portions of Connecticut as few as 2 0 per cent of the people may be affected (Kimball 1922) It must be emphasized again that iodine lack does not act alone in the production of goiter so that no equation of incidence can be formulated which is based solely on the iodine content of the soil and water Under certain conditions it is possible for the thyroid to act efficiently with a very low intake of iodine For example in certain parts of Poland as little as 15 micrograms daily are ingested while the optimum is believed to be in the neighborhood of 200 micrograms Despite this fact goiter is little known in this district Obviously all the predisposing factors already discussed such as the concomitant presence of an excess of calcium in the soil or of a dietary high in cabbage and other goitrogenic foods influence the ability of the thyroid to act efficiently in the production of thyroxin

2 *The Duration of the Exposure of a People to a Deficiency of Iodine* —The longer a group of people be it family, tribe, nation or race remain in a goitrous district the more severe the somatic and thyroid maldevelopment and dysfunction For example, in the goitrous districts of Switzerland myxedematous idiocy or myxidiocy, is relatively common Here the people have lived for many generations, often not wandering during their entire lifetime from the valley in which they were born With each succeeding generation the impress of thyroid deficiency has been more deeply stamped upon the mental and somatic development of the individual, until dwarfism and imbecility result In sharp contrast is the condition around the Great Lakes area of the United States, where iodine deficiency and subiodic goiter are extremely common Here the endemicity is only several generations old and individuals move about freely into and out of the area Cretins are rarely seen The passage of an unchecked thyroid fault from mother to offspring has not coursed through a sufficient number of generations to be genetically effective

3 *The Influence of Age and Sex on the Onset and Incidence of Endemic Goiter* —In totally goitrous areas some evidence of the disease is present at birth with a tendency to affect the sexes equally As the degree of endemicity decreases the age at onset increases and the ratio of females to males rises above unity

If goiter is to appear at all in an endemic area it is rare to find its onset delayed beyond puberty In general the peak of incidence occurs at an earlier age in boys than in girls lying between 11 and 12 years for the former and between 14 and 17 for the latter (Marine and Kimball 1920 Marine 1923-1924 Olesen 1924 1929 Olesen and Taylor 1926a b 1927)

The hormonal differences between the sexes apparently account for rather striking alterations in iodine metabolism and in the behavior of the thyroid gland under conditions of stress particularly those caused by or associated with an insufficient ingestion of iodine Iodine deficiency is less well compensated in girls than in boys In them therefore endemic goiter appears with a much lesser iodide deficit The onset of puberty intensifies this difference In boys there is a decrease in the incidence of goiter from puberty onward in girls the reverse is true Moreover a recession in goiters already present occurs in the former at such a time while intensification of the process often with rapid and marked increase in size of a formerly present goiter occurs in the latter

In areas of the severest and the lightest endemicity respectively these differences in relation to puberty are not so striking but in districts of moderate to moderately severe endemicity such as the Great Lakes area they stand out boldly and clearly For example in Michigan the ratio of goiter before puberty is female to male as 1 to 1 whereas in middle life in the same district it is as 6 to 1

These sex directed differences indicate that in the presence of iodine deficiency ovarian hormone exerts a depressant effect upon the capacity of the thyroid for producing thyroxin whereas testicular hormone acts in a diametrically opposite manner In view of the fact that the basal metabolism of boys is usually higher than that of girls, it seems unlikely that the former conserve or make better use of suboptimal doses of thyroid It rather appears that their glandular balance favors a more efficient operation of the thyroid in the production of greater amounts of specific hormone from a given amount of raw material In other words a higher percentage of ingested iodine is made available for the synthesis of thyroxin in men than in women or such a synthesis is accomplished with less effort on the part of the thyroid gland

As aforesaid despite the influence of sex upon the development and course of subiodic goiter both sexes will be equally affected if the deficiency of iodine is of sufficient severity However as we proceed from areas of greatest goitrogenicity through varying degrees of endemicity to totally nongoitrous regions the ratio of females to males rises steadily until in the least goitrous belts it is approximately 7 to 1 or a ratio identical with that observed in other forms of thyroid disease such as hyperthyroidism A comparison of the sex distribution in Minnesota the most goitrous part of the United States where the ratio is 1 3 to 1 0 with Westford Connecticut a very mildly endemic district where the ratio is 2 8 to 1 0 illustrates this point fully (Olesen and Taylor 1926b)

Pathology and Pathological Physiology—Under normal conditions the iodine content of the human thyroid gland varies from 0 1 to 0 35 per cent with an average of 0 2 per cent (Marine and Lenhart 1909 a) This total iodine content represents an accurate index of hormonal reserve under ordinary circumstances and under those associated with the development of simple colloid or subiodic goiter There is a critical level for iodine in the thyroid at about 0 1 per cent below which the gland attempts to compensate for the iodine deficiency by a work hypertrophy and hyperplasia Up to a certain point these mechanisms of adaptation to the decreased availability of iodine are effective so that the person remains in a normal state of health even though the thyroid may be visibly enlarged

Therefore in connection with this whole problem one must first ask the meaning of normal Ryle (1917) classified groups of apparently healthy children in regard to the ease with which the thyroid could be seen He found that within reasonable limits the visibility varied inversely as the intake of iodine For example in Devon England where the water contained 1 1 micrograms of iodine per liter 26 per cent of the presumptively healthy children had a visible gland whereas in Essex where the iodine per liter of water was 30 2 micrograms only 2 5 per cent of the glands could be visualized He concludes that thyroid size receives a plus or minus bias inversely proportionate to the

2 *The Duration of the Exposure of a People to a Deficiency of Iodine* —The longer a group of people be it family tribe nation or race, remain in a goitrous district the more severe the somatic and thyroid maldevelopment and dysfunction For example in the goitrous districts of Switzerland myxedematous idiocy or myxidiocy, is relatively common Here the people have lived for many generations often not wandering during their entire lifetime from the valley in which they were born With each succeeding generation the impress of thyroid deficiency has been more deeply stamped upon the mental and somatic development of the individual, until dwarfism and imbecility result In sharp contrast is the condition around the Great Lakes area of the United States where iodine deficiency and subiodic goiter are extremely common Here the endemicity is only several generations old and individuals move about freely into and out of the area Cretins are rarely seen The passage of an unchecked thyroid fault from mother to offspring has not coursed through a sufficient number of generations to be genetically effective

3 *The Influence of Age and Sex on the Onset and Incidence of Endemic Goiter* —In totally goitrous areas some evidence of the disease is present at birth with a tendency to affect the sexes equally As the degree of endemicity decreases, the age at onset increases and the ratio of females to males rises above unity

If goiter is to appear at all in an endemic area it is rare to find its onset delayed beyond puberty In general the peak of incidence occurs at an earlier age in boys than in girls lying between 11 and 12 years for the former and between 14 and 17 for the latter (Marine and Kimball 1920 Marine 1923-1924 Olesen 1921 1929 Olesen and Taylor 1926 a b 1927)

The hormonal differences between the sexes apparently account for rather striking alterations in iodine metabolism and in the behavior of the thyroid gland under conditions of stress particularly those caused by or associated with an insufficient ingestion of iodine Iodine deficiency is less well compensated in girls than in boys In them therefore endemic goiter appears with a much lesser iodide deficit The onset of puberty intensifies this difference In boys there is a decrease in the incidence of goiter from puberty onward, in girls the reverse is true Moreover a recession in goiters already present occurs in the former at such a time while intensification of the process often with rapid and marked increase in size of a formerly present goiter occurs in the latter

In areas of the severest and the lightest endemicity respectively these differences in relation to puberty are not so striking but in districts of moderate to moderately severe endemicity such as the Great Lakes area they stand out boldly and clearly For example in Michigan the ratio of goiter before puberty is female to male as 1 to 1 whereas in middle life *in the same district it is as 6 to 1*

The two pathological alterations thus far discussed result directly from the continued attempt of the overstimulated iodine denied thyroid to compensate for the iodine deficiency Sooner or later secondary degenerative changes are superimposed upon this process For instance the colloid distended acini may rupture and coalesce to form large pools or colloid lakes In this process bleeding may occur from the fractured acinar walls thus still further distending and disorganizing the areas affected When such areas become sufficiently large they compress previously normal surrounding thyroid tissue They thus choke off its nutritional supplies with consequent atrophy and replacement by fibrous tissue It is this fibrous tissue which forms the capsule of the adenoma The nodules or adenomas thus developed are subject to still further secondary changes commonest among which are liquefaction clotting organization and calcification Sometimes the thyroid tissue elements in these nodules become overactive and a *toxic nodular goiter* is recognized Histologically it is impossible to distinguish the toxic and the nontoxic nodule

In 4 to 7 per cent of all thyroid nodules a malignant form of degeneration may occur The onset of such *cancer* is insidious and when sufficiently advanced to be recognized clinically is usually not amenable to therapy This one in twenty chance of developing malignancy is the best reason we know for the surgical management of all nodular goiters

While we have been describing a series of changes that occur as a result of the ingestion of a suboptimal or a minimal amount of iodine it is important to bear in mind that other things may interfere with the synthesis of thyroid hormone any one of which may also initiate pathological alterations similar to those just described It is necessary here to mention one because its implications are physiological rather than pathological Diffuse colloid changes and nodule formation increase with increasing age (Martin 1945b) Such alterations occur frequently in those over 45 even though a subiodic goiter has never existed Such nodules are indistinguishable histologically from the nontoxic nodular tumefaction which arises in the course of a subiodic goiter (Martin 1945b)

Clinical Picture—The manifestations of subiodic goiter vary from those of cretinism to those of an otherwise asymptomatic enlargement of the thyroid gland appearing at puberty It is common to see the former condition in areas of greatest endemicity and the latter where the goitrous tendency is slight or scarcely discernible at all Any composite picture of the clinical course is therefore impossible

Olesen and Taylor (1926a b 1927) have collected data which afford us an opportunity to reconstruct the picture of so called simple goiter as it appears in the moderately goitrous areas of the United States These workers found noticeable enlargement of the thyroid gland around the age of 5 to 6 years in both boys and girls perhaps affecting

availability of iodine, but it is also genetically and sexually determined. It is therefore difficult to say where the normal in histology leaves off and where the pathological begins. A further exhaustive study of the alterations which occur in the thyroid in goitrous and nongoitrous districts has been made by King and Hamilton (1940). Their conclusions offer an excellent summary of the background against which the basic pathological changes to be observed in subiodic goiter appear. They are therefore quoted in full:

> A review of the world literature reveals considerable variation in the gross appearance, histological structure and iodine content of the normal human thyroid gland. A number of factors have been shown to affect the thyroid gland to such an extent that the term 'normal human thyroid gland' is practically a matter of geographical definition.
>
> In general, however, it can be stated that in goitrous regions the normal human thyroid gland is largest in size, has the lowest iodine concentration, the smallest sized follicle, the greatest amount of nodule formation and the most extensive proliferation of the follicular epithelium.
>
> In moderately goitrous regions the normal human thyroid gland is medium in size, has a moderately low iodine concentration, a medium sized follicle and a moderate frequency of nodule formation and proliferation of the follicular epithelium.
>
> In nongoitrous regions the normal human thyroid gland is smallest in size, has the highest iodine concentration, the largest sized follicle, the lowest incidence of nodule formation and the least extensive proliferation of the follicular epithelium.
>
> The size of the thyroid gland, frequency of epithelial proliferation and of nodule formation is inversely proportional to the size of the thyroid follicle and the iodine content of the gland.

The changes summarized above are compensatory in nature and vary directly with the need of the tissues for thyroid hormone and inversely as the supply of iodine available to fill such need. The hypertrophy and hyperplasia of the thyroid which accompany the ingestion of minimal amounts of iodine are directly due to stimulation from the increased amounts of thyrotrophic hormone produced by the anterior pituitary gland in the presence of suboptimal or minimal amounts of circulating iodide. When under such conditions the thyroid is no longer capable of synthesizing sufficient hormone for bodily needs, then the simple work hypertrophy and hyperplasia are replaced by secondary pathological changes, the first of which is the formation of a colloid poor in iodine and thyroid hormone. Such colloid is not readily influenced by the anterior pituitary hormone which, among other functions, normally acts to extrude thyroid hormone from the follicle. The result is 'puddling' of the hormone with consequent distention of the acini into *cystic* areas. When sufficiently large these cysts represent one form of nodular goiter. But the damage does not stop there. In an effort at further compensation hyperplasia and hypertrophy of some of the follicular cells continue until groups or nests of such cells are piled upon each other, eventually to form the so-called *adenomatous* type of gland. This is the second way in which a nodular goiter may be produced.

of them if previously present For instance during pregnancy and the menopause the simple goitrous gland routinely enlarges further Hypothyroidism is *uncommon except in the areas of greatest endemicity* where the children of goitrous mothers show a greater tendency to develop goiter and hypothyroidism than their parents did In the majority of instances however the glandular hypertrophy and hyperplasia of the thyroid enables the gland to produce sufficient hormone despite the relative or absolute deficiency of iodine The longer a goiter continues the greater the tendency for the development of the degenerative changes and complications which have already been discussed under Pathology

Diagnosis—In an area of endemic goiter the history of a diffuse enlargement of the neck appearing at puberty or before which moves up and down with swallowing and which may later become irregular in contour but commonly retains a soft cystic consistency on palpation leaves little doubt about the diagnosis of subiodic goiter Only when secondary changes have occurred within the gland may the differential diagnosis offer any difficulties these are discussed under Nodular Goiter (Chapter XXXII)

Treatment—Irrespective of the theory or theories which one may adopt regarding the etiology and pathogenesis of subiodic goiter the fact stands out boldly that the administration of iodine prevents completely the appearance of such a lesion and affords a degree of relief to those already afflicted which is inversely proportional to the duration and severity of their condition

a Prophylactic Treatment—The prevention of endemic goiter in man was begun on a large scale in 1916 (Marine and Kimball 1917) At that time 0 2 Gm sodium iodide was given daily to school girls for ten consecutive school days Such a course of treatment was repeated each autumn and spring with strikingly satisfactory results However such amounts of iodine were much in excess of those required and the spacing of the dosage was probably not optimal

There is not yet any full accord regarding the best way to employ iodine in the prevention of endemic goiter Marine (1923-1924) stated that 50 mg annually if properly distributed through the year were sufficient to prevent goiter No ill effects from such doses have been observed However the most efficient method for administering this required iodine still seems to be not fully determined *Iodized salt* affords a simple and easy medium for increasing the intake of iodine and simultaneously eliminates the aversion many people have toward taking medicine One hundredth per cent by weight of potassium iodide is added to purified salt Thus the average person who ordinarily ingests from 6 to 9 Gm of salt daily in addition to that contained in the food before cooking will receive from 500 to 900 micrograms of

the latter slightly more often than the former, and appearing in from 15 to 30 per cent of the population of goitrous areas. The swelling of the neck in such instances was usually symmetrical, uniformly soft with ill-defined borders and without thrill or bruit over it. Variations in growth were questionable although Olesen and Taylor have the impression that goitrous children were slightly taller, perhaps less robust than their nongoitrous companions. The average size of the gland increased from this age onward as did also the number of children affected until the age of 12 to 14 for the boys and until 14 to 17 for the girls. *In the boys after the age of 12 to 14 the size of the gland and* the number of individuals affected gradually declined whereas in the girls the goiter once present usually persisted and in many instances grew larger throughout life with repeated exacerbations and remissions. It must of course be emphasized in this connection that in the normal individual with an adequate intake of iodine the thyroid attains its greatest size in relation to body weight at or about the time of puberty, from which point onward the thyroid weight/body weight ratio decreases. In the goitrous individual this normal relationship is disturbed in the female as well as in some males the ratio may continue to increase for some years beyond puberty or even throughout life.

Symptoms of thyroid insufficiency do not occur in the mildest forms of colloid goiter. Mild hypothyroidism with basal metabolic rates between −10 and −15 are seen in the moderately severe endemic regions where is cretinism only occurs in areas of the highest endemicity where the disease has persisted for many generations.

The majority of subiodic goiters that cause symptoms are distressing because of the local pressure symptoms they produce. The patient may complain only of a slight fullness of the neck. Later more severe symptoms of compression of the trachea and of the esophagus may occur. Some lateral compression of the trachea is present in *almost all of the* larger colloid goiters. If atrophy of the tracheal rings occurs dyspnea *appears, respiratory stridor is noticed, and fatal asphyxia* has been observed. Dysphagia is very much less common. It is possible for any structure in the neck to be disturbed by the pressure. Paralysis of the cervical sympathetic trunk resulting in Horner's syndrome has been seen in not less than ten cases (Blackwell, 1911).

There are no significant or pathognomonic laboratory findings in subiodic goiter; the blood protein bound iodine, the basal metabolic rate, and the blood cholesterol will all vary with the *functional efficiency* of the thyroid cell.

In summary it may be said that the earlier the age when subiodic goiter appears, the more severe will be its course, and the larger the swelling in the neck will become as the patient grows older. Several factors may aggravate the condition. In either sex, great emotional stress or prolonged physical strain may increase the goiter and cause the appearance of the symptoms of hypothyroidism or *in*tensification

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iodine daily—far above the minimal requirement of 100 micrograms suggested by Marine.

Despite intensive educational campaigns it has been difficult to make people in the goiter belts realize the necessity for the continuous use of iodized salt from generation to generation (Kimball, 1946, 1949). In 1937 in Cleveland, Ohio, the incidence of goiter among children of families in which iodized salt had not been used was 30 per cent; among users it was 7.7 per cent (Kimball, 1939). The overall incidence of goiter in the same locale prior to the educational program in 1924 recommending the ingestion of iodine prophylactically was 31 per cent (Kimball, 1939). From these data it is obvious that the effectiveness of prophylaxis with iodine cannot be challenged. To obtain universal and continued cooperation in the use of this material by *all* people living in goitrous districts is the real problem. In an effort to solve this, Kimball has proposed that *all* salt be iodized and called "natural salt." Kimball's suggestion will completely eliminate the more refined salt from the market, thus doing away with the thought in the minds of all people that some salts are medicated and others are not. Some states have legislation prohibiting the sale of noniodized salt which represents the practical way to inaugurate and maintain Kimball's program.

Tablets containing from 1 to 5 mg. of iodine as potassium iodide administered once weekly will usually prevent the appearance of thyroid enlargement among school children of goitrous belts (Marine, 1923-1924). This practice should be continued until the sixteenth year of life. All pregnant women living in goitrous districts, irrespective of the gross appearance of the thyroid, should take such tablets once weekly during the periods of pregnancy and lactation.

Lugol's solution (Liq. Iod. Fort. USP) 1 minim weekly is believed sufficient to prevent goiter, as it yields not less than 8,000 micrograms or 1,110 micrograms per day. This is tremendously in excess of the amount believed to be necessary to maintain satisfactory iodine metabolism.

The amounts of iodine recommended above for the prophylaxis of goiter have never been shown to increase the incidence of Graves' disease, nor have they aggravated such a condition when already present (larger but not the largest doses may). On the contrary, Kimball's surveys (1946) show that iodine decreases the incidence of exophthalmic goiter in goiter belts. Four and one tenth per cent of those in a goitrous district who used iodine continuously for four years developed symptoms of toxic goiter, whereas of those who had not employed iodine 3.5 per cent became thyrotoxic. Therefore, there seems to be little reason for any person or group of persons in this country at least to fear the small doses of iodine recommended prophylactically.

The prophylactic treatment of subiodic goiter rightfully includes other recommendations in addition to iodine therapy. The control of

infectious and contagious diseases will lower the incidence of goiter Higher standards of living including improved sanitation better housing and more careful selection of food protect the thyroid to some extent An excess of goitrogenic substances such as cabbage and other members of the Brassica family should be excluded from the diet

b Curative Treatment—The treatment of an already existing subiodic goiter is far less successful than its prevention a fact which only serves to emphasize the importance of continuous prophylaxis in goitrous districts Moreover the longer a goiter has been present the less the chance that it and its consequences can be relieved by iodide therapy If the patient is treated while still young or shortly after the appearance of his goiter a decrease in the size of the thyroid and a disappearance of all symptoms may be expected Certainly those who are treated with iodine do better than those who are not Marine and Kimball (1920) showed this conclusively in their early experiments in Akron Ohio where recession of the goiters in approximately 70 per cent of the treated individuals was obtained as compared with a decrease in size of the neck in about 10 per cent of the untreated school children Other investigators have obtained even better results than those indicated above However it is generally agreed that long standing cases are but moderately if at all responsive to iodine therapy Iodine may be given in the forms above mentioned under Prophylaxis Syrup of hydriodic acid has been advised as a convenient and palatable preparation One to four cubic centimeters daily make available from 1100 to 5600 micrograms which is seven to 28 times the dose considered optimal for the normal person Therefore the frequency of dose may be reduced to once or twice weekly after several days

Hypothyroidism in subiodic goiter must be treated with desiccated *thyroid substance in dosages of from 0 5 to 3 0 grams daily* In the long standing case there is no other indication for its use Early in the disease it may serve to suppress the formation of thyrotrophic hormone in the pituitary and thus lessen the hypertrophy and hyperplasia within the thyroid Even here little should be expected of it If used however in such instances its administration should be intermittent rather than continuous The patient should be watched for any and all signs of overdosage

Treatment with thyrotrophic hormone has been recommended on the ground that it furthers the evacuation of colloid from the thyroid This is certainly true of its effect upon a normal gland containing a normal type of colloid (Bassett Coons and Salter 1941 Berg 1944 Taurog Chaikoff and Bennett 1946) However this agent is only of value when an actual deficiency of thyrotrophic hormone of the pituitary exists as was true in the case described by Hertz and summarized by Means (1937)

Summary—Simple or subiodic goiter is a condition of the thyroid gland in which numerous predisposing causes are at work but in which the precipitating factor always appears to be an absolute or relative deficiency of iodine. The primary pathologic changes are hypertrophy and hyperplasia of the acinar cells and the formation and retention within the follicles of a colloid low in its content of thyroid hormone. Secondary pathologic alterations include cyst formation, hemorrhage and calcification, frequently leading to the development of nodular goiters. Less commonly malignant degeneration occurs. Clinically the common picture is that of an enlargement of the neck appearing over any portion of the gland and varying considerably in size and shape. Symptoms of pressure due either to the size or location of the mass may or may not be present. Thyroid function is usually not disturbed at least until late when hypothyroidism may appear. Iodine represents the most important agent in the prophylactic and curative management of the disease.

Chapter XXIX

HYPOTHYROIDISM I BEFORE FULL MATURITY CRETINISM

The term hypothyroidism may be most simply defined as a state in which the thyroid gland fails either partially or completely to elaborate its specific hormone thyroxin In rare instances the deficiency may result from a lack of the raw materials iodine and tyrosine from which this hormone is synthesized However it is commonly the result of the failure of the functioning cells of the thyroid itself The resultant clinical disturbances vary as the degree of the deficiency and the age of the patient at the time it makes its appearance Usually recognized are (1) adult myxedema (2) childhood myxedema (3) cretinism and (4) hypothyroidism without myxedema or according to Shelton's (1941) designation mild or moderate hypothyroidism

While the above classification is quite simple it is of very little help in aiding the clinician to identify the widely variant case material that must be brought under one or more of the headings mentioned For instance what criteria shall we regard necessary for inclusion under cretinism a term which has very frequently been used incorrectly to denote any and all types of thyroid deficiency occurring in early life? Since even the origin of the word cretin is somewhat in doubt it is little wonder that it has been much too loosely used in connection with hypothyroidism It was first applied to the peoples of certain valleys of the Alps who had congenital goiters and moderate to severe disturbances in mental and physical growth and development In these persons a specific etiological factor a lack of iodine can be identified and shown to be operative upon mother and fetus simultaneously But the term may apply equally to the characteristic clinical picture which develops in the child of the iodine deficient mother and not to the etiological factor at all In this connection it must be emphasized that the exact clinical picture can arise in infancy or even later as a result of conditions which may not have affected the parent or resulted from a deficiency in iodine Thus the loose application of this word makes it more rather than less difficult to distinguish by descriptive terms the various types of hypothyroidism which may occur between conception and maturity By limiting its use to that type of thyroid deficiency

Summary—Simple or subiodic goiter is a condition of the thyroid gland in which numerous predisposing causes are at work but in which the precipitating factor always appears to be an absolute or relative deficiency of iodine. The primary pathological changes are hypertrophy and hyperplasia of the acinar cells and the formation and retention within the follicles of a colloid low in its content of thyroid hormone. Secondary pathological alterations include cyst formation hemorrhage and calcification frequently leading to the development of nodular goiters. Less commonly malignant degeneration occurs. Clinically the common picture is that of an enlargement of the neck, appearing over any portion of the gland and varying considerably in size and shape. Symptoms of pressure due either to the size or location of the mass may or may not be present. Thyroid function is usually not disturbed at least until late when hypothyroidism may appear. Iodine represents the most important agent in the prophylactic and curative management of the disease.

may occur endemically or sporadically with or without the development of a goiter Clinically the endemic and sporadic cases may be indistinguishable When goiter is present obviously the terms athyreosis and thyroaplasia do not apply Goiter is more commonly present in the endemic cases and athyreosis in the sporadic patients who show no evidence of an enlarged thyroid gland In this latter group hypothyroidism of some degree is always present and persistent unless thyroid hormone is administered in adequate amounts If goiter is present it is quite possible for the functional status of the thyroid to vary considerably from time to time In such instances not only hypothyroidism but euthyroidism and even hyperthyroidism may be encountered in different cretins and in the same cretin from time to time On the basis of a changing activity of the thyroid tissue present Hurxthal and Musulin (1946) and Hurxthal (1948) were able to divide their cretins with goiter into three distinct groups

1 Cretins with goiter and concurrent thyroid deficiency

2 Cretins with goiter antecedent thyroid deficiency and concurrent euthyroidism

3 Cretins with goiter antecedent thyroid deficiency and concurrent hyperthyroidism

It is clear from the above that considerable variation in the clinical picture of cretinism is to be observed which will depend in major part upon the amount and functional capacity of any thyroid tissue which may be present

It must be emphasized that the word cretin may and has been defined in a wide variety of ways by different investigators The typical cretin the cretin as Benda (1946) calls him is well represented by the sporadic case which is usually athyreotic and therefore without goiter His condition and that of his fellows is amazingly uniform so that as a class they appear like one big family of sisters and brothers (Means 1937) Many cases of endemic cretinism belong also to this group as they have no functioning thyroid tissue Others fall into the patterns suggested by Hurxthal and Musulin (1946) because of the presence of follicular tissue varying the activity of which may alter considerably the clinical picture to be observed Moreover the existence of such a goiter may make difficult or well nigh impossible a differentiation between a thyroid deficiency arising in utero and one which occurs in postnatal life as the result of trauma infection or degeneration of unknown etiology

The typical cretin is athyreotic It seems best for the sake of simplicity to detail the clinical findings in terms of such an athyreotic or sporadic cretin Against this background it will then be possible to emphasize certain points of clinical value in distinguishing infantile and juvenile myxedema from each other and from cretinism

which begins in intra uterine life it is possible to amplify the above classification in the interests of clarity and effective therapy

A Hypothyroidism before full maturity

I Cretinism

1 Sporadic } — without goiter (athyreosis is usually present)
2 Endemic } — with goiter and
i hypothyroidism
ii euthyroidism or
iii hyperthyroidism

II Infantile myxedema

III Juvenile hypothyroidism with or without myxedema

B Hypothroidism after maturity

I Adult myxedema

II Hypothroidism without myxedema

It seems that all forms of hypothyroidism that are associated with a primary deficiency of the production of thyroid hormone can be included under one of the above headings For instance among the primary types of hypothyroidism are endemic and sporadic cretinism juvenile and adult myxedema postthumatic hypothyroidism postirradiation hypothyroidism postoperative hypothyroidism postthyroiditis hypothyroidism, burned out Graves disease, replacement of the thyroid by cyst or adenoma chronic overtreatment with iodine senile alterations and chemical suppression of thyroxin formation by drugs closely related to thiourea and thiocyanates

Secondary hypothyroidism occurs in all cases of pituitary underactivity (dyspituitrous myxedema) such as Simmonds cachexia Frohlich's syndrome and chromophobe tumors adrenal insufficiency gonadal underfunction and malnutrition with a lack of iodine tyrosine or phenylalanine

Miscellaneous reasons for hypometabolism include chronic wasting diseases convalescence from severe acute illnesses hypovitaminosis malnutrition excessive use of sedatives prolonged inactivity for any reason fatigue depressed mental state and so forth

Classification and Synonyms—I *Cretinism* Congenital athyreosis thyroaplasia sporadic and endemic cretinism congenital myxedema congenital athyroidism II *Infantile myxedema* Thyroid aplasia of infancy III *Juvenile hypothyroidism with or without myxedema* childhood myxedema

Definition and Types—Cretinism is most simply defined as that type of thyroid deficiency which begins in intra uterine life The condition



Fig 31 B (For legend see opposite page)

a The Nervous and Mental Manifestations—A lowered metabolism of every cell and tissue in the body follows the loss of thyroid function No tissue suffers more severely from the resultant chronic anoxia than does the brain A variety of symptoms appear all of which are manifestations of a decreased alertness lack of responsiveness and lowering of excitability The mentality varies inversely as the amount of functioning thyroid tissue which remains The earlier treatment is begun the greater the development which occurs in the brain and the higher the level of mental attainment This does not imply however that either genius or intelligence can be created by the use of thyroid hormone The cretinous subject cannot reach beyond the developmental level predetermined by his or her particular hereditary background While the end or effector organs of hearing and speech are mechanically crippled by the myxedematous process that accompanies cretinism at some or all stages of its development disturbances in the corresponding cerebral centers may also play a considerable role in the re

The Clinical Picture of Cretinism.—As aforesaid sporadic and endemic cretinism are clinically indistinguishable. The manifestations of adult hypothyroidism will be present in a degree varying with the functional status of the thyroid at the time the patient comes under observation. Superimposed upon this there are always disturbances in development the nature and severity of which depend upon the period of life between conception and maturity at which the thyroid deficiency is manifest.



Fig. 34.4.

Fig. 34.4 *A* and *B*.—Roentgenograms of a hypothyroid cretin (I.S. MII # I.C. 00.X.4). This partially treated cretin shows no pathognomonic local change on which a diagnosis of cretinism can be made. Indeed if considered singly any one of the features to which attention is called has been seen in the local hypothyroidism or combination of a few out of the constellation.

In *A* note the thinness of the bones and the late closure of the fontanelle the clarity with which the suture lines are detailed (age 33) the absence of the frontal sinus and the small facial bones. Among the features which are completely lacking are the heavy cleidocranial fusion of the main body of the flat bones and short thick bones of the skull.

In *B* are shown the common specific growth indicating thyreotic period during childhood and long secondaries that persist at the knee and wrist with retention of a zone of increased density along the ends of epiphysial lines but also retarded epiphysial appearances and delayed union as the rule.

periodic thyrotic inhibition of endochondral ossification (Goetzky and Weihe 1911) The crest of the pelvic bone may be irregular as a result of the irregularity with which ossification proceeded in its initially cartilaginous structure Woolley and McCammon (1915) have observed that the epiphyseal plate of the long bones is hard and densely calcified by the time cretinism is recognized clinically This change which can be roentgenographically distinguished from that seen in rickets scurvy syphilis or lead poisoning is as diagnostically dependable a finding as retardation in the appearance of ossification centers Variations in this epiphyseal and plate are believed by these and other workers (Rouques 1918 Anderson 1949) to be the best index available to determine adequacy of therapy during the first two years of life when other tests of thyroid function are not readily applicable

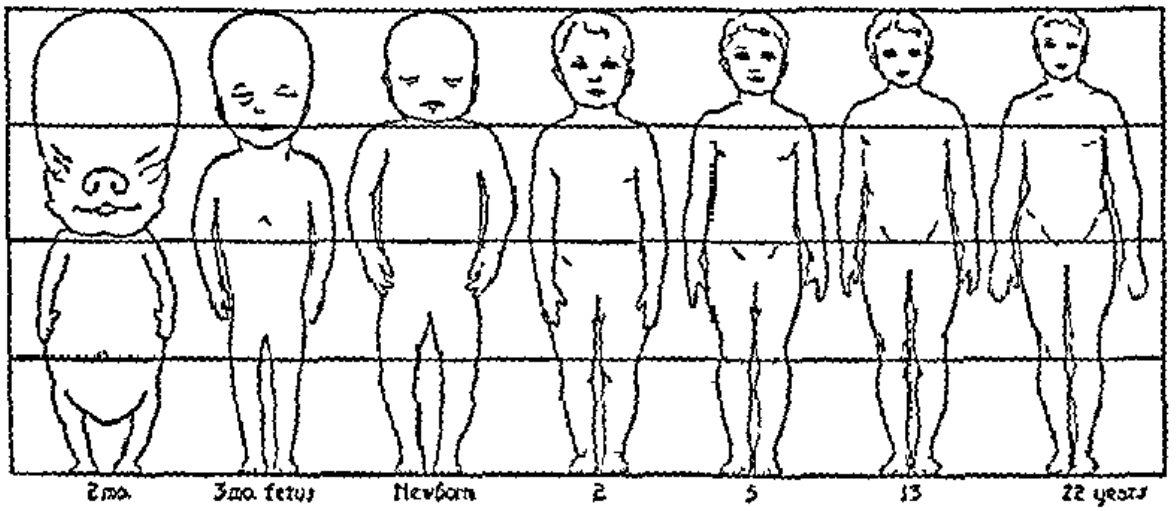


Fig 3 —The proportions of the human body are here represented at various developmental periods in prenatal and postnatal life all drawn as of the same height As the organisms mature one of the great decreases in the size of the head the constancy of the length of the trunk the relatively early development of the arms and slow growth of the legs the steady upward shift in the position of the symphysis pubis and umbilicus and the downward drift of the mid point of the total height

Inasmuch as thyroid hormone plays important role in growth and differentiation of the organism tissue is compensated by a very all retardation with a tendency for bodily proportions to remain infantile (Aub Arch) 1946)

(a) Status of the adult cretin The adult cretin is a dwarf due to retardation in growth so that infantile proportions may remain throughout life (Fig 35) He may be as short as 3 feet and never exceeds 4 feet 6 inches in height The subject with infantile myxedema may be equally dwarfed but both may be often although not always differentiated from the child with juvenile myxedema on the basis of their lesser height The curvature of the spine the laxity of the hip joints and the slightly bent legs only serve to accentuate the cretin's short stature (Fig 36)

tardation of these functions In endemic districts approximately one in three cretins is a deaf mute and an additional third is hard of hearing

b Physical Characteristics—Inasmuch as early treatment is important it is essential to recognize cretinism at birth or as shortly thereafter as practicable In the athyreotic cases this should not be difficult while in those with goiter sufficient thyroid activity may remain to cloud the picture considerably—even for several years

(1) Status at birth In the typical athyreotic cretin the weight at birth is almost never below 8 pounds and has been observed to exceed 11 pounds

Changes in the skull of the cretin are characteristic even at birth The base of the skull is short with a persistence of the cartilaginous junction between the pre and postsphenoid which normally ossifies early in the eighth month of fetal life There is a delay in the ossification of all the membranous bones so that at birth the frontal suture is unusually wide and the anterior fontanel exceptionally large Later in life the major portion of each flat bone of the skull becomes heavily calcified but about the area of the fontanel the bone remains thin a feature which will aid in distinguishing most of the other conditions that are associated with a thickening of the calvarium (Table XI and Fig 31)

The nose of the cretin is broad flat and depressed Cheek bones and forehead are both prominent The dry scaly edematous skin causes narrowing of the palpebral fissures unusual wrinkling of the forehead loose folds of skin about the wrists and ankles and a disappearance from view of the smaller subcutaneous blood vessels

The umbilicus and abdomen of the athyreotic individual are generally protuberant There is a laxity both of the abdominal musculature and also of the ligamentous structures of the bony framework of the body which contributes to the development of the prominent abdomen

The cretinous baby responds slowly and shows a lack of interest even in his food often falling asleep during the nursing period Roentgen ray examination will usually settle the diagnosis and should certainly not be neglected in any suspicious case (Table XI) Pictures of the pelvis and hips will afford the most information The primary centers of the hipbone and the shaft of the femur are not normally developed The epiphysis at the lower end of the femur normally appearing during the ninth month of intra uterine life may not be present at all The center for the head of the femur which is normally present by the sixth month may appear much later and the neck of the femur may remain underdeveloped and poorly calcified for many years If seen later in life the neck and shaft of the femur may form a right angle As growth proceeds ringlike shadows often appear in the shaft not only of the femur but also of the humerus probably representing

AND SEXUAL FORMS OF HYPOTHYROIDISM OCCURRING BEFORE FULL MATURITY

MONGOLISM	PITUITARY INFANTILISM OR DWARFISM (SOUES-CHOUVETTE OR LEVI LORAIN)
Early intra uterine abnormalities causing widespread developmental changes	Hypofunction of the anterior lobe of the pituitary with or without embryonic defect (Rathke pouch or cleft)
Pre- and postnatal anterior pituitary deficiency of the gamma cell system, secondarily interfering with eosinophilic and basophilic cell development and differentiation. Alteration of pituitary function results in abnormal development of the gonads adrenal cortex and thyroid Edema and degeneration of cerebral nerve cells accompany	Decreased function of entire anterior pituitary with or without tumor Secondary atrophic changes in other glands especially thyroid adrenals and gonads
Normal Increased (quality ?) Decreased— Resting colloid thyroid of Benda (1942)	Present but decreased Present but decreased Present but decreased
In utero	From birth to maturity
Rounding of features short neck arms legs, hands and feet	Gracile childlike
May reach normal ratio late	Always below normal
Retarded—mental age rarely beyond 5 years	Usually normal may appear retarded after puberty due to absence of normal sex behavior
Happy and docile	Childlike
Very flexible due to decreased muscular tone	Normal
Microbrachycephalic	Large in proportion to face childlike

TABLE

SOME DISTINGUISHING CHARACTERISTICS OF MONGOLISM PITUITARY INFANTILISM

	HYPOTHYROID STATES		
	CONGENITAL	ACQUIRED	
	CRETINISM (THYROID APLASIA)	INFANTILE MYXEDEMA (THYROID APLASIA OR HYPOPLASIA)	JUVENILE HYPOTHYROIDISM (THYROID HYPOPLASIA)
Etiology	Failure in embryonic development associated with athyreosis	Birth injury infection such as measles, scarlet fever or whooping cough	Infection emotional or physical stress in constitutionally inferior
Glandular Pathology	Follicular degeneration and fibrosis of the thyroid Decrease in eosinophiles and basophiles of pituitary with appearance of large stainless cells and colloid cysts	Some variant of the disturbances seen in cretinism	
Functional Changes in the capacity of the thyroid for colloid			
a Formation	Lost	Partial or complete loss	
b Storage	Lost	Partial or complete loss	
c. Extrusion	Lost	Partial or complete loss	
Onset Clinical Condition	In utero	First year of extrauterine life	Early and late childhood Puberty
Bodily Development			
a General proportions	Large rounded head curved spine protuberant abdomen shuffling gait	Cylindrical or sac-like large head long trunk short square extremities	Variable
b Lower measurement/height ratio	Remains less than 0 5 throughout life if not treated		Low if onset before 11 years normal thereafter
Mentality	Retarded—mental age rarely beyond 8 years		Retardation varies inversely as age at onset
Disposition	Changeable or lethargic		Changeable
Joints	Laxity of ligamentous structures but muscles may be spastic	Lax	Usually normal
Head	Relatively large	Large	Usually normal

AND SEVERAL FORMS OF HYPOTHYROIDISM OCCURRING BEFORE FULL MATURITY

MONGOLISM	PITUITARY INFANTILISM OR DWARFISM (SOUES-CHOUVETTE OR LEVI-LORAIN)
Early intra-uterine abnormalities causing widespread developmental changes	Hypofunction of the anterior lobe of the pituitary with or without embryonic defect (Rathke pouch or cleft)
Pre- and postnatal anterior pituitary deficiency of the gamma cell system," secondarily interfering with eosinophilic and basophilic cell development and differentiation. Alteration of pituitary function results in abnormal development of the gonads, adrenal cortex, and thyroid. Edema and degeneration of cerebral nerve cells accompany	Decreased function of entire anterior pituitary with or without tumor. Secondary atrophic changes in other glands, especially thyroid, adrenals, and gonads
Normal Decreased (quality ?) Decreased—Resting colloid thyroid of Benda (1941)	Present but decreased Present but decreased Present but decreased
In utero	From birth to maturity
Rounding of features, short neck, arms, legs, hands, and feet	Gracile, childlike
May reach normal ratio late	Always below normal
Retarded—mental age rarely beyond 5 years	Usually normal, may appear retarded after puberty due to absence of normal sex behavior
Happy and docile	Childlike
Very flexible due to decreased muscular tone	Normal
Microbrachycephalic	Large in proportion to face, childlike

SOME DISTINGUISHING CHARACTERISTICS OF MONGOLISM PITUITARY INFANTILISM

	HYPOTHYROID STATES		
	CONGENITAL	ACQUIRED	
	CRETINISM (THYROID APLASIA)	INFANTILE MYXEDEMA (THYROID APLASIA OR HYPOPLASIA)	JUVENILE HYPOTHYROIDISM (THYROID HYPOPLASIA)
Face			
a Expression	Stupid full moon appearance apathetic		Dull
b Color	Pale yellow pasty		Pale to normal
c Eyes	Thick heavy puffed lids with narrow slitlike palpebral fissures		Usually puffy thick lids but may be normal
d Nose	Broad flabby depressed bridge		Normal
e Lips	Thick		Thickened puffy or normal
Tongue	Large often protruding		Normal or large
Speech and Voice	Delayed voice roughened and hoarse		Voice deep and hoarse or little changed
Skin	Thick doughy rough dry myxedematous hair of head coarse and black other areas scanty	Same as cretinism save that hair corresponds to general coloring	Varies as degree of hypothyroidism from normal to that of infantile myxedema
Heart	Bradycardia common pulse often rapid if temperature is 97° F or below		Not characteristic
Extremities	Square short fingers toes hands and feet thickened brittle nails Stiffness reflexes normal		Variable
Sexual Development	Retarded early later may approach normal		May or may not be disturbed
Roentgenographic Features			
Skull			
a Shape	Rounded or slightly dolichocephalic	Relatively large	Usually normal
b Flat bones	Small thick heavily calcified except about fontanels which are thin	Resembles cretinism	Usually normal
c Sutures	Open at birth later when closed adjacent bone remains thin	Suture line usually distinct although closed	Closed
d. Anterior fontanel	Closure delayed	Closure usually delayed	Normal

VI—Contd

and Several Forms of Hypothyroidism Occurring Before Full Maturity

MONGOLISM	PITUITARY INFANTILISM OR DWARFISM (SOQUES-CHOUVETTE OR LERI LORAIN)
Cheerful comic or stupid	Childish fine delicate features
Intensely red cheeks	Pale to normal
Close together short palpebral fissures, slanting upward and outward epicanthic fold eyelashes short and sparse	Normal occasionally blue sclerae
Saddle nose with button like end	Normal in childhood remains childlike and small throughout life
Normal thickness dry fissured and excoriated due to drooling of saliva	Normal
Fissured (scrotal) pointed protruding because oral cavity is small athetoid movements	Normal
Delayed rarely completely normal certain letters difficult	Normal
Soft smooth elastic (velvety) at times marmorated hair fine silky scanty	Thin fine textured normal by most fine scanty hair
Congenital malformations especially interauricular septal defect	Normal in proportion to body size
Short thick hands and feet short curved little finger gaping between first and second toes muscular hypotonus hyporeflexia	Small hands and feet with short but normally tapered fingers
Markedly retarded	Prepuberal or infantile
Microbrachycephalic	Normal relatively large as compared with face
Thin	Thin
Wide at birth may later close completely	Normal at birth
Closure delayed	Closure delayed

TABLE

SOME DISTINGUISHING CHARACTERISTICS OF MONGOLISM PITUITARY INFANTILISM

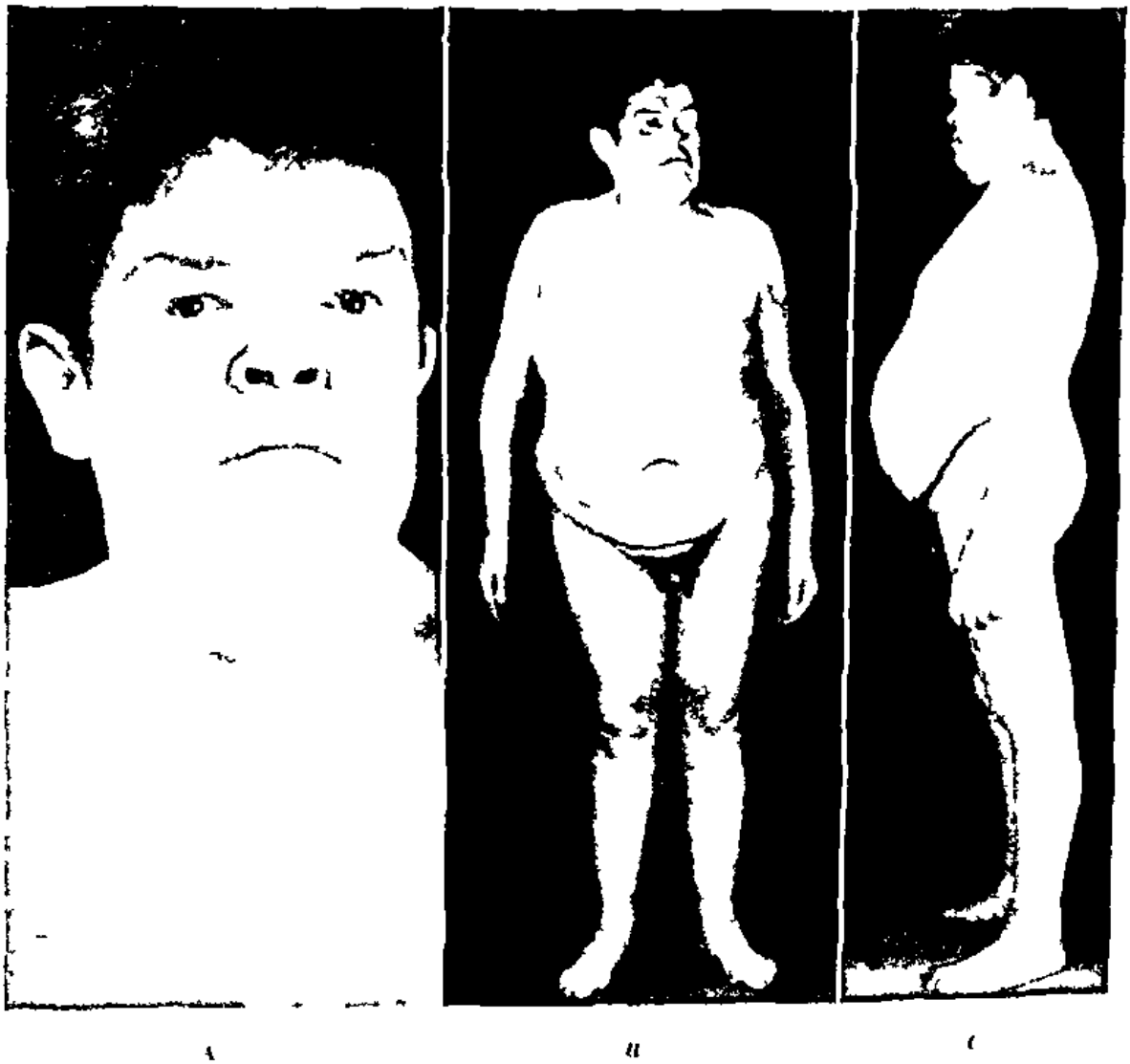
	HYPOTHYROID STATES		
	CONGENITAL	ACQUIRED	
	CRETINISM (THYROID APLASIA)	INFANTILE MYXEDEMA (THYROID APLASIA OR HYPOPLASIA)	JUVENILE HYPOTHYROIDISM (THYROID HYPOPLASIA)
Sphenoid bone			
a Declivity	Normal	Normal	Normal
b Cartilaginous disc between pre- and post-sphenoid	Unossified for variable period of time	Normally ossified by eighth month of intra uterine life	
c Sinuses	Absent or very small	Small	Small if onset of disease before puberty
Anterior clinoid acanthion distance	May be shortened or normal	Usually normal	Normal
Maxilla			
a Size	Small		Small to normal
b Plane of alveolar crest	Level nearly normal or normal (i e opposite skull base)	Normal level	
Orbits			
a Size	Normal or slightly large	Normal or lar e	Normal
b Shape	Normal	Normal	Normal
Carpal bones	No centers (athyreosis) very little development without treatment	Retarded	Normal or retarded
Metacarpal bones	Delay in the appearance of normal epiphyses		Delayed or normal appearance of epiphyses usually delay in closure
Phalanges	Bones short broad well-calcified $\frac{\text{Length first phalanx}}{\text{Length third phalanx}} = 2\ 5 \text{ to } 3\ 0$		Usually normal
Resistance to Infection	Normal		
Response to Treatment	Improvement remarkable if treatment begun early and persistently maintained Mental attainments vary inversely as age at which treatment was started and age of onset of disease		

XI—Cont d

AND SEVERAL FORMS OF HYPOTHYROIDISM OCCURRING BEFORE FULL MATURITY

MONGOLISM	PITUITARY INFANTILISM OR DWARFISM (SOQUES-CHOUVETTE OR LEVI LORAIN)
Upright throughout life Unossified—*sometimes* for years	Usually normal Usually normal
Absent	Small
Always shortened	Usually normal at birth Later may be short
Small and disproportionately small even at birth	Small childlike
High opposite anterior or posterior clinoids	Normal level
Small but disproportionately large Egg-shaped long diameter slanting upward and lateral ward	Proportionately small Normal
Retardation most marked first 4 years of life when bone age rarely exceeds 1 year (two centers) Defect never as severe as in cretinism. Beyond age 15 all centers usually present and normal in appearance	Always delayed in appearance and development but less retarded than athyreotic cretin
Epiphyses slow in appearance but not as retarded as in cretin Abnormal distal epiphysis of the thumb and proximal epiphysis of index finger commonly seen Foreshortened middle phalanx of little finger with incurving	General retardation with maintenance of childlike hand Cortices of all long bones disproportionately thin
Bones delicate slender short poorly mineralized $\frac{\text{Length first phalanx}}{\text{Length third phalanx}} = 1.6 \text{ to } 2.5$	
Poor	Poor
No specific treatment available Thyroid should always be tried and may be useful in large doses begun shortly after birth	Potent pituitary preparations not available. Testosterone and adrenocorticoids afford some relief

All movements of the cretin are slow and awkward This may be due in part to certain disturbances of the nervous system but the broad based shuffling waddling gait is also well explained by the angulation of the neck and body of the femur the slightly bent knees and the slow cerebration The moderate muscular rigidity the increased deep tendon reflexes the ataxia and occasionally tremors suggest a nervous component in the difficulties with locomotion which may result from birth injury (big baby) rather than from the influence of thyroid deficiency upon the nervous system



A B C

Fig 36 *A B* and C —Photographs of a euthyroid cretin (M B Mil #108840) At the time of these photographs this 23 year-old male Bantu Highlander by birth was euthyroid— BMR +10 total cholesterol 1 8 mg per 100 cc total serum protein 6 9 per cent and blood protein bound iodine 5 6 micrograms per 100 cc His height was inches his weight 160 pounds and his mental age did not exceed years He first walked and talked at the age of 3 years Note the disproportionately large head the coarseness of features (despite the smallness of facial bones revealed by roentgenography) the stupid expression the broad saddle nose the thick short neck the protuberant abdomen and the laxity of flabby adipose tissue around the hips and knees The genu varum is accentuated by the wide carrying angle at the elbow of the femur

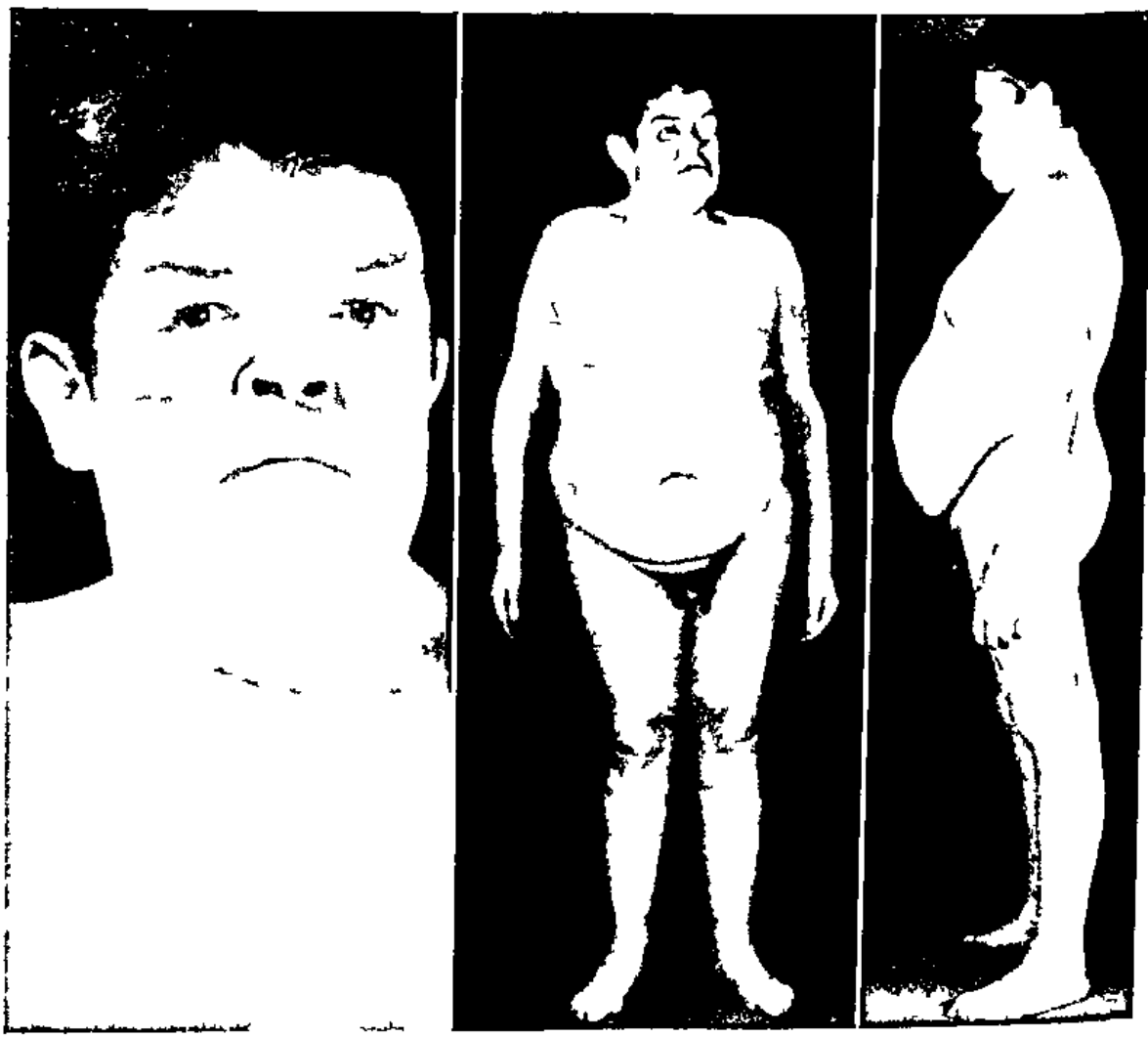
The head of the cretin is disproportionately large (Fig 37) rounded or slightly dolichocephalic and covered with an abundance of black coarse wiry hair (Figs 36 37 and 38) *Benda (1946) has never seen* congenital athyreosis in a subject with blond hair In his opinion cretinous subjects with blond hair are cases of acquired thyroid deficiency (infantile myxedema) or congenital cretins to whom early effective treatment has been given



Fig 3 —Photograph of a hypothyroid cretin (IS MH #1C 00 4) Except for period of treatment with 3 0 grains of desiccated thyroid substance this 33 year-old woman had always been very short in stature had received no treatment for eight years prior to the taking of this photograph Note the characteristic expression (mental age approximately 3 years) the ruffle of hair on the forehead the broad sad facies the broad short thick hands and short thick fingers She was backed the protuberant abdomen slightly and found it difficult to maintain an erect position at the time the photograph was taken See enlargement in Fig 34

Because of the slow development of the membranous bones of the skull the orbit holes of the adult cretin are large the palpebral fissures are long and the eyes are set horizontally However despite the roomy orbits the swelling of the soft tissues narrows the palpebral fissures to small slits making it somewhat of an effort for the subject to keep his eyes open Both cartilaginous and bony portions of the nose are underdeveloped The resultant retraction and flexibility of the soft parts

All movements of the cretin are slow and awkward This may be due in part to certain disturbances of the nervous system but the broad based shuffling waddling gait is also well explained by the angulation of the neck and body of the femur the slightly bent knees, and the slow cerebration The moderate muscular rigidity the increased deep tendon reflexes the ataxia and occasionally tremors suggest a nervous component in the difficulties with locomotion which may result from birth injury (big baby) rather than from the influence of thyroid deficiency upon the nervous system



A *B* *C*

Fig 36 *A* *B* and *C*—Photographs of a euthyroid cretin (M B MII #108810) At the time of these photographs this 3 year old male Bavarian Highlander by birth was euthyroid—BMR +10 total serum cholesterol 1 8 mg per 100 c c total serum protein 6 9 per cent and blood protein bound iodine 6 microgm per 100 c c He was 11 height and 11 his weight 160 pounds and his mental age did not exceed year He first walked and talked at the age of 3 years Note the disproportionately large head the coarseness of features (despite the smallness of facial bones revealed by roentgenography) the stupid expression the broad saddle nose the thick short neck the protuberant abdomen and the laxity of the soft tissue structures around the hips and knees The genu varum is accentuated by the wide medial angle at the neck of the femur



Fig 38—Ph t g ph of a ase of c eti l m with my ed ma (co g nit l myxed ma) (E.S FFAll #?} 14 33) at 1 month of ge \ te the ou d : oon fa b oad saddl n se dull stupid expre l n the h a y h ad of c se bla k hair the pot b lly th fl bby at ni mu ul tu and the l rg sacklik xtremiti H weight w ?9 pound h r bi th w ght l ad be n 10.ɔ pound She could neither walk n r talk n r c ld he t un pported She had lw ys be n a feeding p obl m" Con tipati n w an eq ally n jor d fficulty Th fi t tooth h d erupted one month p e lously Both ant ri r and p terior fontan ls w e widely open These children share with the vi t m f dult myxed ma an int l ranc f r thyr id h rm n H r 0.3 g ain d lly was tl e maximum t l rated dose d ing the flr t five months of t eatm nt

account for the characteristically broad flat saddlelike flabby proboscis the tip of which can be freely moved from side to side

Because of disturbances in cartilaginous development similar to those seen in the nose the ears show abnormal flexibility

Indeed all bones of the face are underdeveloped (Fig 37) despite which the swelling and thickening of the overlying soft tissues leave the general impression of a heaviness and coarseness of features (Figs 37 and 38)

Characteristically the neck of the cretin is short and broad The myxedematous infiltration of the skin overlying the supraclavicular region often gives it a rubbery consistency which may be mistaken for a lipomatous or cystic tumor The body of the cretin is relatively long as compared with the extremities The protuberant abdomen usually accompanied by umbilical hernia is accentuated in the upright position by the curvature of the spine Hard sausage shaped masses of feces may be frequently palpated through the relaxed abdominal wall and indicate the sluggish bowel function commonly present

Conforming to the bony structure of the cretin (Table XI), his extremities are short and broad The square hands and stubby fingers are covered with a cold thickened wrinkled skin a surface which has been likened to that of a toad (Benda 1916) The nails are square brittle and thickened Except on the head the hair is scanty this is particularly striking about the genitals The external genitalia and mammae are usually small although if the patient compensates later for his thyroid deficiency (cretinism with euthyroidism), normal sexual development may take place The phenomena of menstruation will be governed accordingly Indeed in infantile myxedema sexual maturation has been described while the thyroid deficiency continued (Mussio Fournier et al 1948) The inability of sex hormone to effect epiphyseal closure under such circumstances has been emphasized

In the cases with the uncompensated thyroid deficiency the skin remains thickened and cold with a persistent subnormal body temperature The pulse is variable and is an unreliable index of the degree of thyroid function The heart is usually large but lacks the disproportionate increases in size seen in untreated adult myxedema

The roentgenographic changes observed in the cretin are summarized in Table XI and are there compared with the disturbances seen in mongolism pituitary infantilism and acquired hypothyroidism The appearance of ossification centers is chronologically more normal in mongolism than in the other conditions mentioned but such centers remain for long periods of time poorly and irregularly developed

In essential features cretinism infantile myxedema juvenile hypothyroidism with and without myxedema and adult myxedema represent different aspects of the same process dependent upon the severity of the thyroid deficiency its course and the age of the subject at onset

Laboratory Findings in Cretinism —Most of the findings in cretinism are in agreement with those found in adult myxedema (q v) so that we shall list here only those which are at variance with the ones found in adult myxedema or which are not mentioned under that disease (Chapter XXX)

The Blood Count —The total white count in the cretin is relatively low otherwise the findings are as noted in myxedema under Disturbances in the Hematopoietic System (Chapter XXX) (q v)

The Basal Metabolic Rate —This is always low in cretinism but often not as low as in adult myxedema

Blood Serum Proteins —The total protein of the blood is usually normal to low normal in cretinism The fibrinogen fraction may be high (Benda 1916)

Blood Sugar and Glucose Tolerance Curves —Fasting blood sugar values are normal Tolerance curves are low with a late peak indicating a high tolerance for sugar There is a tendency for an exaggerated effect of insulin upon the blood sugar and for a failure of adrenalin to produce the usual degree of hyperglycemia Benda (1916) believes that these responses are due to a depletion of hepatic glycogen stores as the other phenomena attendant upon the administration of these drugs are usually seen in lesser or greater degree

Pathology of Cretinism —

1 The Thyroid —Essential to the development of cretinism is the loss of functioning thyroid tissue In sporadic cretinism this is usually the result of malformation associated with an imperfect descent and differentiation of both the median and lateral anlagen of the thyroid (see Congenital Anomalies Chapters XX and XXI) If no functioning thyroid tissue remains myxedema is always present in connection with the cretinous state Rarely however is the subject left with no rests of thyroid cells somewhere in the body In endemic cretinism these aberrant or even normally placed cells may retain sufficient function to prevent myxedema although they may not be capable of supplying sufficient hormone to prevent one or more of the developmental disturbances already described

In endemic cretinism there may be simple absence or aplasia of the thyroid as is the case in the typical or sporadic cretin However in endemic goitrous areas it is more common for the initial hypertrophy of the thyroid to give way to an exhaustion degeneration The normal thyroid response to an insufficient intake of iodine is hypertrophy and hyperplasia Thus a goiter is formed If the iodine intake remains low as in goitrous regions a colloid degeneration follows in which degeneration of the parenchyma proliferation of the connective tissue stroma loss of blood supply and a deficiency or complete lack of colloid even

The absence of overt disturbances in skeletal development readily differentiates adult myxedema and adult hypothyroidism from the other forms. Such alterations are maximal in cretinism, and mildest in juvenile myxedema, becoming increasingly less in degree as the age of the child at onset advances.

Infantile myxedema may become manifest early in infancy so that a sharp clinical differentiation between it and congenital thyroid aplasia is extremely difficult (Fig. 38). The date of onset of the thyroid failure is best ascertained by roentgenographic study (Table XI). The number of carpal bones present and the development of the femoral will give the most accurate indication of the time at which the thyroid aplasia appeared. Bronstein and Shadakhnoff (1950) consider the absence of the inferior epiphysis of the femur an important finding in congenital cretinism representing the retarded osseous development which occurs in utero.

Physical characteristics are often helpful in distinguishing infantile and juvenile types of myxedema from the congenital or cretin type. In the two former the hair is sparse and thin rather than abundant as in cretinism. Its color is that of the child's natural hair so that blond or light brown hair is seen as frequently in infantile myxedema as is black hair. The skin of the subject with infantile myxedema is more apt to be puffy than that of the cretin frequently associated with a superimposed "pitting edema" particularly about the ankles. Not infrequently an antecedent severe exanthematous or other infection can be related to the onset of myxedema in infancy or early childhood. Of these measles and scarlet fever appear to have been most frequently at fault. Birth injuries have been described in which bleeding into the thyroid was followed by athyroidism.

The matter of sharply distinguishing congenital and acquired hypothyroidism is often complicated by the fact that the congenital variety particularly in endemic form may be associated postnatally with euthyroidism until some severe period of stress for example puberty precipitates a complete breakdown of thyroid function. Indeed the rather characteristic bodily build of subjects who develop adult myxedema (see Fig. 34) may represent a congenital disturbance with latent thyroid abnormality.

The diagnosis of mild hypothyroidism without myxedema is difficult in both children and adults as many of the classical features may be missing. The clinical picture and laboratory findings are at times not well correlated particularly in children. The basal metabolic rate and blood cholesterol may be uninformative. Blood iodine studies are not yet commonly available. The most reliable criteria include a history of a delay in teething, walking and talking, roentgenologic evidence of osseous retardation even though mild in degree, and a favorable response to desiccated thyroid substance.

immeasurably high Therefore in *every* child with any degree of retardation in mental or physical development the diagnosis of cretinism should be discarded only after careful examination and in the doubtful cases following a persistent trial of specific therapy

The condition must be differentiated from all of the various forms of dwarfism including those due to other endocrine involvement inherent or constitutional factors congenital disturbances of the skeleton anomalies of the circulatory and urinary systems altered nutrition and chronic infections

Disturbances in differentiation and complete formation of bony and other parts do not occur in eumorphic dwarfism the so called Tom Thumb individual

In achondroplasia congenital cardiac and renal disease angioplastic infantilism cystic disease of the pancreas and renal rickets mental disturbances are usually absent

The state of malnutrition which follows an inadequate intake of food is never seen as a result of cretinism or one of its closely allied thyroid disturbances

Intestinal parasites may produce an anemia not unlike that of myxedema as well as an over all lack of growth However specific characteristics of myxedema are lacking and the retardation of growth never occurs as early or in as severe a form as in cretinism Stool examination in this and other disturbances of the gastrointestinal tract such as celiac disease may be informative

Other endocrine and metabolic disturbances such as diabetes glycogen storage disease hypopituitarism and so forth possess specific metabolic or developmental faults that will usually aid materially in their differentiation from cretinism and allied forms of hypothyroidism The recent review of Clement and Goodman (1950) illustrates the diagnostic problems posed by one or a combination of specific faults with their secondary nonspecific repercussions upon the development of the soma

While the orthopedist may experience some difficulty in distinguishing the so called osteochondral form of hypothyroidism in children from Perthes disease the differentiation is therapeutically important as the former responds fully to thyroid hormone and the latter demands prolonged immobilization to prevent deformity In the hypothyroid condition a general retardation of bony development can be demonstrated Hermon (1913) emphasizes several other points The roentgenological appearance of the epiphyses in osteochondral hypothyroidism varies from a slight loss of homogeneity to a coarse stippling or fragmentation Despite the roentgenological appearance actual fragmentation of the epiphysis does not occur in hypothyroidism but is present in Perthes disease In osteochondral hypothyroidism the femoral capital epiphysis is not as flat as in Perthes disease but a line

tually occur. If all thyroid epithelium and follicular structure are destroyed aplasia results and myxedema is evident in conjunction with the endemic cretinous development. Not infrequently some islands of hypertrophic tissue remain and continue to function normally. It is upon the capacity of these thyroid follicles to *manufacture store and* extrude colloid that the functional status of the individual depends. The severity of the cretinous state will vary inversely as the amount of thyroid gland still capable of normal activity. Therefore among endemic cretins the intensity of the clinical picture will be predicated upon the amount of cellular degeneration and fibrosis and the functional capacity of hyperplastic follicular remnants. In some instances the hypertrophic islands may prove capable of sufficient hyperplasia to produce thyrotoxicosis (Hunthal and Musulin, 1916; Hunthal 1918).

Acquired cretinism implies a degeneration of the thyroid after birth. In such instances the development and differentiation of the gland have been normal but postnatal destruction with fibrous tissue replacement has accompanied or followed an infectious process. When this occurs within the first two or three years of life the entire thyroid is usually destroyed and the picture is that of infantile myxedema.

In juvenile myxedema a prenatally or postnatally damaged but not completely destroyed thyroid may fail to meet periods of added stress such as puberty and thus give rise to the clinical picture of hypothyroidism with or without myxedema.

2. *The Pituitary.*—Enlargement of the pituitary is common in cretinism. In conjunction with this alterations occur in the cellular structure. Large stainless cells appear which probably arise from the basophile cells. The basophiles and the eosinophiles are greatly reduced in numbers. Indeed the latter may almost completely disappear. Occasionally extreme degrees of destruction of the pituitary may be seen due to myxedematous infiltration with the subsequent formation of cystic areas.

3. *The Adrenals and the Gonads.*—The pathology of the adrenal and the gonad will be set forth in connection with the adult types of hypothyroidism (Chapter XXX) and needs no further consideration here.

4. *Other Pathologic Changes.*—Changes in skeletal structure in cretinism have been emphasized in connection with roentgenological findings (Table XI). Secondary disturbances in the organs and other soft tissues of the body and observed alterations in calcium and phosphorus metabolism will be discussed in the chapter on adult myxedema (Chapter XXX).

Diagnosis and Differential Diagnosis.—The importance of recognizing thyroid deficiency early cannot be overemphasized for the cost of effective treatment is remarkably low but the expense of negligence is

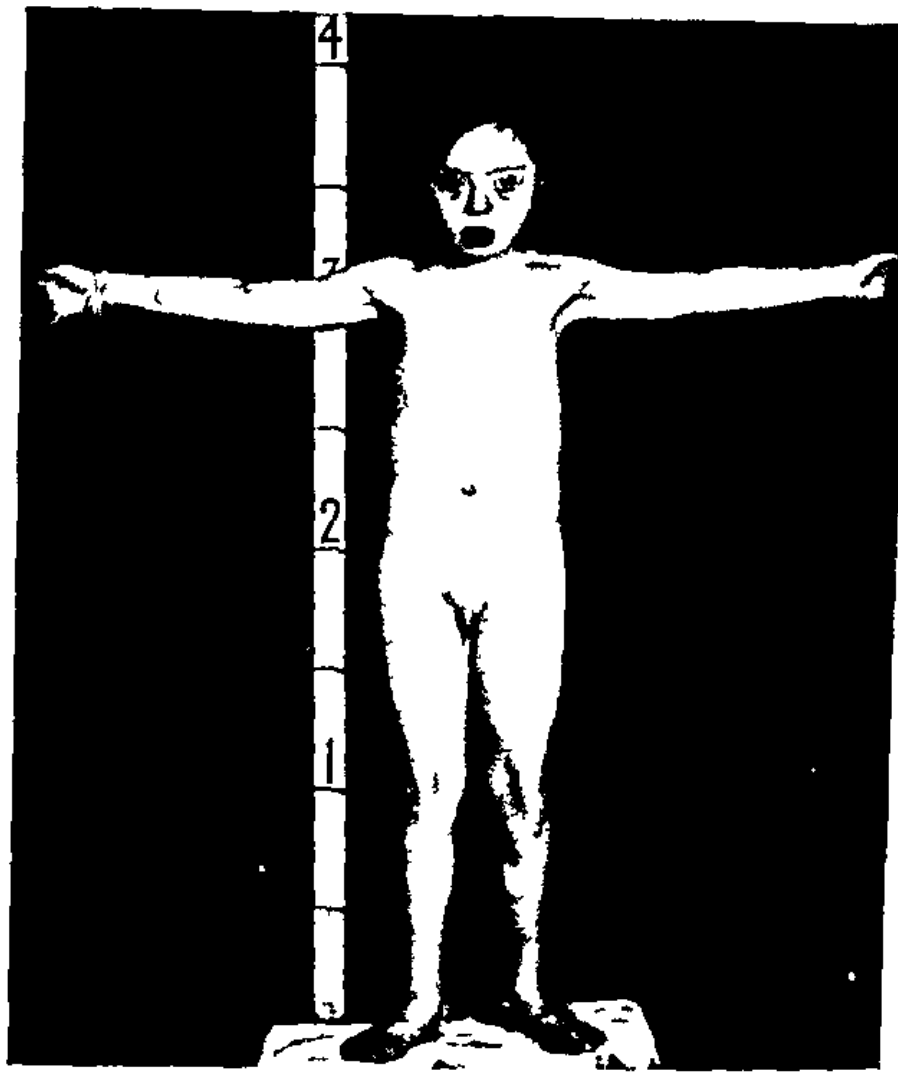
of cleavage probably caused by splitting of the relatively brittle bone divides it into inner and outer halves and may lead to extreme deformity

Major difficulty is experienced in separating the several varieties of hypothyroid function from each other and from pituitary infantilism and mongolism (Fig 39) The finding of cretinism and mongolism in siblings emphasizes the importance of this differentiation (Gronemeyer, 1950) Some of the more important features which distinguish each are included in Table XI In this connection it must be remembered that cretinism mongolism and pituitary infantilism share several developmental faults in common which may appear in various degrees and combinations the small underdeveloped sphenoid body failure of or late ossification of the cartilaginous disc between the pre- and postsphenoid which should normally occur at about the eighth month of intrauterine life foreshortening of the base of the skull because of the lack of growth in the cartilage of the spheno occipital articulation which normally remains in an actively growing state until about the twenty fifth year of life failure in the pneumatization and full



B *C*

F 39 *B* d C (F I g d ee pp lf pag)



A

Fig. 39. *A, F.*—Photograph and roentgenogram of a 9 year old boy with mongoloid idiocy (A. D. FARAH—MCG 194). Birth had been normal but he had been subject to repeated respiratory infection and showed a moderate delay in starting walking and talking. He was capable of taking care of his own physiological needs and had a mental age of about 3 years.

In the photographs (*A, B, C*) note the dull stupid expression the disproportionately small face the brachycephaly the low placed somewhat small ears with characteristic overlapping of the helix and some flattening of the trague the closely set eyes with slightly slanting palpebral fissures and definite although not markedly epicanthal folds saddle nose the open mouth with slightly everted lips due to drooling and the well proportioned body. The skin was thin and of good texture the testes had not descended.

In the lateral roentgenogram of the skull (*D*) note the brachycephaly the shortened distance between the acanthion and the anterior clinoid processes the small size of the sphenoid body the absence of frontal sinuses the smallness of the sphenoid sinus and the hypoplasia of the facial bones. In the posteroanterior view of the skull (*E*) the hypoplasia of the facial bones is accentuated the arch of the palate is high and the thinness of the flat bones with a deficient diploe is evident. The orbital holes are not typical although on the left the supraorbital foramen is present the highest point of the orbit which should be normally displaced laterally is not as striking as it is in the healthy subject. The roentgenograms of the wrists (*F*) which show a normal development for a child of 9 years serve to differentiate the condition from that of cretinism in which the appearance of ossification center is always retarded. Some retardation may occur in mongolism but it is never as marked as in the cretin. The entire body framework of the mongoloid individual is small although eventually fairly well differentiated as contrasted with cretinism in which epiphysis and vertebrae is markedly retarded.

of cleavage probably caused by splitting of the relatively brittle bone divides it into inner and outer halves and may lead to extreme deformity

Major difficulty is experienced in separating the several varieties of hypothyroid function from each other and from pituitary infantilism and mongolism (Fig 39) The finding of cretinism and mongolism in siblings emphasizes the importance of this differentiation (Gronemeyer, 1950) *Some of the more important features which distinguish* each are included in Table XI In this connection it must be remembered that cretinism mongolism and pituitary infantilism share several developmental faults in common which may appear in various degrees and combinations the small underdeveloped sphenoid body failure of or late ossification of the cartilaginous disc between the pre and postsphenoid which should normally occur at about the eighth month of intrauterine life foreshortening of the base of the skull because of the lack of growth in the cartilage of the spheno occipital articulation which normally remains in an actively growing state until about the twenty fifth year of life failure in the pneumatization and full



B *C*

Fig 39 *B* and *C* (For legend see opposite page)



D



E



F

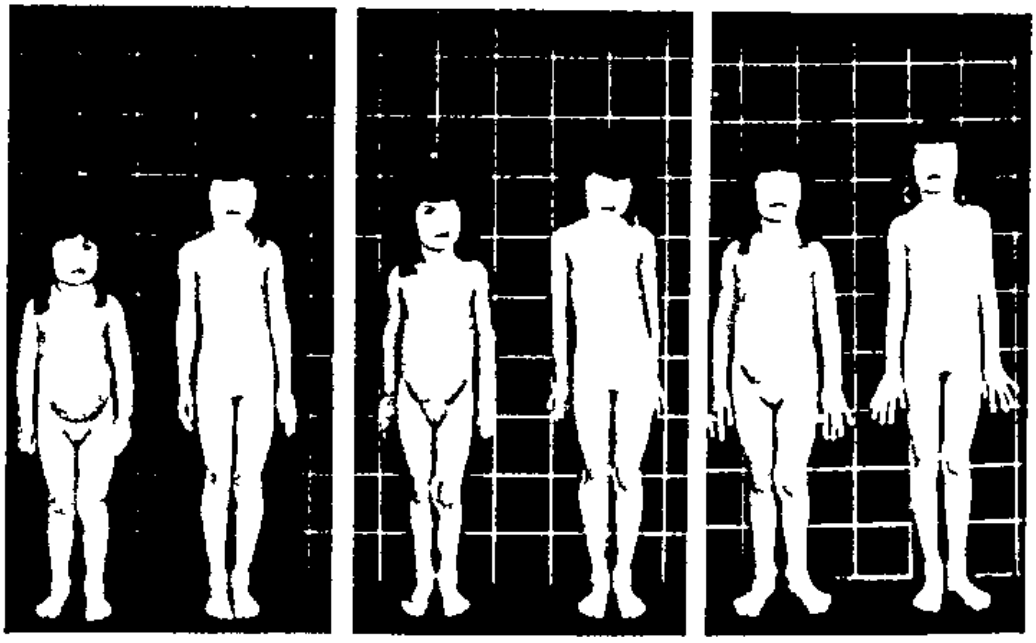
Fig. 39. *D–F (For Legend see page 368)*

development of the nasal accessory sinuses and interference with the appearance and development of ossification centers throughout the body In the table (Table XI) in which these conditions are contrasted we have used the sporadic cretin with thyroid aplasia to typify the congenital form of hypothyroidism The term infantile myxedema is meant to embrace acquired cretinism with or without actual myxedema of the tissues and juvenile hypothyroidism includes all degrees of hypothyroidism which may arise from early childhood to maturity However none of the comparisons gives consideration to the categories of cretinism in which euthyroidism and hyperthyroidism occur as established by Hurxthal and his associates (1946 1948)

Prognosis —The prognosis of cretinism and its closely allied forms of hypothyroidism varies directly with the time which elapses between the onset and recognition of the disease the severity of the thyroid fault and the persistence with which adequate therapy is maintained Therefore when physical or mental development of the infant or child shows *any recognizable* retardation it is important to utilize every possible facility for determining the presence or absence of thyroid insufficiency

Treatment —In the congenital cretin the chance for a normal development and opportunity is good *provided therapy is begun in the first few months of extra uterine life and is maintained without omission until the patients death* Delays in beginning treatment affect the outlook for mental achievement more than the outcome for physical development If treatment is not begun until after the age of 5 years the probability of creating a self sustaining sociologically independent individual is extremely slight Nevertheless irrespective of the age at which the patients condition is first properly managed some improvement can be expected (Figs 40 and 41)

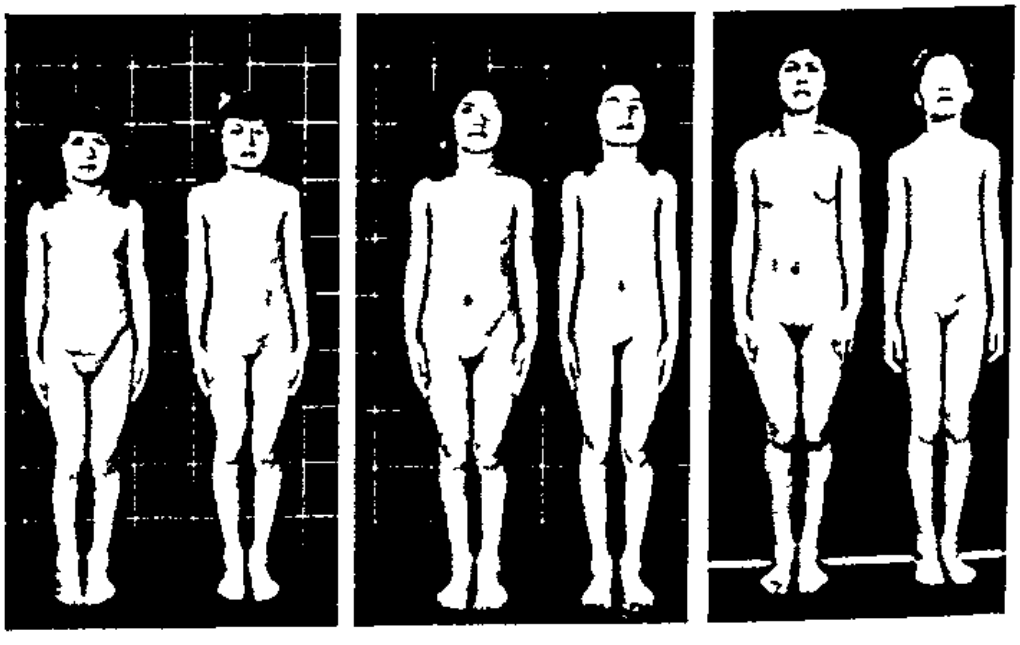
The dosage of desiccated thyroid substance to be used will vary from individual to individual and should be pushed to an optimal effect or to tolerance whichever is the lesser During the first eight months of life 0 1 to 0 2 gram daily usually suffices From that point forward to the end of the second year 0 75 gram daily should be employed From the second year onward the dosages may be regulated as in the adult forms of myxedema No single symptom or sign suffices to tell us when the optimal level of dosage has been passed However restlessness a tendency to perspire easily fitful sleep heightened irritability and an increasing pulse rate despite normal temperature commonly signify that too much hormone is being used Periodic roentgenographic examinations (Fig 41) blood iodine determinations blood cholesterol estimations and metabolism tests should be employed as a check against our clinical judgment regarding the adequacy of therapy In evaluating the results of hormonal administration particularly relating to mental attainment the hereditary background must not be forgotten for it is obvious that thyroid hormone cannot in any dose add to the hereditary



Patient (L) 10yrs
Norm sister (R) 6yrs

After 6 mos

18 mos



3yrs

4yrs

5yrs

Fig 40.—The r p i se of cret i isi i to treat n nt The r po se of this l ypothyroid subj ct (left in each et of pictu e) illust at the point that *m ll ing* an be c mplished no i att r how late treatment of cretinism i b gun Tl e i atient t ilure and p ogress re ompar d with those of a ist r fo r y ars younger wl o was 6 ar ol l wl i the fi t i l ot gr ph were tak n Thyroid in lo es of 1 to 1½ gra n d ily w mi loy d in the t atn i t of th patient For the fi t two ye rs of tr atn nt sh grew s ti al hut dr l per c ot more rap i ily tl n tl e n r al rate While mental tt i n ent did not k ep i with tl hy leal d v l n e t l wa ble to stay al east of the yourg r si ter i i gr ar sc l ool The cas ther for e iphas z tl im i ortance of beginning treatment at the arliest po ll le i om nt pref bly at birth lf at th t t me sufficient stigmata exist to make a positi e dia nosis (After Shelton 1912)

endowment of the individual nor can it reverse the irreparable damage which *long* continued hypothyroidism may do to the central nervous system

In areas of endemic goiter iodine should be added to the therapeutic regime (see Chapter XXX) In so doing it must be recalled that this procedure will be of value only when some functioning thyroid tissue is present

A high carbohydrate high protein low fat diet may be of help in correcting some of the metabolic faults present in the cretin but is without effect unless thyroid hormone is employed simultaneously

Early continuous treatment of all forms of hypothyroidism is essential for normal growth and mental development It locks the door against mental incompetence and physical inferiority *Delay* in initiating therapy affords opportunity for these undesirable tenants to enter and become permanent occupants

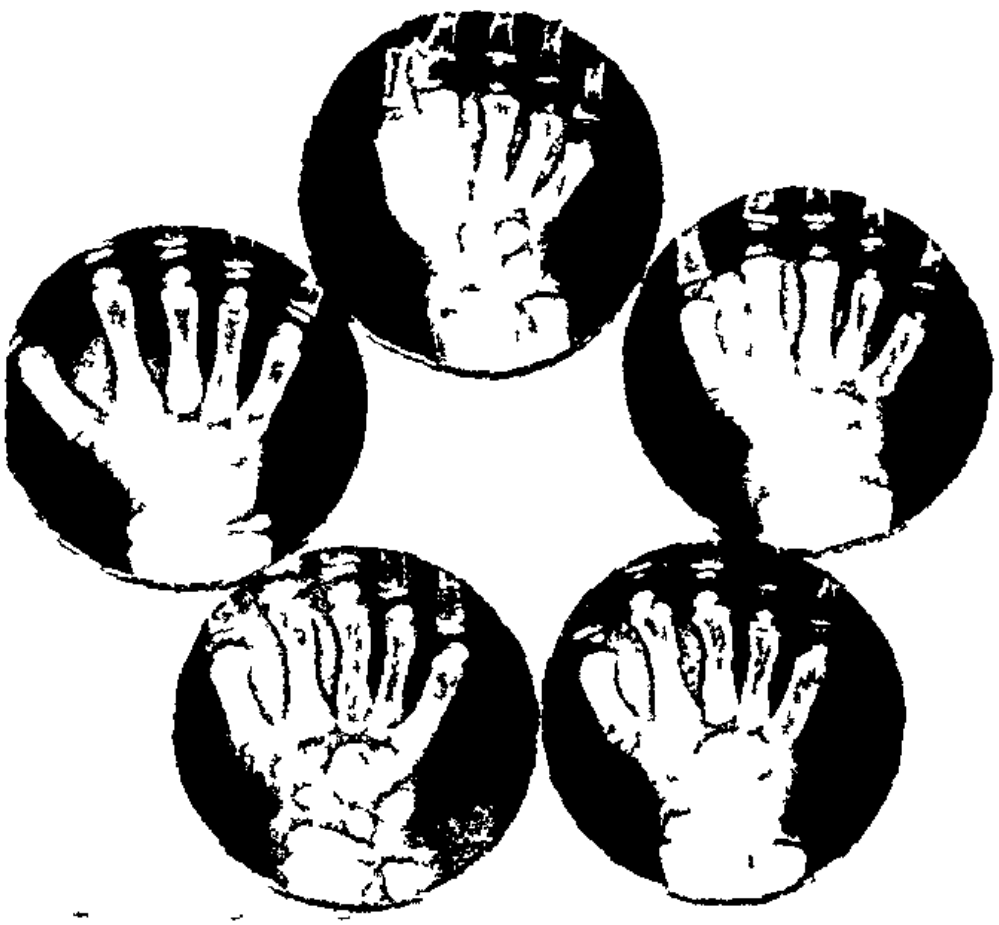


Fig 41 —Osseous development as affected by treatment of the growth of the carpal bones during treatment of the subject in the condition pictured in Fig 40 The carpus at the age of 10 years is shown at the top of the figure Reading clockwise we find successive pictures at 6 9 12 and 18 months after therapy was begun At the age at the beginning of treatment was only about two thirds of the carpal centers (the eighth is often missing) in the normal wrist at 7 years while 7 of 8 to 10 the eighth is often missing in the normal wrist at 6 years and compatible with an age of 8 years or more

Chapter XXX

HYPOTHYROIDISM II AFTER MATURITY ADULT MYXEDEMA

Synonyms—Cachexia thyreopriva; cachexia strumipriva; Gull's disease.

Classification and Pathogenesis—Adult myxedema may be artificially produced or appear spontaneously. It invariably follows total thyroidectomy if replacement therapy is not used. It may be caused by chemically blocking the activity of the thyroid gland which such agents as thiourea and its closely related compounds (McGavack and Schwimmer 1944; McGavack, Lange and Schwimmer 1945; Cornell Univ. Med. Coll. II; DuBois 1944). It is obvious that either of these types of myxedema may be induced almost at will in any individual subjected to one of the procedures just mentioned. Such artificially produced myxedema will lack certain constitutional and clinical features that are diagnostically characteristic of the spontaneously occurring disease. From an etiological standpoint the latter may be subdivided into five groups.

1. Secondary to Thyrotoxicosis.—Marine (1935; Cornell Univ. Med. Coll. II, 1944) has frequently emphasized the relationship which may exist between Graves' disease and Gull's disease. He stresses the somewhat similar geographical distribution and sex incidence of the two conditions—female to male as 7 to 1. In consonance with these observations are the appearance of myxedema in burned-out cases of hyperthyroidism and the greater susceptibility of patients with Graves' disease to develop myxedema postoperatively as compared with individuals who have their thyroids removed for other reasons. There is little doubt that some cases of myxedema occur in patients who were previously thyrotoxic but exception should be taken to statements which suggest a relevant sharply defined connection between the two. For instance, Lisser and Anderson (1931) disagree with Marine's concept that myxedema and Graves' disease have the same geographical distribution. In fact they very pointedly state that the disease (myxedema) is probably scattered fairly evenly throughout the world and impressions of preponderance in certain localities are apt to *originate from* the fact that a few physicians in these regions have been sufficiently alert to collect many cases and place them on record.

It is our experience that a very small but definite number of cases of adult myxedema arise in patients who have previously had frank thyrotoxicosis In other words when hyperplasia of the thyroid has *persisted a sufficiently long time* it may result in atrophy associated with hypothyroidism The sequence of events is well illustrated in the case of H H a male who was first seen at the age of 37 with outspoken signs of myxedema He had developed a frank exophthalmic type of goiter at the age of 22 for which he had refused surgery The condition subsided spontaneously within two years and the patient was symptom free for an additional six years when there was recurrence of the toxicity Iodine was used intermittently for several months after which there was again a disappearance of all signs of toxic goiter except the exophthalmos The first evidences of hypothyroidism had appeared approximately two years prior to his first examination by us at the age of 37 This case is rather classical and demonstrates that years are usually required for the complete evolution from marked hyperplasia of the thyroid with thyrotoxicosis to atrophy of the thyroid cells with myxedema A former well proved diagnosis of thyrotoxicosis does not exclude the present possibility of a borderline or full blown myxedema

2 *Secondary to Chronic Thyroiditis*—Myxedema occurs occasionally in the course of Hashimoto's form of chronic thyroiditis rarely in the Riedel's type In both instances surgery increases the tendency for myxedema to appear Inasmuch as chronic thyroiditis (Chapter XXVI) in the usual sense of the term is itself a condition of considerable rarity relatively few cases of adult myxedema arise from this source

3 *Secondary to Underfunction of the Anterior Lobe of the Pituitary*—This condition commonly termed dyspituitrous myxedema (Chapter XXXI) may be differentiated from other forms of myxedema through the symptoms and signs of the severe dysfunction which exist concomitantly in other glands of internal secretion and possibly by the response to the administration of thyrotrophin (Querido and Stanbury 1950) While the disease is rare its recognition is very important as thyroid therapy so well indicated in the commonly observed varieties of myxedema may not only be harmful but even prove fatal in this form The adrenal gland is always in a state of underfunction in dyspituitrous myxedema but care must be taken not to confuse the condition with the adrenal atrophy which accompanies *primary* hypothyroidism (Despopoulous and Perloff 1950) Perhaps we shall soon speak of a closely allied hypothyroidism produced by the prolonged administration of ACTH or cortisone (Wolfson et al 1950) in which indeed the cause appears to be the presence of an *excess* of pituitary or adrenal secretion

4 *Secondary to Simple Atrophy (Primary Atrophy)*—The majority of all cases of spontaneous myxedema are due to an atrophy of the thyroid gland the etiology of which is still undetermined Occa

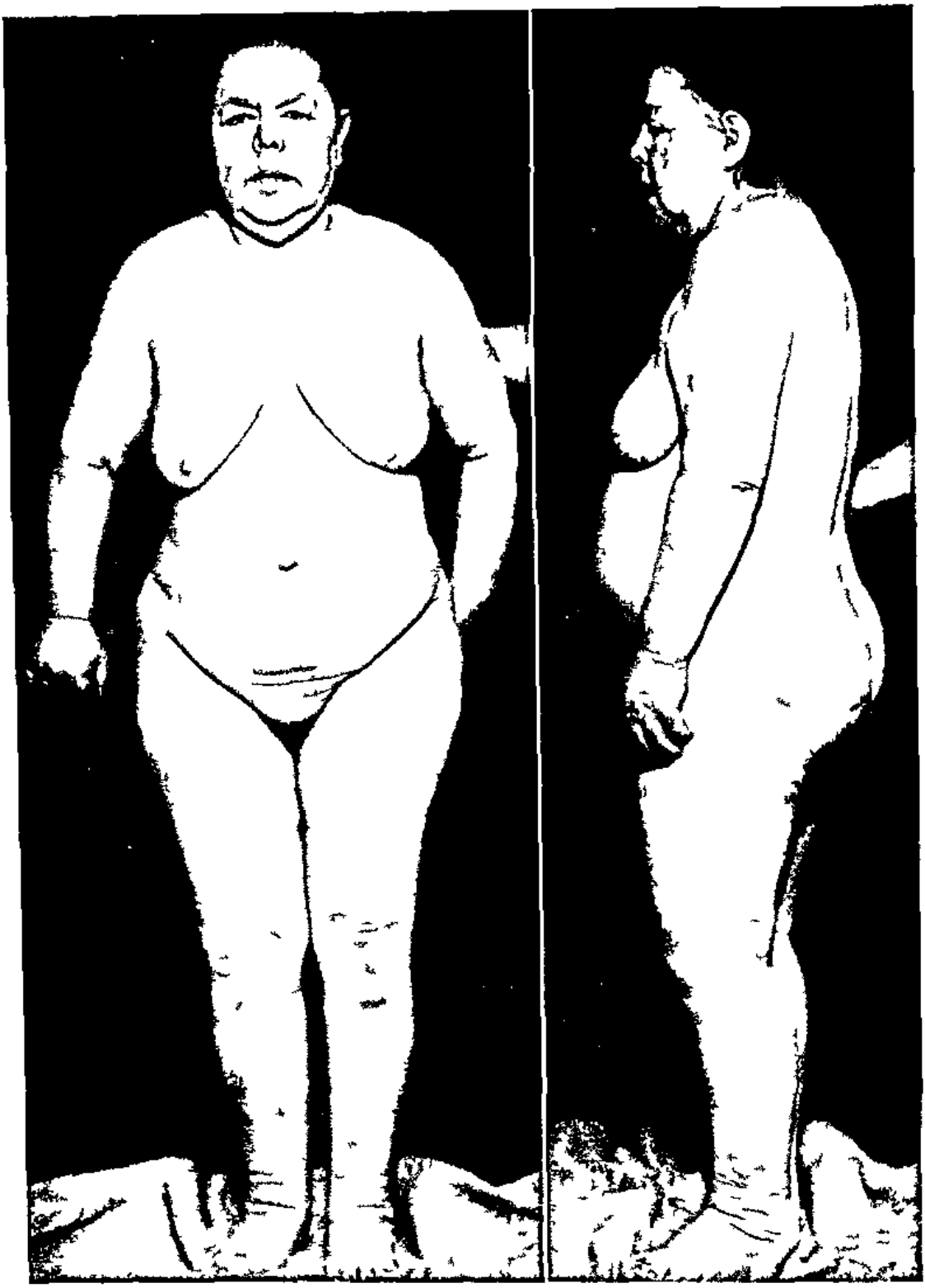
Chapter XXX

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A *B*

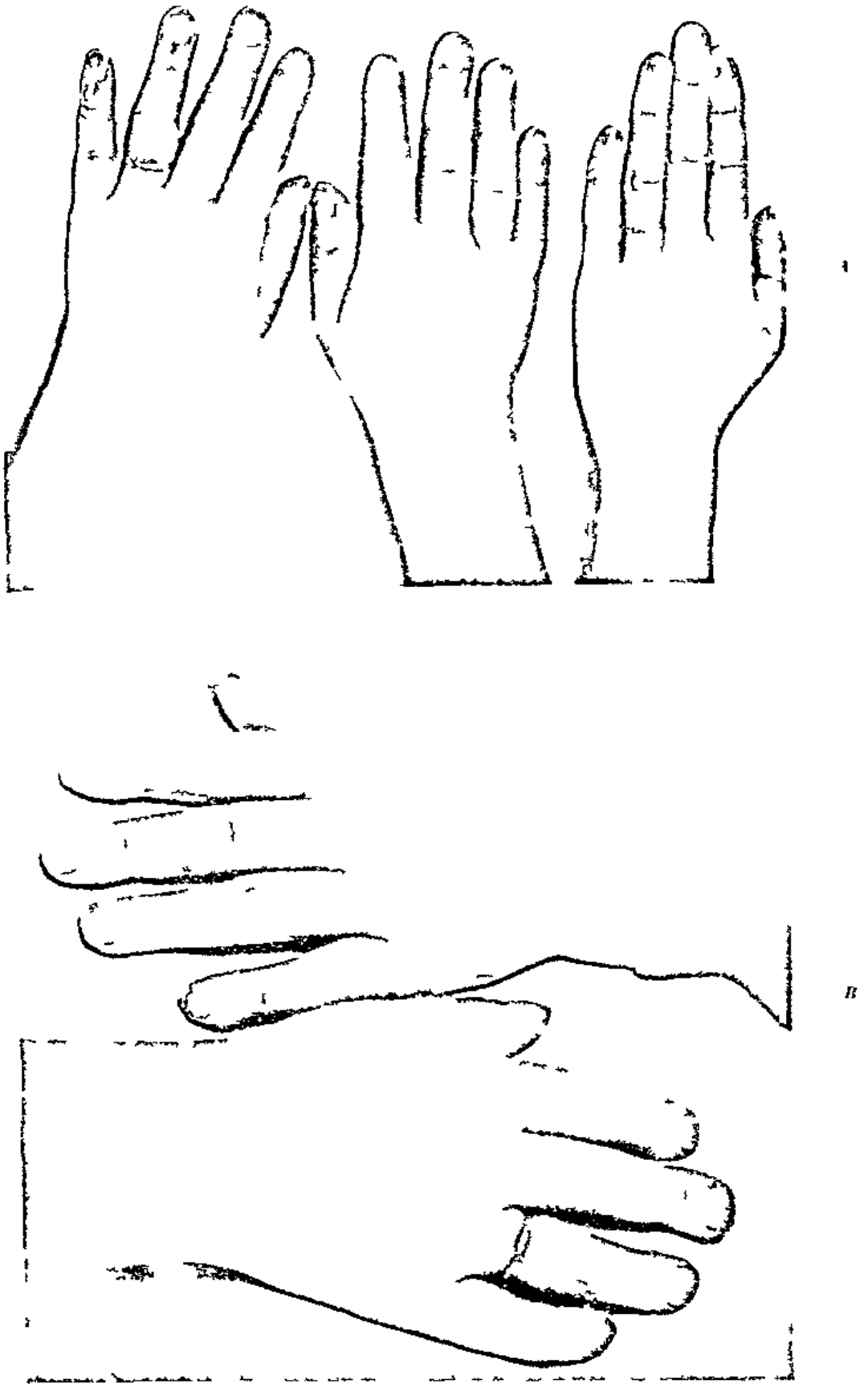
Fig. 4. *A* and *B*—Adult myxedema (MS. MH #1 6940). The photographs were taken at the age of 61 seventeen years after the onset of clinical symptoms of myxedema—chilliness, lethargy, fatigue, mild dyspnea, and edema of face and other parts of the body. Seven years before the skin and other tissues had been subjected to repeated roentgen irradiations for basal cell carcinoma. Treatment with desiccated thyroid had been begun two weeks before the photographs were taken. Note the heavy jowls, the puffiness of the eyelids, the dull expression, the swollen, thickened, pachydermatous skin, especially about the face, hands and ankles, the pendulous abdomen, the difficulty in standing, lordosis and the thickened, flabby legs and arms. The basal metabolic rate was —5 per cent. The circulation time was prolonged by 50 per cent, the total nitrogen was 80 per cent and total cholesterol 440 mg. per 100 c.

sionally attempts at regeneration may be observed in the thyroids of patients suffering from this form of adult myxedema This suggests that the condition may be an exhaustion atrophy

5 *Secondary to Thyroidectomy or the Administration of Drugs (Artificial Myxedema)* —Myxedema has been observed following thyroidectomy, particularly when performed for chronic forms of thyroiditis Graves disease or cardiac failure (Fig 15) Wilson and Mayo (1940) in a series of more than 15 000 thyroidectomies found myxedema in 1 2 per cent They recognized a definite positive relationship between the presence of exophthalmic goiter or thyroiditis and the occurrence of myxedema postoperatively Histologically 71 per cent of the cases developing myxedema following thyroidectomy were shown to have had chronic thyroiditis

Drugs may produce myxedema Hurxthal (1945) recorded the case of a 6-year-old girl who developed the condition following the use of iodine in the treatment of a simple goiter That thiouracil can suppress thyroid function to the point of producing clinical myxedema has now been well established (McGavack and Schwimmer 1944 McGavack Lange, and Schwimmer 1945, Cornell Univ Med Coll II 1944) About 4 per cent of the patients taking potassium thiocyanate for hypertension over long periods of time have developed large thyroids and manifestations of myxedema (Barker Lindberg and Wald 1941 Freis 1948 Richards Brockhurst and Coleman 1949) including classical cardiac disturbances (Estes and Keith 1946)

Incidence —Myxedema is a relatively common disorder More than 10 cases have been observed by us in a period of four years on the wards of a general city hospital (McGavack and Schwimmer 1944 McGavack Lange and Schwimmer 1945) From data collected by Means (1937) hospital admissions for myxedema occur a little less than one tenth as frequently as for diabetes mellitus slightly less than one half as commonly as for pernicious anemia and Hodgkin s disease and a little more than one half as frequently as for leukemia Means further states that in his thyroid clinic he sees one case of myxedema for approximately each eight of toxic goiter Eight of every 10 000 admissions to the Massachusetts General Hospital are for myxedema In our own work the ratio of patients with myxedema to those with toxic goiter is approximately 1 to 15 There are probably no statistics in existence which accurately measure the number of cases of myxedema for undoubtedly many of the milder cases and some of the more severe ones go unrecognized for several years The distribution of the disease is apparently not influenced geographically as is the case with simple subiodic goiters Women are from 4 to 7 times as frequently affected as men



l g 43 4 n1 *B*—Tl h d n n y d a (J C MH #1 4040) Th the h nd of a 49 y -old w an h h d l d y pt n f l y1 ths o d n f 4 e nd f nk gns of my1 I n a f r y tr t) nt s b un 3 k b fo opp tun ty w ff ded to n ke tl s p t s Not th gl nc p tln nd d) f tl e k and th dg ng a)d m ttling f th fing all n 4 (r ht) th l l of a r) l w n u g d 38 ye w s pl t g aphed f r om1 o

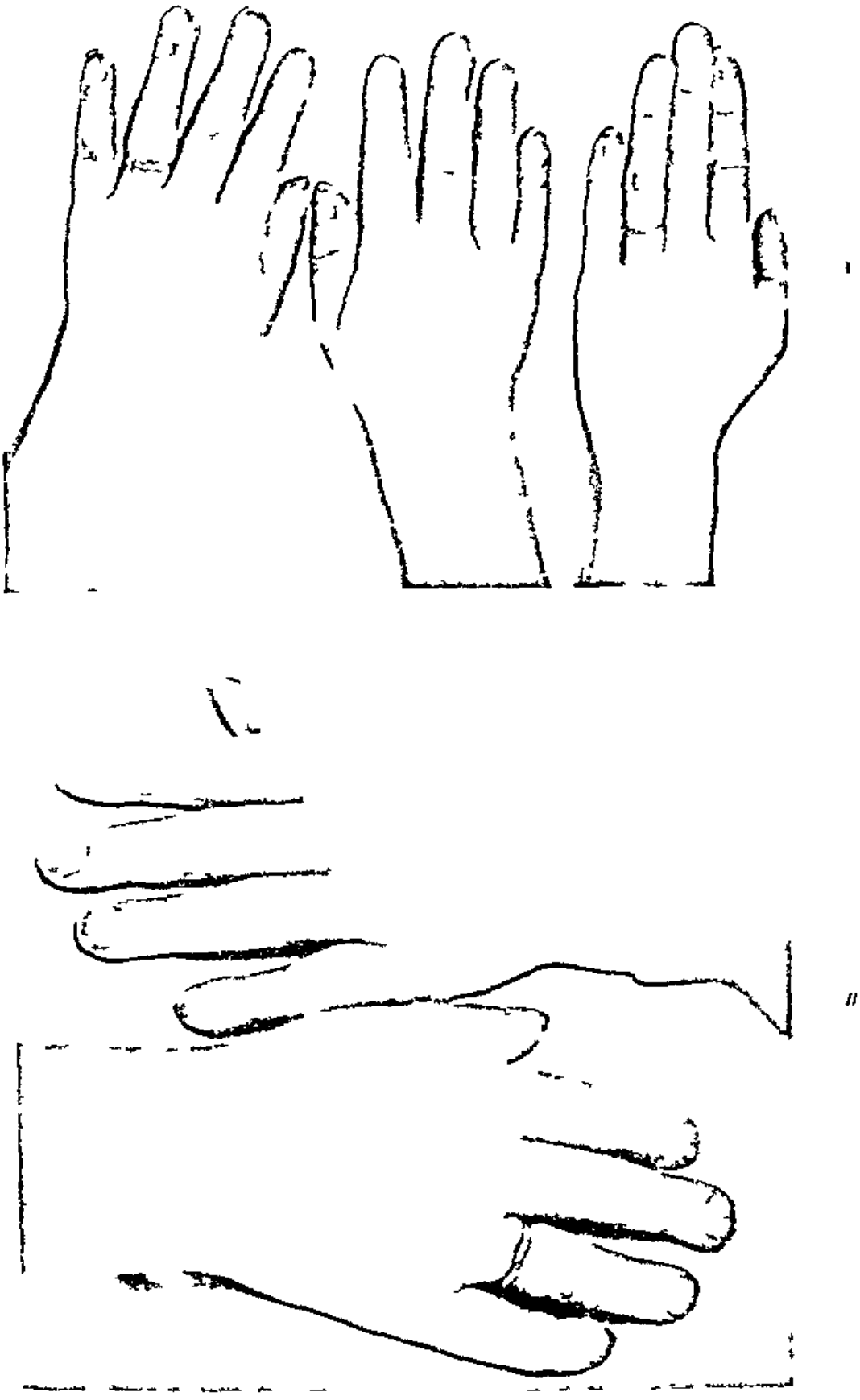
Clinical Features

Rarely are we confronted with a more classical picture in clinical medicine than the short frequently overweight pudgy faced somewhat expressionless individual who responds to questioning slowly but accurately in a hoarse voice and complains only of extreme weakness (Fig. 12). This is the full blown picture of adult myxedema all too frequently the stage in which it is first recognized. The majority of cases are seen between the ages of 35 and 50 years.

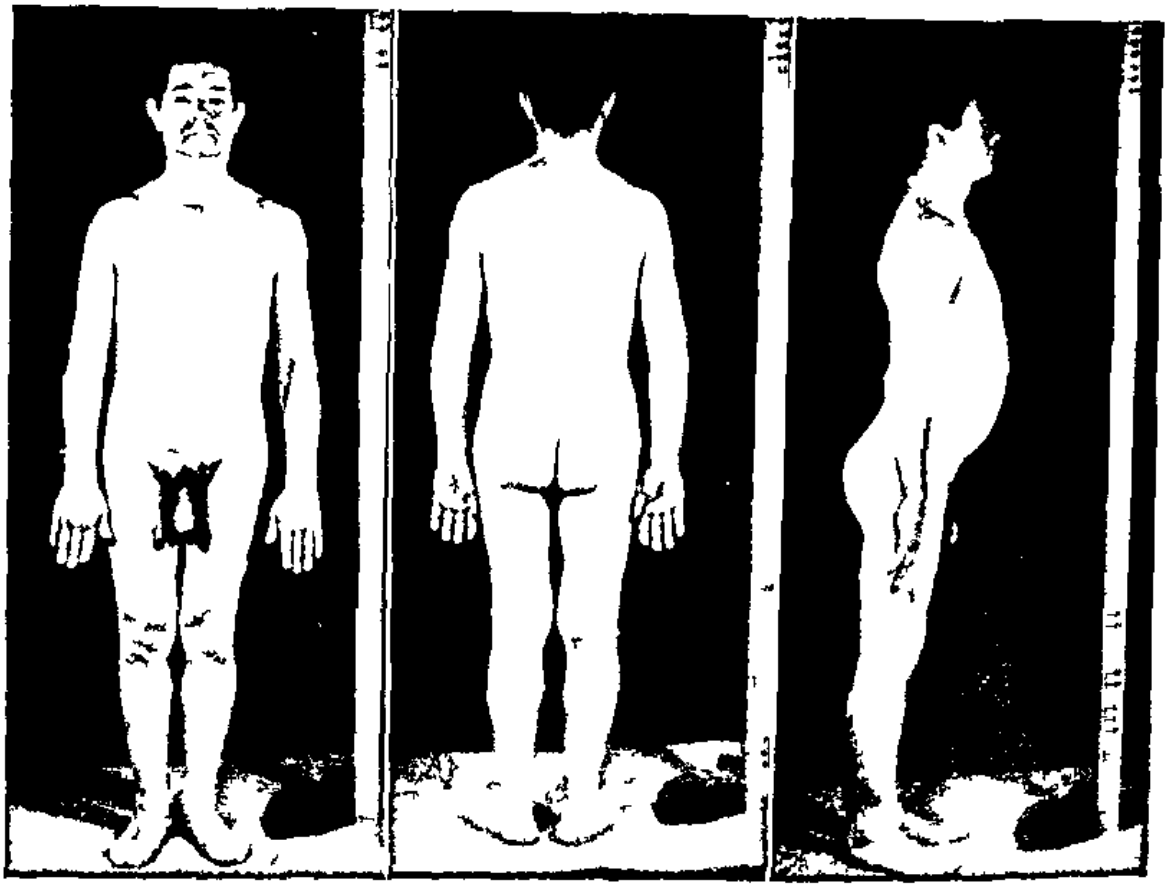
The Myxedema Constitution.—A number of investigators have called attention to the definite characteristics which occur in individuals who sooner or later suffer from spontaneous myxedema (Means and Lerman 1935, Draper 1930, Hertoghe 1914). Physically they are short statured, broad shouldered and short and thick necked with chubby hands and stubby fingers (Figs. 13 and 14). The rounded face and generalized deposition of moderate amounts of fat especially about the shoulders and upper trunk appear early. Prior to the development of their myxedema these people are well extroverted and have sunny dispositions. The Victorians would have called them amiable, amazingly so (Means and Lerman 1935). When the myxedema is fully developed, however, it may be better said that they exhibit a rapidly changeable disposition. Ordinarily euphoric they may be quickly angered for no obvious reason. By the same token they frequently revert to good humor following a chance remark or gesture.

As the condition progresses, dryness of the skin appears and deposits of fat over the neck and supraclavicular regions occur. The short stubby appearance of the hands and fingers is accentuated and probably accounts in part for their clumsiness.

When the disease is well established the mental and emotional symptoms are even more prominent. Difficulty in concentration is experienced. Loss of memory becomes more extreme. Initiative is lost and indecision with disinclination to any work takes its place. Listlessness, apathy, sleepiness and a low pitched, slow, monotonous speech with hoarseness complete the picture. Some moderate gain in weight occurs as a result of the increased fluid in the myxedematous tissues. All tissues share in the myxedematous infiltration. In consequence there is swelling of the eyelids with narrowing of the palpebral apertures (Figs. 12 and 14) and thickening and enlargement of the lips, tongue and mucous membranes of the nose, pharynx and larynx. The impairment in hearing and the low pitched hoarse voice are further evidence of the peculiar edema. Late in the disease the skin is not only dry but rough, cold and doughy in consistency (Fig. 12). The appendages of the skin are also affected. The hair is coarse, dry and brittle and falls out easily. When the myxedema is profound there is even blunting of the normal contours at the wrist and ankle.



I g 43 4 d *B*—The h n is in n y l a (J C Mff =121040) Th th hand f a 49 y -old w a who l l d y ut f hs t ths li n f y nd f nk sl s of myx d m f r y s t t nt s l g 3 w k l f r oppo t ity ff d f t n ke th p cture N te th gl s fllin nd trs of th k s d th rid s g d n otlll g f the fing r t i s 4 (ht) th l d of o r l wo ged 38 y w s hot g s h d for mp is n



A *B* *C*

Fig. 44.—*A*, *B* and *C*.—Spontaneous adult myxedema under treatment (C. P. M. #1 0 41). This 41 year old man represents rather classically the type of body build which appears to be subject to the development of spontaneous myxedema. Prior to taking these photographs he had had a total of three months' treatment beginning with 0.25 grain daily and increasing the dose each month by 0.5 grain per day so that 0.75 grain had been taken daily for approximately four weeks immediately preceding the making of these pictures. At the beginning of treatment his basal metabolic rate was —43 per cent. Serum cholesterol 410 mg. per 100 c.c. total protein 8.0 with albumin 0 per cent and circulation time approximately twice normal. At the time the photographs were taken he was not yet euthyroid as the basal metabolism was — per cent with all other findings similarly improved but not normal. Eighty per cent of the myxedematous infiltration had disappeared. Note the remaining myxedematous the short stocky build (height 63 inches) the narrow palpebral fissures the broad nose the puffy face the short neck the quare hands with short stubby fingers the slightly accentuated lumbar lordosis the relatively short lower extremities and the well-developed genitalia. In our experience this is the classical body configuration upon which spontaneous adult myxedema is usually superimposed.

Onset of the Disease.—Myxedema is classically insidious in onset. Since we know that only a small fragment of the parenchyma of the thyroid is necessary for the production of an adequate supply of hormone it is probable that the destructive atrophic process which finally produces a state of athyreosis has been developing for years before the patient shows any clinical symptoms or signs of it. When the condition is well established the patient's mental state is often such that it is difficult to obtain an accurate story of the complaints which first appeared. However sensitiveness to cold and a decrease in sweating are the ones most frequently enumerated. As a rule the sensitiveness to cold is an unbearable chilliness of the whole body necessitating the

use of extra clothing and extra bedclothes Often associated with this is a subnormal temperature occasionally as low as 35 C (Lisser and Anderson 1931) These symptoms may precede by a number of years the appearance of any others and since they can be produced by a large number of conditions other than thyroid disease the difficulties of early diagnosis are obvious Means (1937) cites a case in which the patient's hypersensitivity to cold existed for twelve years at the end of which time the picture of full blown myxedema rapidly occurred However any symptom of the fully developed condition may be its initial manifestation If the general decrease in bodily activity is associated with an equally severe lack of interest in work and in surroundings inertia and lethargy dominate the mental state If on the other hand the patient's sense perception and memory association are less disturbed and make him aware of his flagging functions then nervousness irritability fretfulness or peevishness will better characterize his mental attitude In our experience excessive irritability is more common than lethargy

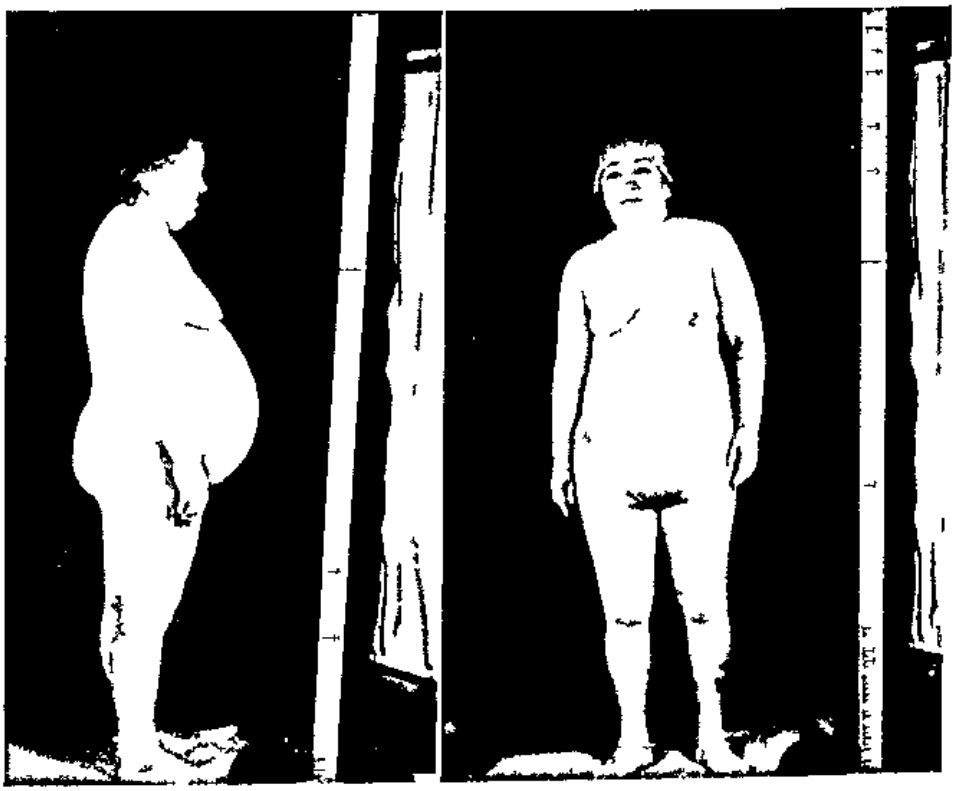
It bears repeating that any manifestation of the disease may be first in its appearance Lisser and Anderson (1931) illustrated this point well when they reported three cases in which paroxysmal tachycardia a pernicious anemia like picture and severe menorrhagia respectively were the problems for which the patient consulted his physician In other instances low grade urinary tract infection with backache may bring the patient first to the urologist (Grollman 1948)

Duration of Myxedema Prior to Recognition —In our experience the average duration of symptoms when a correct diagnosis was made has been 12 years This period has varied from a minimum of approximately 3 months to a maximum of some 13 years (McGavack and Schwimmer 1944 McGavack Lange and Schwimmer 1945) Means (1937) observed a case first diagnosed 15 years after the onset of symptoms The most difficult cases to treat are those who have had symptoms of the disease for the longest periods of time In fact Means and Lerman (1935) have demonstrated that the severity of the disease varies directly with its duration prior to treatment and emphasize that patients may die of myxedema despite the fact that it is a readily curable disease Of 21 patients (McGavack and Schwimmer 1944) 5 died before adequate therapy was attained or before it could be instituted at all

The Order of Frequency of the Manifestations Seen in Myxedema — In our experience the most commonly mentioned complaint of the myxedematous patient has been weakness It is exceeded in frequency only by the myxedema itself Of our patients more than 80 per cent have had one or more of the following with the relative frequency indicated by the order in which they are named weakness coarseness and dry



A



B *C*

Fig. 4. *A*, *B*, *C* and *D*.—Lo top t e my el ma (M A 1124640 MH #144646). This f4 y ar old wo n h d u l rgo n p at on f r a toxi ad o of tl thyr id wl n he w 43 year of ge Sym t of vxele h d l gu t th ge of 8 veais Sc n of tl stigmata of spoi taneous mjx d a are p nt—sh t tocky t ture h ght J i ches h avy f ture nd expression thick neck mjx l a laxe l abdo ni l all—l ut oth rs a e ab e t D pite tl e yxedema the fl g s and legs ar norn lly taper g nd the low r n easur j nt (2J l ch) is approxim ately h lf the height It must l e f tl r a n e b d that s ve e p stop ratl e hypo- thyroidism may o w thout mjx d ma h l ch i ibility l n ognlz d In this ca e this won an m ght ha e b en saved t lc t t n y a of ill l ealth with n ider ble l ngtl ni g f her p n of life

ness of the skin sensitivity to cold apathy decrease in sweating cold skin slowness of speech edema of the eyelids and/or face impairment of memory coarseness of the hair and thick tongue Between 50 and 80 per cent of the subjects developed an increase in weight loss of hair an enlargement of the heart myxedematous pallor of the skin and lips hoarseness or aphonia constipation dyspnea and irregularities of menstruation From 30 to 50 per cent of the patients suffered from anorexia nervousness and irritability peripheral edema palpitation precordial pain and weakened heart sounds Still less frequently observed were poor vision disturbances of hearing choking sensations atrophy of the tongue difficulty in swallowing and so forth

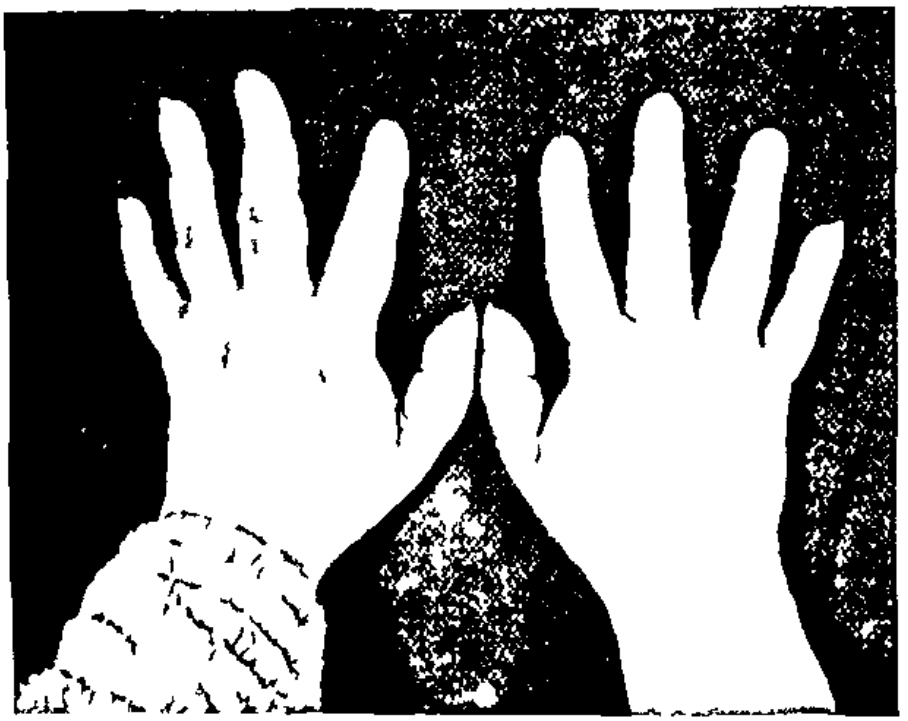


Fig 4 *Myxedema (Hurwitz et al 1949)*

Analytical Review of the Clinical Picture of Myxedema—Normally the thyroid plays an important role in the functioning of every organ tissue and cell in the body When it fails to supply sufficient thyroxin therefore a wide variety of symptoms and signs are referred to every portion of the body A brief review of these permits a simple anatomical classification and simultaneously some discussion of the physiologico-pathological characteristics of each

1 *Disturbances in the Mental and Psychic Spheres*—The emotional level of patients with myxedema is often low The picture is one of extreme complacency In some degree drowsiness lack of initiative disinclination for effort and loss of memory can be detected Percep

tion usually remains accurate although the speed with which it proceeds may be markedly reduced Except in the most severe cases reasoning remains good although here again the time required for the synthesis and expression of the thought is decidedly increased

Frequently memory association is so accurate and thinking so clear that the patient is acutely aware of his deficiencies *In some instances* placidity vanishes and a highly irritable state occurs in which lack of self confidence to the point of an inferiority complex and marked lability of emotions to the extremes of a manic depressive psychosis or a melancholia may dominate the picture Outbreaks of rage or fury interspersed with periods of apathy and despondency are common With these psychotic manifestations hallucinations particularly of smell but also not uncommonly of sight and hearing, may appear Delusions, usually of persecution have been seen A wide variety of phobias especially fear of being alone fear of new places experiences or people associated with varying degrees of melancholia are equally common

In view of the very prompt response of the myxedema psychosis to the administration of thyroid extract Zondek and Wolfsohn (1911) have emphasized its probable relation to a myxedematous state of the brain Relief following the administration of thyroid extract is probably due to the mobilization of extracellular water and the loss from the body of both sodium and potassium

2 *Disturbances of the Nervous System*—The myxedema of the tissues apparently plays a leading role in the production of the nervous symptoms and signs that are encountered in the patient with myxedema

A Vegetative nervous system Constipation is easily the most commonly observed symptom in myxedema that points to an imbalance of the autonomic nervous system Characteristically this costiveness defies all types of therapy except the administration of thyroid hormone Why constipation should occur has never been fully explained While several factors have been responsible such as imbalance between the sympathetic and parasympathetic control of the bowel and alterations in calcium metabolism it seems quite likely that the myxedematous infiltration of the musculature of the bowel in itself is sufficient reason for the sluggish state of gastrointestinal activity *In some instances* more severe conditions within the bowel may be observed such as megacolon generalized abdominal distention and even intestinal obstruction due to paralytic ileus Indeed Basteme (1916) in a review of 29 cases of severe hypothyroidism states that intestinal paresis may appear as the first important sign of unrecognized or latent hypothyroidism *It is extremely important to recognize* its true nature in order to avoid usually disastrous surgical intervention

Many other disturbances of the vegetative nervous system also occur but are perhaps best discussed under the system of the body most involved (q v) such as the circulation the intestinal tract the skin and so forth

B Central nervous system The sensory side of the nervous system is predominantly involved in the manifestations of myxedema although the motor portion does not completely escape Of the paresthesias which are common numbness and tingling in the extremities are the most often observed Reactivity to all external stimuli is decreased as a result of the impaired function of the special senses Even the peculiar uncertain gait and the clumsy movements of the hands have been ascribed to an impaired sense of touch (Sloan 1936) There is a sluggish phase of relaxation following motor response to an external stimulus This can be readily demonstrated by noting the speed of relaxation after eliciting an Achilles tendon reflex It is best observed when the patient is on his knees with the feet hanging free over the edge of the examining table or bed Sloan (1947) and Lambert and his associates (1948) recognize this as a very reliable easily observed diagnostic sign in borderline cases of hypothyroidism While the above are the commonly observed nervous signs and symptoms actually the disturbances may vary from an acute multiple motor neuritis to a peripheral neuropathy resembling in neurological signs the symptoms and pathological changes that occur in pernicious anemia (Currier and Brink 1948) Goldblatt (1948) believes loss of vibratory sense is a highly confirmatory sign capable of quantitation in relation to therapeutic response

Of the special senses vision and hearing are most severely affected *probably because even moderate degrees of edema within the organs* concerned with these activities can produce pronounced variations in function In any event the manifestations are disproportionately great when compared with the general decrease in sensitivity In both instances there is an unusually long lagtime between the application of the stimulus and any registration in memory association centers or in a necessary motor response Certain manifestations of myxedema deserve special consideration in relation to

a The eye Coachman (1945 1947) has described the presence of latent vertical phoria in a number of patients with lowered basal metabolic rates While the condition is also observed in other endocrine conditions as well as in those of a nonendocrine nature it is apparent that a combination of this condition with thinning of the outer third of the eyebrow puffiness of the lids subnormal temperature low blood pressure slow pulse and frequently generalized swelling of subcutaneous tissues points toward a myxedematous condition Thyroid therapy is essential to any permanent relief of the condition but must be accompanied by prismatic correction of the local condition Symp

toms growing out of this syndrome include headaches facial neuralgias cervical myalgias and reflex symptoms referable to the vestibular apparatus and the gastrointestinal tract Therefore the differential diagnosis must always include Menieres syndrome, migraine, sinus or sick headaches brain fag and so forth During the past two years since we have been aware of the existence of this condition we have observed at least three patients in whom the administration of thyroid hormone while normalizing many of the general manifestations of hypothyroidism failed to relieve the eyestrain and its associated paresthesias and reflex symptoms until the vertical phoria was corrected

b The ear Vertigo and tinnitus are common accompaniments of myxedema Less frequent, but even more distressing may be the auditory hallucinations and delusions that sometimes suggest a psychotic condition Some workers believe hypothyroidism should be considered more frequently in the differential diagnosis among patients whose presenting symptom is vertigo and in whom a final diagnosis of Menieres syndrome is made by the otologist Twenty five of 30 patients who had recurrent attacks of vertigo fatigue low basal metabolic rates bradycardia and low blood pressure responded completely to the administration of desiccated thyroid substance (Athens 1916)

The myxedematous state of the aural tissues is the recognized cause of the vertigo The boggy myxedematous infiltration of nerve by tissues undoubtedly accounts for the deafness that all too frequently accompanies hypothyroidism (Barnes 1917) This too should respond completely to thyroid hormone provided the edema has not been present sufficiently long to produce secondary fibrous tissue changes of *an irreversible* nature

3 Body Weight in Myxedema —The impression that patients with myxedema are fat is a fallacy Indeed in the more severe cases a decrease rather than an increase in weight is the rule When a gain in weight is observed it is usually due to the added fluid occasioned by the myxedematous infiltration *Inasmuch as all of the elements concerned* in normal bodily activity are slowed down ' including the ingestion *absorption and assimilation of food there is little or no opportunity* to store fat in the body s depots On the contrary as the disease progresses *and the metabolism falls to lowest levels* there may be sufficient interference with cellular nutrition and all of the anabolistic processes to cause tissue wasting and actual loss of weight despite the retention of water and electrolytes A correct diagnosis of spontaneous myxedema would certainly be made more often if physicians would disabuse themselves of the idea that overweight is an inseparable feature of the disease

4 Disturbances in the Skin and Its Appendages —The coldness of the skin in myxedema is due in major part to natures effort to conserve

heat and is a reflection of the patient's extreme sensitivity to low temperatures From a teleological viewpoint the roughness dryness and scaliness of the skin in association with an absence of sweating may be similarly explained Mechanistically these changes in the skin are consequent upon the absence of normal stimulation of sebaceous and coil glands by thyroid hormone (Fig 42) Secondary changes in the skin such as the easy tendency to develop acute and chronic inflammations are due not only to the lowered nutritional activity of the individual cell but also to the accumulation of sebaceous material in the accessory glandular structures which acts as an irritating foreign body (Marks 1946) The dryness of the skin gives rise to pruritus often widespread secondary infection frequently follows scratching The lesions may vary from a transient erythema to superficial single traumatic erosions *and multiple deep excoriations and ulcerations with and without* secondary infections (Goldblatt, 1941)

The slow healing of the ulcers of the leg described by Cohen (1934) is probably due to disturbances in the normal function of the skin The skin may become scaly or even ichthyotic This does not imply that true ichthyosis is due to hypothyroidism for while the ichthyotic lesions of myxedema disappear completely under appropriate therapy we have failed to see any improvement in true or idiopathic ichthyosis even though 15 grains of thyroid extract were given daily

Lesions resembling lupus erythematosus have been described in myxedema (Means 1937) Means states that Lerman has seen two cases of facial epithelioma which despite radium treatment failed to heal until desiccated thyroid substance was given These unusual cases seem merely to emphasize the important role which the thyroid normally plays in the physiology of the skin

Another rare (78 cases recorded to the time of Cohen's report—1946) but interesting condition is localized usually pretibial myxedema which in more than half of the cases thus far reported in the literature has been associated with or has followed hyperthyroidism (myxedema circumscriptum thyrotoxicum) (Pillsbury and Stokes 1931 Levin and Tolmach 1945 Cohen 1946 Hubschmann and Charvat 1948 Grahlow 1948 Cordero 1948 Ebert and Baker 1948 Gibans 1949 Villanova and Canadell 1949) The affected skin of these patients has been claimed to contain an excess of acid mucopolysaccharides including hyaluronic acid (Watson and Pearce 1947a b) It is postulated that the normal hyaluronic acid hyaluronidase balance is distributed in the skin of the persons with pretibial myxedema (Watson and Pearce 1947b) Hurst (1949) obtained improvement in one of seven patients by injecting hyaluronidase into the lesions

Clinically there appear more or less symmetrically placed sharply outlined patches or nodules over the anterior surfaces of both legs or on the dorsal aspects of the feet They vary in size from barely discernible

toms growing out of this syndrome include headaches, facial neuralgias cervical myalgias, and reflex symptoms referable to the vestibular apparatus and the gastrointestinal tract Therefore, the differential diagnosis must always include Menieres syndrome migraine sinus or sick' headaches, brain fag and so forth During the past two years since we have been aware of the existence of this condition we have observed at least three patients in whom the administration of thyroid hormone while *normalizing many of the general manifestations of hypo* thyroidism failed to relieve the eyestrain and its associated paresthesias *and reflex symptoms until the vertical phoria was corrected*

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in myxedema as the direct result of the combined action of the myxedema the lowered nutritional status of the individual cells and the alterations in the metabolism of cholesterol

5 *Disturbances in the Cardiovascular System*—Dysfunction of the heart is an integral part of the myxedematous state The longer the duration of the disease and the older the patient the more diffuse and irreparable is the damage Twenty of twenty four patients with myxedema entered the hospital for a cardiac condition (McGavack and Schwimmer 1944 McGavack Lange and Schwimmer, 1945) Myxedematous patients tire easily on the slightest exertion Dyspnea and occasionally orthopnea are observed Cardiac pain was present in 20 per cent of the cases of myxedema with cardiac damage observed by Bartels and Bell (1939) In fact these symptoms and others pointing to cardiac weakness may so dominate the picture that the patient is often treated as a sufferer from heart disease only Even if a correct diagnosis is made the danger from cardiac manifestations is far from over The improper management of the myxedema may produce or intensify the cardiac difficulty We have seen untreated myxedematous patients with fully compensated hearts in whom 1½ grains of desiccated thyroid substance continued for as much as 7 days have caused both *right and left cardiac failure of severe degree* *In other instances* we have observed the occurrence of angina pectoris while the patient was taking as little as 0 1 grain of thyroid hormone daily In one instance a coronary occlusion was precipitated by a sudden increase in the dose of thyroid hormone from 0 1 grain to 1 0 grain daily for a period of six days

The cause of angina pectoris in the patient with untreated myxedema is usually sclerosis of the coronary arteries as part of a generalized arteriosclerosis probably due to the associated disturbances in lipid metabolism (Herrmann 1946) When angina pectoris appears only during treatment it may arise as a result of several factors First of all the coronary arteries are already narrowed as a result of the arteriosclerotic process or as a result of the infiltration of lipids such as cholesterol In this connection a case has recently been described in which death was due to massive pericardial effusion with cholesterosis (Howard 1946) When treatment with thyroid hormone is begun an increased demand is placed upon the heart before the lipid disturbances in that organ can be corrected Under such circumstances the danger of cardiac failure directly connected with treatment is obvious Bartels and Bell (1939) in a careful study of 59 cases of spontaneous adult myxedema found that approximately one third of those who had had the disease for less than two years had damaged coronary arteries In about 65 per cent of the patients in whom the disease had lasted 2 to 5 years prior to treatment there was evidence of a disturbance of the circulation to the cardiac musculature In all of the cases of over

lesions to areas involving most of the distal segment of the lower extremities The surface is erythematous, cyanotic or yellowish white and the associated dilatation of the follicular structures of the dermis may give rise to the pigskin or orange skin appearance The lesions are painless cold and dry to touch, and fail to pit on pressure Hypoalbuminemia with an absolute increase in the beta and gamma globulins has been observed (von Fischer 1919) Otherwise the clinical laboratory findings are not remarkable

Amersbach and Kanee (1941) believe localized myxedema is confused frequently with thrombophlebitis or erythema nodosum like dermatitis medicamentosa due to iodides or bromides They call attention to the fact that the condition is quite rare being recognized in but one of 525,000 admissions to the skin and cancer unit of a general hospital The condition is of importance because it frequently (Levin and Tolmach 1945 Cohen 1946) if not always (Trotter and Eden 1942) occurs in a previously thyrotoxic subject and because it may be associated with serious cardiac dysfunction and a high degree of exophthalmos (Curtis Cawley and Johnwick 1949 Klotz 1949)

In general therapy of localized myxedema has been unsuccessful Thyroid hormone administration has been pronounced a failure (Green and Freudenthal 1948) Vilanova and Canadell (1949) draw several analogies between the mode of onset and course of the disease and those of malignant exophthalmos simultaneously making a rather comprehensive review of the literature in relation to pathogenesis and treatment Their two cases were cured by the administration of estrogens in moderately large doses (0 5 mg stilbestrol or 2 0 mg estradiol benzoate daily) Such therapy was tried in the belief that the condition is caused by a high production of thyrotrophic hormone of the pituitary which can be suppressed by ovarian follicular hormone or a synthetic analogue

Myxedema papulosum has no apparent connection with thyroid function (Green and Freudenthal 1948) but is a dermatologic adaptation of the word myxedema in a literal sense to indicate mucinous infiltration of the skin'

In myxedema the nails grow very slowly and become thick and brittle The hair is coarse and tends to fall out The thinning of the outer portion of the eyebrows (Hertoghe s sign) is not as characteristic of myxedema as originally believed for it occurs rather infrequently and may be seen in a number of other conditions

Many other skin conditions have been ascribed to underfunction of the thyroid gland including scleroderma xanthoma multiplex keratoderma pityriasis rubra pilaris lichen nitidal and so forth Some admittedly tentative efforts at a logical grouping of these conditions have been attempted recently (Goldblatt 1941) Nevertheless in our present state of knowledge it seems best to look upon the skin changes observed

Changes in the heart itself in myxedema include an increase in size (Fig 46) a dilation of both the left and the right sides of the heart a decrease in the pulse rate with a tendency to a lowered systolic blood pressure and variations in the electrocardiographic tracings (Fig 47)

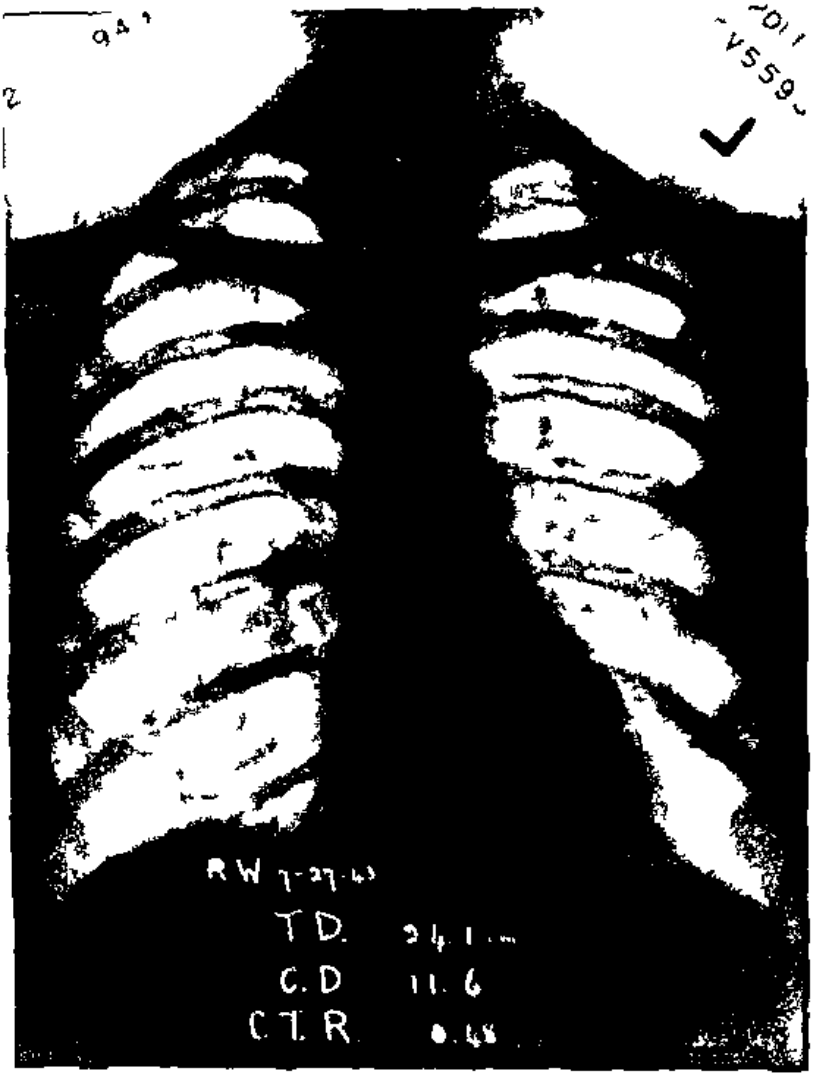
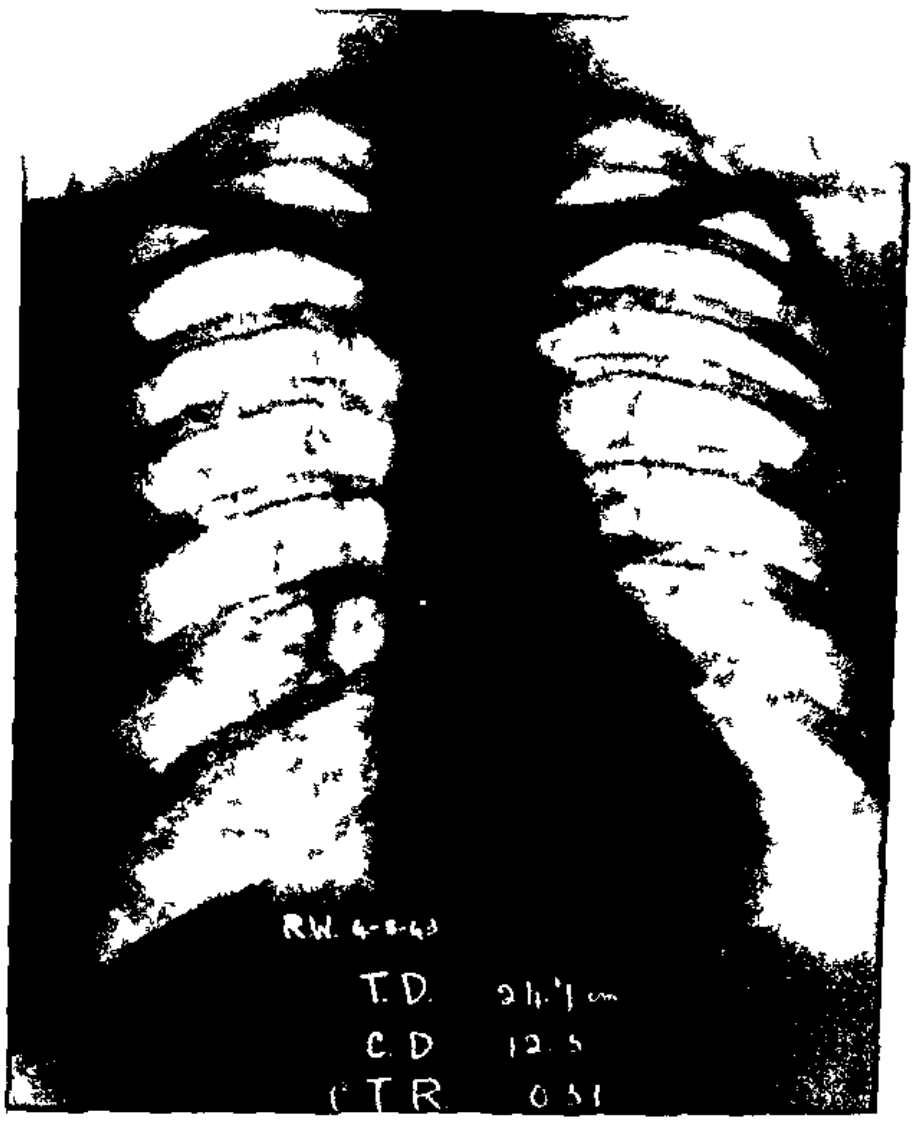


Fig 46 B *(For legend see opposite page)*

(Scherf and Boyd 1946) The size of the heart is increased in nearly all cases we found it so in 18 of 19 cases of myxedema studied (McGavack Lange and Schwimmer 1945) This enlargement involves all chambers Following adequate thyroid therapy over a period of from three to six months the size of the heart is normal The reason for the increased size of the heart is still not entirely clear Most authorities are agreed that the infiltration by myxedematous tissue is not alone responsible and it seems that such infiltration is rarely proved (Boyd 1950)

5 years duration prior to recognition, pathological changes in coronary arteries were demonstrable There was no direct correlation between the level of the basal metabolic rate, the values for blood cholesterol and the degree of coronary sclerosis present



A

Fig 46 *A* and *B*—Roentgenogram of the large heart in myxedema There is here an increase in the size of the heart in myxedema (*A*) in the absence of demonstrable pericardial effusion or primary cardiac disease with a return to normal after a euthyroid state has been established (*B*) by the administration of thyroid hormone (After McGavack Lange and Schwimmer 194)

A second reason for cardiac failure due to early overtreatment of myxedema depends upon the fact that myxedema is commonly associated with a decrease in the activity of the adrenal cortex Therefore there is frequently a reduction in the available stores of carbohydrate in the liver As a result, the normal mobilization of sugar does not take place Under these conditions of all the muscular organs of the body the heart must suffer most for lack of readily available sources of energy

dema is far from clear LaDue (1913) has critically analyzed this point in reporting a case in which death was caused by 'myxedema heart' The microscopic appearance of the lesions in his patient was indistinguishable from that seen in several other conditions but therapeutically the changes in cardiac function responded specifically to hormone therapy alone These changes included hydropic vacuolization loss of striation branching pyknotic nuclei and irregularity in staining properties of the muscle fibrils They were associated with a hydroscopic edema similar to that noted in other tissues of myxedematous patients and to which the other cardiac alterations were believed to be due (Schultz 1921 Behr and Mulder 1938 LaDue 1913) It is believed by some observers that the slight enlargement of the cardiac silhouette seen roentgenographically in uncomplicated myxedema can be ascribed to this interstitial edema and its associated changes

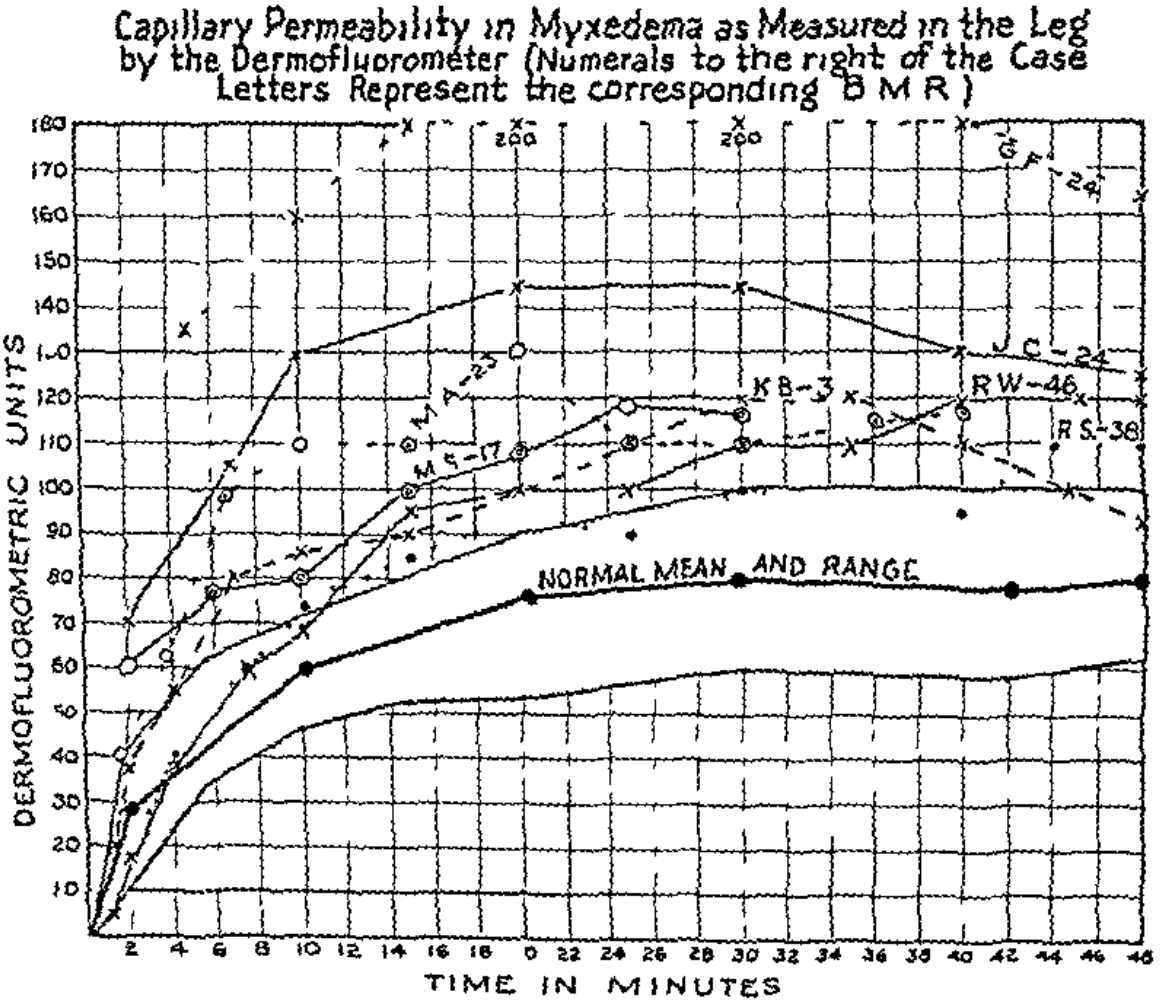


Fig 48—Capillary permeability in myxedema as measured by speed and intensity of the diffusion of fluorescein from the leg In our experience as in the several cases shown in this figure increase in capillary permeability is usually present (Modified from Landis and Schwimmer 1941)

In addition to the increase in size of the heart, there is a decrease in its functional capacity with a lowering of minute volume output Under the fluoroscope the heart shows extremely feeble pulsations There is a tendency to hypotension with a lowered pulse pressure however there are many individual exceptions to this rule Despite the slow pulse rate the patient frequently complains of palpitation Occasionally this palpitation may be associated with a rapid heart rate as was observed in the case of paroxysmal nodal tachycardia described by Lisser and Anderson (1931) Other arrhythmias are not uncommon and we have seen them in six of 24 cases with myxedema

Pericardial effusion is found in some cases of myxedema We have observed it in 2 of 19 patients (McGavack Lange and Schwimmer 1945) While the change in the size of the heart has been ascribed by some authors to pericardial effusion (the subject has been recently reviewed by Kern Soloff Snape and Bello 1949) this is certainly not always the case *Indeed the nature of the enlargement in uncomplicated myxe*

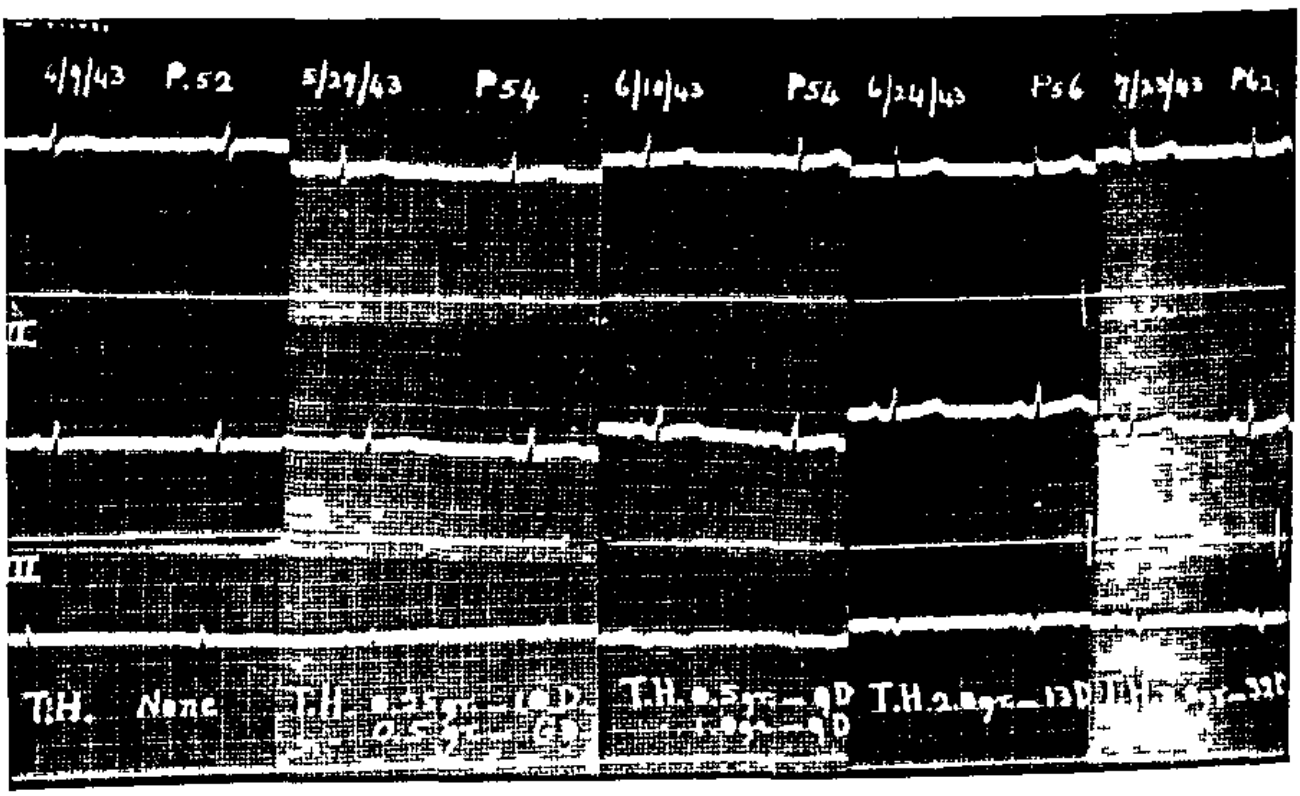


Fig 4 —Electrocardiographic tracings in the subject whose roentgenograms are shown in Fig 46 The tracing at the extreme left was taken before any thyroid therapy the one at the extreme right after a euthyroid state had been established by the administration of thyroid hormone This 3 year old woman had suffered from myxedema for thirteen years and had a basal metabolic rate of —46 prior to the institution of therapy *I* represents the pulse at per minute *TH* thyroid hormone *D* the duration of hormonal therapy in days at the indicated level of dosage Note the changing of all initially low complex T waves toward normal as the treatment progressed particularly significant is the appearance of normal T waves This patient was clinically well at the time of the last tracing with a normal circulation time capillary permeability serum cholesterol and protein but a basal metabolic rate of —12 (After McGavack Lange and Schwimmer 1945)

tation stand clinically in the foreground The changes in pulse rate blood pressure capillary permeability size of the heart and electrocardiogram must all be looked upon as a true part of the picture of myxedema and not as a separate disease process complicating the thyroid disturbance

Disturbances in the nutrition of the cardiac musculature which probably play a major role in the production of the changes in cardiac function may be attributed to one or more of several influences In the first place the lack of thyroid hormone interferes with the activity of each individual cell In the second place the metabolic alterations in myxedema particularly those concerned with lipid metabolism favor the deposition of cholesterol and calcium salts in the coronary arteries thus narrowing the channels through which nourishment reaches the musculature In the third place the diminished activities of the adrenal cortex and the liver combine to make the energy producing intermediaries of carbohydrate metabolism less readily available within the continuously working cardiac muscle cell

Hearts altered as above by myxedema will not respond well to digitalis therapy Means (1937) states that on the contrary myxedematous patients tolerate digitalis badly just as they do morphine ' This does not mean that digitalis should never be given in cases of cardiac failure due to myxedema or its overzealous treatment with thyroid hormone Indeed where failure has been precipitated by over treatment we have found digitalis a necessary part of successful therapy (Fig 50 *A* and *B*)

6 *Disturbances in the Gastrointestinal Tract* —Rarely does the person with myxedema escape some gastrointestinal complaint and he frequently consults the physician only on that account At least three factors combine to interfere with normal activity of the stomach bowel and accessory structures These are (1) an imbalance of the autonomic nervous system (2) interference with the absorption of certain food stuffs and (3) myxedematous infiltration of the tissues generally

The symptoms consequent upon the above alterations in activity somewhat in the order of their frequency are constipation flatulence anorexia abdominal pain and rarely nausea or vomiting

The myxedematous infiltration and a disturbance in the balance of the autonomic nervous system combine to lower intestinal tone and to decrease peristalsis in myxedema One of the results of the lowered muscular activity is a diminution in the fecal excretion of calcium (Althausen 1939) which further relaxes the intestine It is little wonder therefore that constipation is so prominent so constant and so obstinate a symptom in myxedema rarely responding satisfactorily until thyroid hormone is administered

(Schultz 1921 Lerman Clark and Means, 1933 Behn and Mulder, 1938 LaDue 1913)

The most common abnormality in the electrocardiographic tracings of patients with myxedema is a flattening or inversion of the T waves The T wave in Lead II is most frequently involved *Abnormal axis deviation*, small T waves and notched and widened QRS complexes are usually present *A decrease in the amplitude of all complexes in all* leads often occurs, sometimes in cases in which the presence of pericardial effusion cannot be proved (Fig 17)

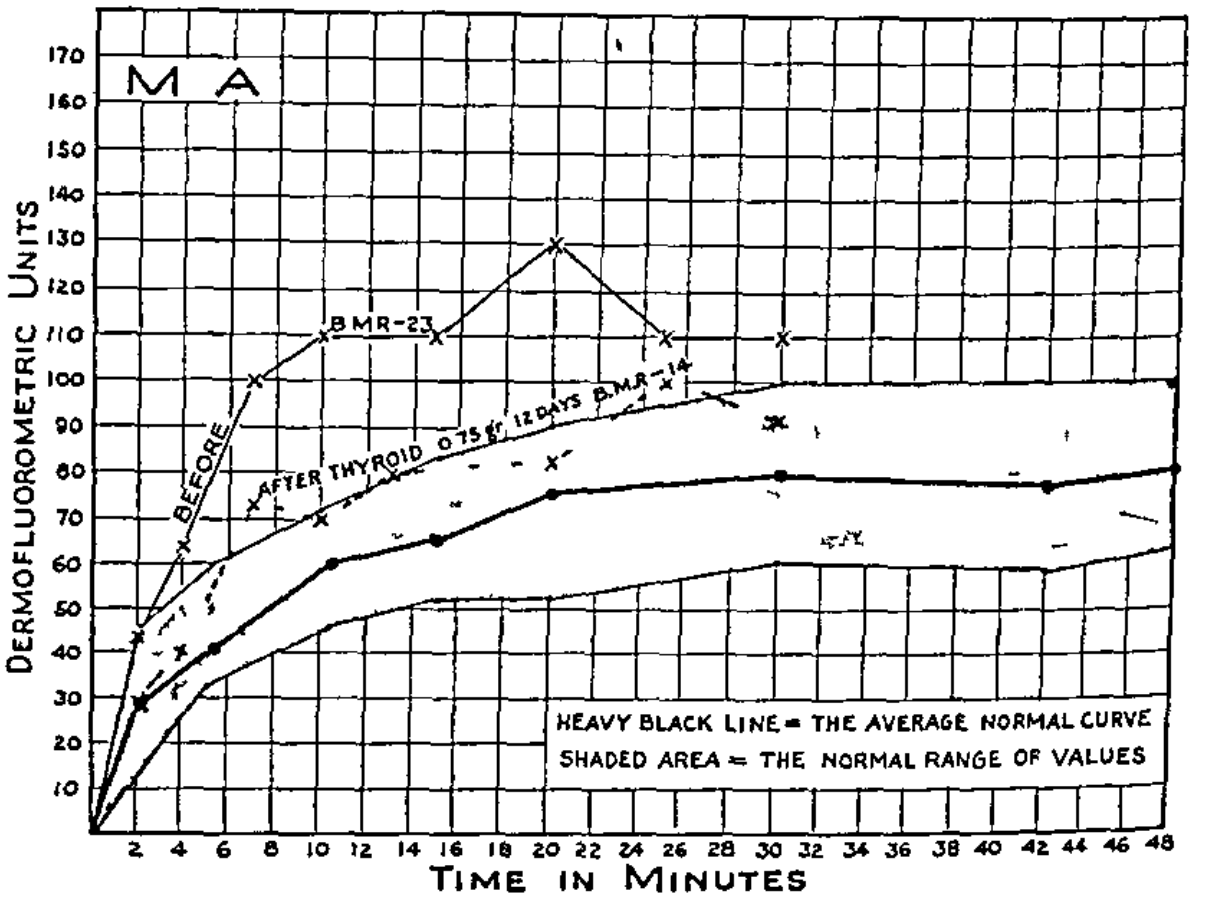


Fig 49—Capillary permeability in myxedema before and after adequate therapy with thyroid hormone After twelve days of treatment with 0 3 grain daily the previously increased permeability of the tissue has been reduced to a high normal level while the basal metabolism still remains low (−14) In the majority of cases a decrease in permeability occurs early in the treatment of myxedema with thyroid hormone (After McGavack and Schwimmer 1944)

In the periphery we find a low hypotensive pulse associated with a marked increase in capillary permeability (Figs 48 and 49) (McGavack and Schwimmer 1941 McGavack Lange Schwimmer 1945 Lange 1944) The close relationships of these changes in capillary permeability to the myxedematous state is demonstrated by their rapid disappearance under therapy (Fig 49)

In summary then it must be emphasized that disturbances in cardiac function are an integral part of myxedema in which lowered tonus of cardiac musculature and feebleness of cardiac action with dila

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Flatulence is usually present in myxedema. Poor absorption from the gastrointestinal tract probably due to an interference with the phosphorylating mechanism concerned in the transfer of certain food stuffs particularly carbohydrate and fatty acids, is responsible for the fermentative indigestion that produces excessive bloating and flatulence. The hypoacidity or anacidity which is commonly present in myxedema is undoubtedly a contributing factor and may simultaneously account for the anorexia that is nearly always present.

Abdominal pain with or without abdominal distention may be the presenting symptom in myxedema, as was the case with Bissler's patient (1910). The etiology of such pain is not clear, but it may be so

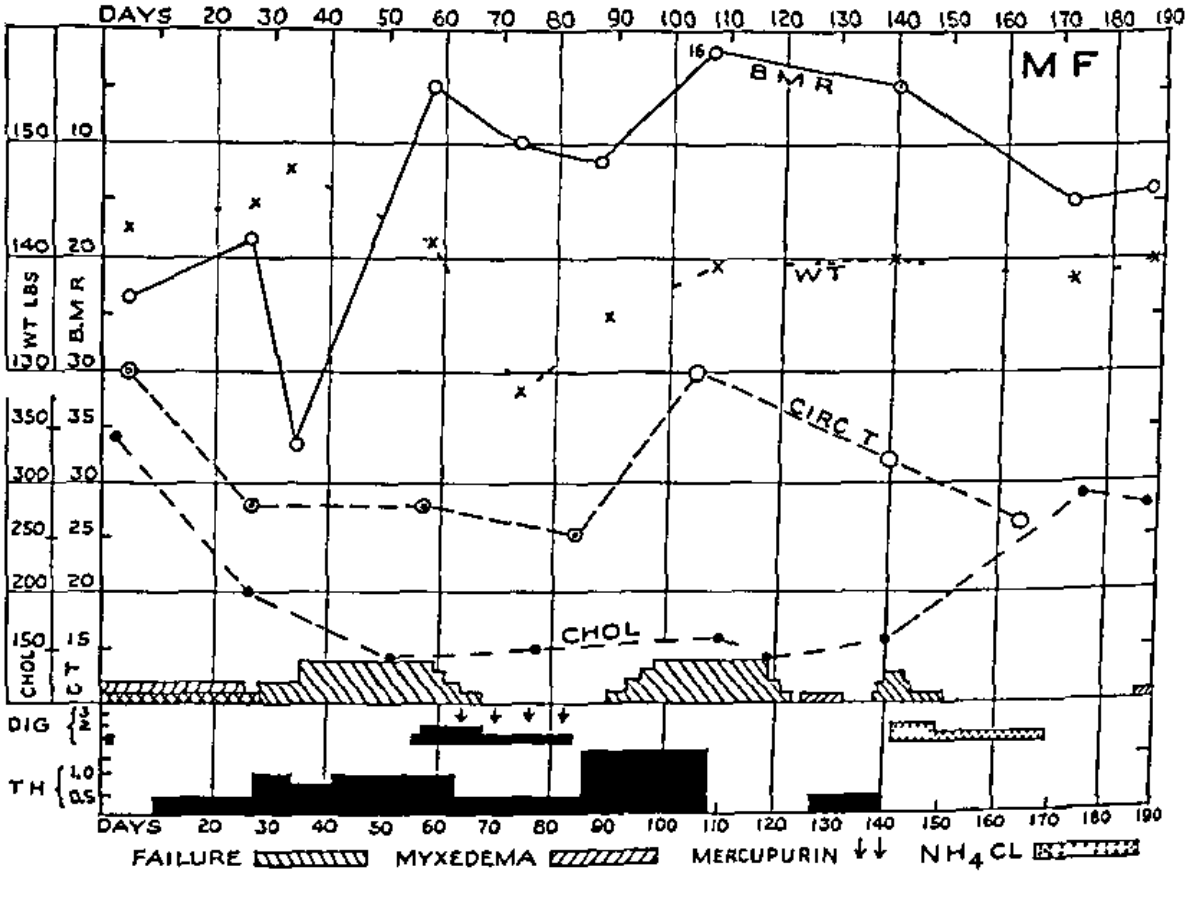


Fig. 50. *A* and *B*.—The balanced action of digitalis and thyroid hormone in the control of the right sided cardiac failure sometimes associated with myxedema. On admission to the hospital this patient was in a state of myxedema with cardiac failure. Thyroid therapy while relieving the myxedema increased the severity of the cardiac manifestations when digitalis of 1 grain daily and adequate doses of digitalis with diuretics were simultaneously employed. The optimum balance of the medications finally proved to be 1 grain of desiccated thyroid substance and 1 grains of powdered digitalis leaf daily. If both were omitted while there would be no recurrence of cardiac failure the myxedema would return. If thyroid hormone were given without digitalis cardiac failure shortly recurred. If the dose of thyroid hormone were raised above 1 grain daily the requirement for digitalis immediately increased and if the dose of thyroid hormone was sufficiently large cardiac failure could not be prevented. Note that the determinations of her basal metabolic rate were not as accurate an index of the status of thyroidal activity as were the serum cholesterol and the circulation time. (After McGavack and Schwimmer 1944.)

severe and the accompanying abdominal symptoms so distressing as to be confused diagnostically with peptic ulcer cholecystitis or appendicitis It has been emphasized that people with such symptoms may wander from physician to physician over periods of time up to twenty years without obtaining relief because the underlying hypothyroid state is completely overlooked (Hinton 1935) Hinton points out that the pain unlike that of the conditions for which it may most often be mistaken bears no constant relationship to the type of food nor to the time of its ingestion Moreover he has been unable at least by roentgen ray examination, to observe any intrinsic abnormality of the gastrointestinal or biliary tracts in his patients However a delayed emptying time of the gall bladder has been demonstrated by others in man (Ladd man 1917) and in laboratory animals (Simendinger 1911) Probably the myxedematous infiltration accounts for this sluggish response in the biliary tract which in turn may further impair the motility of and ab

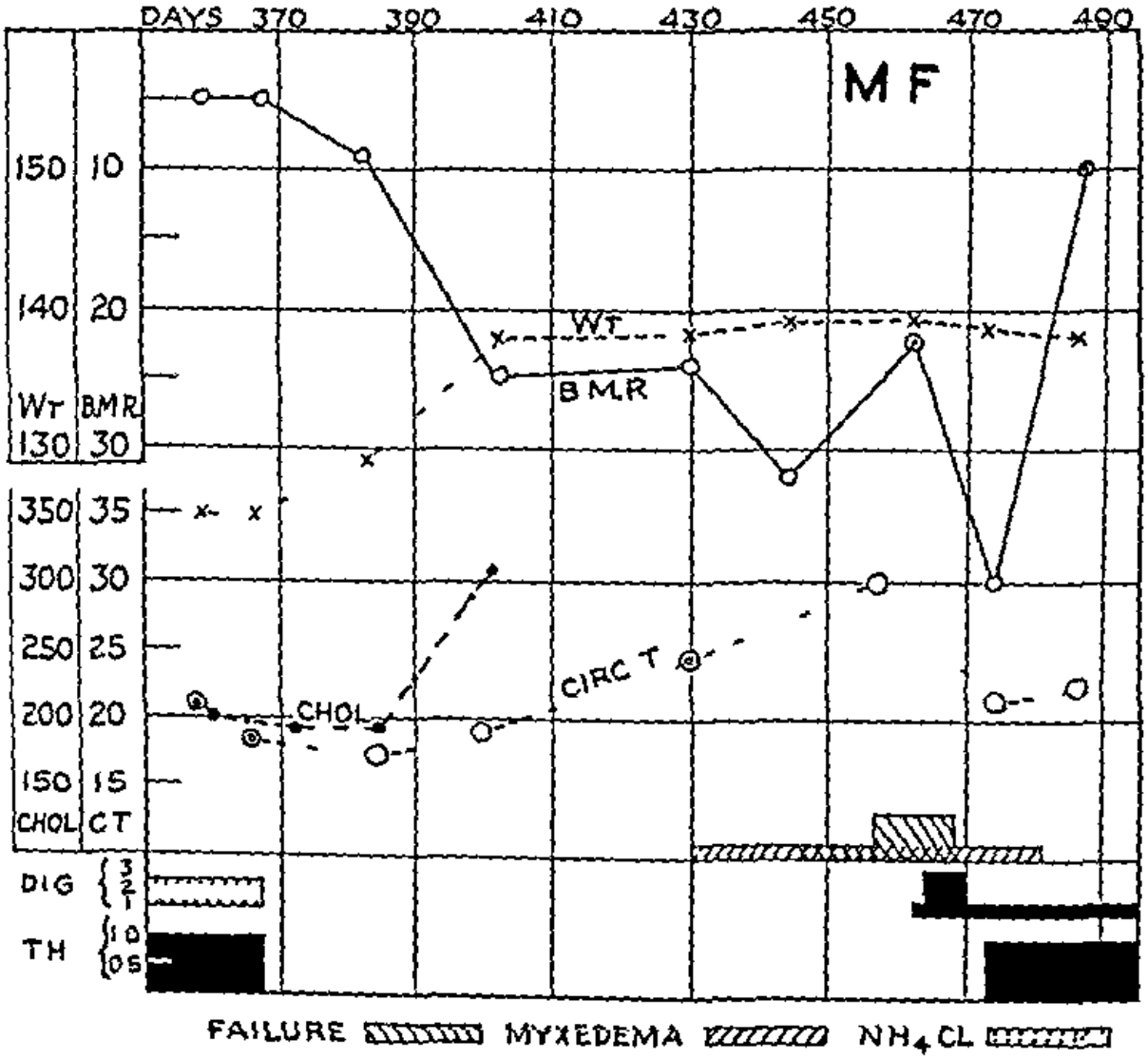


Fig 0 B (For legend see opposite)

sorption from the gastrointestinal tract Pain may give rise reflexively to nausea and vomiting although this occurs infrequently

Rarely ascites, hepatic dysfunction and even megacolon may form part of the clinical picture of myxedema (Hinton 1935 Bassler 1940 Ravault et al 1948) The response of these conditions to therapy with thyroid hormone is striking and etiologically significant (Lisser 1933)

In the more severe cases of myxedema the achlorhydria the severe sometimes macrocytic anemia, and the well preserved nutritional state of the patient in conjunction with pallor may simulate a pernicious anemia However therapy with extracts of liver affords only partial relief

7 *Disturbances in the Hematopoietic System*—Three fourths of *the patients with myxedema have a secondary type of anemia Because* of this fact it is not surprising that in the hurried routine of daily practice the weakness and tiredness of which these victims so persistently complain are ascribed to the anemia and treatment with iron and extracts of liver is accordingly instituted Lisser (1933) believes that many cases of this type can be differentiated by noting the appearance of the face carefully—certainly not a time consuming or difficult procedure Ordinarily myxedematous or hypothyroid patients exhibit a pasty complexion occasionally it may be slightly yellowish and when truly unique for myxedema the cheeks are like Christmas red apples a blush red flush in the center upon a yellowish background

The anemia of myxedema is always of a secondary type Approximately one third of our cases with anemia have shown red cell counts between three and four million per cubic millimeter and a hemoglobin between 60 and 70 per cent Means (1937) has called attention to the fact that secondary types of anemia seen in myxedema can be divided into three groups (1) the red cells and hemoglobin may be proportionately reduced giving a color index of 1 0 (2) the hemoglobin may be reduced much more than the red cells giving a color index of less than unity or (3) the hemoglobin only may be reduced thus also giving a color index of less than unity

In our experience the patients with the higher color indices have usually shown the lower red counts In one subject the red cell count was 1 8 million per cubic millimeter with a hemoglobin of 10 per cent and a color index of 1 02 *It is important therefore to rule out* pernicious anemia which may develop concurrently and necessitate its own specific therapy (Means Lerman and Castle 1930 Lisser and Anderson 1931)

A direct relationship between the degree of anemia in myxedema and the basal metabolic rate can probably not be made although Lisser and Anderson (1931) gain the impression from the literature that the anemia is more apt to occur when the basal rate is below 30 per cent minus ' In a study of 52 cases Lerman and Means (1932a) found the

anemia of myxedema more common in patients with anacidity than in those showing free acid in the gastric juice

In many patients the anemia will improve remarkably following the administration of desiccated thyroid substance Nevertheless the majority of patients will recover more rapidly and completely only after a simple hematinic is added to the regime Where pernicious anemia coexists both liver and thyroid substance will be required to restore the patient to health

8 Disturbances in the Urinary Tract—The low urinary volume in myxedema is directly dependent upon diminished thirst and a small intake of fluid Albuminuria is common but evidence for primary renal damage is rarely obtained although occasionally urinary tract infection may be the first evidence of the disease (Grollman 1948) When present such intrinsic diseases of the kidney are more likely to be coincidental than causally connected With the albuminuria of myxedema there is an absence of the formed elements characteristically present in nephritis

In a series of eleven untreated cases of myxedema the inulin clearance was consistently low (Weissberg and McGavack 1948) Under satisfactory treatment with desiccated thyroid substance this was completely restored to normal in each instance This has led us to believe that the diuresis caused by thyroid hormone is related in part at least to its ability to increase the rate of glomerular filtration

9 Disturbances in the Genital System—Gonadal function is invariably disturbed in hypothyroidism and myxedema The thyroid is responsible for both a direct and an indirect effect upon the gonad the latter by way of the pituitary gland (Chapter XIV)

In general the over all effect of hypothyroidism upon the gonad is one of suppression of *primary* sexual activity with a suppression of follicle production (Szontagh and Lichner 1949) Diminished libido is present in both sexes and impotence occurs commonly in the male Sterility is usual

In women any type of menstrual irregularity may appear In the milder cases hypothyroidism may masquerade as premenstrual tension and dysmenorrhea In such instances the patient is usually thin of wiry muscular build mentally alert and generally hyperirritable In other words she lacks completely the classical stigmata of a waning thyroid function She has run the gamut of gynecological therapy including dilatation and curettage for her dreaded episodes of pain When her flow is once established it is usually profuse prolonged dark in color and associated with the passing of clots A therapeutic test with thyroid substance is always warranted even though the basal metabolic rate remains within the limits of normal To eliminate the possibility of

a psychic influence from such therapy, the effects of withdrawal should also be checked (Berglas 1947)

By far the most commonly observed irregularities of menstruation in myxedema are menorrhagia and metrorrhagia They are often the complaints that first bring the myxedematous patient to the clinician (Lisser and Anderson 1931, Lisser, 1933) In the past many therapeutic curettages were performed on such patients, but in the absence of positive pelvic findings the alert gynecologist today checks the status of the thyroid before proceeding with any type of local therapy When myxedema occurs at the end of or after the active period of sexual life spotting or even severe hemorrhage at irregular intervals promptly arouses *the suspicion that a cancer may be present Some attention to* the general status of the patient may save needless diagnostic curettages as they might have in a 65 year old woman whose symptoms of myxedema had been present for eleven years before the true nature of the condition was recognized During that time she had undergone four diagnostic curettages and had been variously treated for uremia nephritis and hyperplastic endometritis" but had never had a determination of her basal metabolic rate Myxedema sometimes has its onset during or shortly following pregnancy One woman developed menorrhagia and the first symptoms of myxedema at the age of 28 following the birth of a child Her first curettage was performed when her baby was three months old in the belief that the early return of flow and the prolonged period of postpartum bleeding with subinvolution of the uterus were due to retained membranes At the age of 36 this patient had a fullblown myxedematous state a severe secondary anemia and a persistence of her menorrhagia All of these were relieved by the use of desiccated thyroid substance and a dietary rich in blood building materials

When the basal metabolism is low in pregnancy although no signs of myxedema are present there is an increased incidence of true toxemia (Colvin *et al* 1912) *In such instances* it is believed that the accompanying hypercholesterolemia predisposes to cholesterol vascular changes in the placental vessels leading to thrombosis infarction and true toxemia of pregnancy (Colvin et al 1912)

The gynecological aspects of hypothyroidism and myxedema can hardly be overstressed When careful pelvic examination fails to reveal any satisfactory cause for menorrhagia or metrorrhagia with or without dysmenorrhea then a therapeutic test with desiccated thyroid substance is justified even though sharply defined manifestations of diminished thyroid function are absent

The role of hypothyroidism in infertility seems to be well established It may be a *predominant factor in from 10 to 25 per cent* of all women who are sterile Here too clinical trial of thyroid therapy is justified Indeed it has recently been suggested that when indications

for the same are good but oral administration seems ineffective resort should be had to intramuscular or intravenous injections of 0.2 to 0.4 milligrams of thyroxin every second day (Brown and Bradbury 1950).

10 Disturbances in the Osseous System.—Because the framework of the entire osseous system has been completed prior to the onset of adult myxedema no disturbance in bodily development occurs. There is however considerable infiltration of the joints and ligamentous structures with myxedematous tissue which results in stiffness decreased mobility and lowered activity. Hypoplasia of all myeloid elements of the bone marrow sometimes with fat replacement is commonly seen and is the cause of the changes to be noted in the peripheral blood (Axelrod and Berman 1950).

11 Interglandular Relationships (See Chapter XIV).—As has already been emphasized in the section on Physiology underfunction of the gonads is the rule in patients with hypothyroidism and will not be mentioned further at this point.

More important in relation to the management of myxedema is the commonly associated decrease in function of the adrenal cortex. The known combination of thyroid and suprarenal atrophy (Schmidt syndrome) emphasizes the clinical importance of the connections between these two glands. In at least one such case the adrenal insufficiency was preceded by outspoken symptoms of myxedema treatment for which aggravated the adrenal cortex deficiency (Demol and Herlant 1947). Indeed in the course of myxedema the development of Addison's disease although uncommon must not surprise the clinician. The completed picture is readily recognized and may call for vigorous treatment but even the milder forms of underactivity of the adrenal secondary to the atrophy of the thyroid gland deserve attention.

In the absence of functioning thyroid tissue the adrenal cortex atrophies (Despopoulos and Perloff 1950) when the thyroid is overactive the adrenal cortex hypertrophies. In myxedema the administration of thyroid extract affords the atrophic adrenal the needed stimulus to return it to a normal state. If however the dose of thyroid hormone is too large the hypoadrenia may be aggravated as sufficient time may not have been allowed for the resumption of a normal level of secretory activity by the adrenal cortex. In such instances the thyroid hormone withdraws glycogen from the liver faster than the adrenal can stabilize the manufacture storage mobilization and utilization of new sugar. Addisonian crisis has been observed under such circumstances particularly in myxedema of pituitary origin (Lerman and Stebbins 1942). The danger of such a catastrophe is an excellent reason for proceeding slowly with the administration of thyroid substance in myxedema.

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cholesterol are unusually low without any disturbance in the total esterification (Benda 1916) It has been reported that thyroid extract will not restore to normal the elevation of serum cholesterol which results from the administration of an antithyroid compound (Fleischmann Stubbs and McShane 1919)

6 Blood Serum Protein—When the micro Kjeldahl direct Nesslerization technique or some modification thereof is used for the determination of total serum protein and its albumin fraction, an increase in the total value is usually observed without appreciable alteration in the albumin globulin ratio However in 6 of 16 patients (McGavack Lange and Schwimmer 1915) the value for total protein was normal while in the remainder it lay above 7 6 mg per 100 c c

When the serum protein is studied electrophoretically the normal albumin fraction of approximately 55 per cent (Edsall 1917) may be relatively but not absolutely lowered with a significant increase in the concentration of beta globulins and a decrease in the alpha globulins (Stern and Reiner 1916) Normal values for the various fractions obtained by electrophoresis (Edsall 1917) expressed in percentage of the total value are albumin 55 total alpha globulins 11 beta globulins 13 5 gamma globulins 11 and fibrinogen 6 5

7 Tests for Renal Function—As aforementioned albuminuria is common in untreated myxedema but is not accompanied by formed elements pointing to primary renal damage In more than half of our subjects (unpublished data) the inulin clearance has been low (normal range from 100 to 140) and has risen to normal under treatment Beaumont and Robertson (1913b) have demonstrated a decrease in urea clearance which tends to improve but never reaches normal under therapy These same workers found the concentrating and diluting power of the kidney unaffected by the myxedematous state Corcoran and Page (1947) conclude that sluggish renal function in myxedema is demonstrated by a decrease in renal blood flow glomerular filtration and the tubular secretory capacity for diodrast

8 The Urinary 11 Oxycorticoids—The value for urinary 11 oxycorticoids is lowered in hypothyroidism (Talbot Albright Saltzman Zygmuntowicz and Wixom 1917) As contrasted with an average normal excretion in 24 hours of 0 22 mg with a range of from 0 10 to 0 44 mg subjects with hypothyroidism showed an excretion of less than 0 10 mg

9 Capillary Permeability—In some patients with myxedema very little if any change may be observed in capillary permeability as measured by the fluorescein technique (Lange and Boyd 1913 Lange and Kriewer 1913) However as a rule the increase is very marked (Fig 18) (McGavack Lange and Schwimmer 1915 McGavack and Schwimmer 1944)

The Laboratory Diagnosis of Myxedema —

1 Basal Metabolic Rate – In the absence of any functioning thyroid tissue, the basal metabolic rate is usually —10 or below, myxedema is one of the few conditions in which metabolism is so depressed While myxedema is rarely observed when the basal metabolic rate is above —20 authenticated cases have been described The same limitations to the interpretation of the basal metabolic rate apply here as in all other conditions for individual variations may be great

2 Blood Count —Anemia is a common finding in myxedema In the white count there may be a relative lymphocytosis The findings have been discussed in detail above (q v)

3 Blood Calcium and Phosphorus —The blood serum calcium and inorganic phosphorus levels are within normal range in myxedema and cretinism However in the individual myxedematous patient under treatment the values for serum calcium tend to fall and those for inorganic phosphorus to rise (Robertson 1911a) There is a tendency for the body to retain calcium during myxedema as shown by the calcium balances for myxedematous as compared with normal patients (Aub et al 1927 Robertson 1911a) The levels for alkaline phosphate in the serum are normal in cretinism and lowered in myxedema In the case of adult myxedema they return to normal under thyroid therapy

4 Protein Bound Iodine of the Blood Serum —In both the diagnosis and management of all forms of hypothyroidism the determination of various iodine fractions in the blood stream is most helpful provided proper conditions for the performance of the tests are scrupulously observed Values for the protein bound fraction of iodine are of prime importance and by the standard test elsewhere described (see Chapters VII and XXXVI) rarely exceed 4 0 micrograms per 100 c c in myxedematous subjects In untreated cretins the value may be even lower Man and her associates (1917a b) have found this determination of extreme value in gauging the response of cretinous children to therapy with thyroid substance In these children the determination of basal metabolism is impossible and changes in the values for blood cholesterol often slight or unpredictable

5 Blood Cholesterol —Myxedema tends to raise the values for cholesterol in the blood but rarely if ever disturbs the ester total ratio While the total usually lies above 250 mg per 100 c c in the untreated case normal or even subnormal values may be observed in the untreated patient (McGavack and Schwimmer 1911 McGavack and Drekter 1915 McGavack Lange and Schwimmer 1915) The range of values for each laboratory varies from that of others so that one must acquaint himself with the figures usually obtained by the technical service available to him In cretinism occasionally the values for

have been produced by the anemia alone myxedema should always be considered If in addition some puffiness of the skin exists to simulate nephritis the clinician is truly remiss not to exclude myxedema *first*

2 *Pernicious Anemia*— That pernicious anemia may resemble myxedema and that myxedema may resemble pernicious anemia has long been apparent (Means Lerman and Castle 1930) Moreover that the two may coexist must be remembered Pallor edema paresthesia anemia achlorhydria and smoothness and beefy redness of the tongue are shared in common by the two conditions

The pallor of myxedema is of a waxy pasty type whereas in pernicious anemia there is a greenish yellow hue to the skin In addition to the paresthesias other disturbances of the peripheral nervous system such as loss of vibratory sense are present in pernicious anemia Findings in the peripheral blood in hypothyroidism have been previously discussed (see Analytical Review of the Clinical Picture of Myxedema) there is nothing in the bone marrow which vaguely resembles the appearance in pernicious anemia The achlorhydria of myxedema usually disappears following stimulation with histamine while characteristically that of pernicious anemia does not In the former condition the tongue is large and clumsy in the latter small atrophic and sore Except when the patient is nearing death the mentality responsiveness and reflex time are all normal in pernicious anemia Moreover the basal metabolic rate in this disease is never depressed and may be slightly elevated

3 *Chronic Nephritis*—The pasty puffy face the generalized edema the secondary anemia the albuminuria and the enlargement of the heart are responsible for the extreme frequency with which a diagnosis of chronic nephritis is made in a patient actually suffering from myxedema Tragically such a mistake results in the dismissal of the patient with a more or less hopeless prognosis and little effort to institute any form of therapy whatsoever

In actuality little difficulty should be encountered in distinguishing one condition from the other The basal metabolic rate is significantly lowered in myxedema The mucous edema of this condition does not pit on pressure although some confusion may exist in those instances in which a nutritional edema is superimposed Formed elements in the urine accompany the albuminuria of Bright's disease but are rarely seen in that of myxedema When the heart is enlarged in nephritis the condition usually results from hypertension with resultant hypertrophy particularly of the left ventricle In myxedema dilatation and edema are both present Therefore the roentgenological shadow cast by each condition may be quite characteristic

4 *Dyspituitrous Myxedema*—For reasons already mentioned dyspituitrous myxedema (Chapter XXXI) and primary thyroid myxedema

10 Examination of the Chest by Roentgen Ray—The feeble pulsations and the enlarged contours of the heart seen fluoroscopically help to confirm the diagnosis of myxedema (see Fig 16)

11 Electrocardiographic Tracing—Findings in the electrocardiogram due to or associated with myxedema have already been detailed but it may be well to reiterate the fact that low or absent T waves are almost invariably observed (Fig 17)

12 Clinical Tests—The hyporeactivity to the hypertensive action of epinephrine the increased sensitivity of the heart to atropine, abnormal sensitivity to quinine the electric impedance angle the oculocardiac reflex the acetonitrile test of Reid Hunt and other presumptively specific tests have been introduced for confirming the clinical diagnosis of hypothyroidism and myxedema All mentioned above are unreliable the first three are not without danger to the patient and if one thinks of the diagnosis of hypothyroidism at all it is relatively easy to confirm without resort to tests of doubtful value

In making these statements regarding clinical tests it is not intended to ignore the presence in hypothyroidism of rather characteristic alterations capable of pharmacological and neurological evaluation For instance Gantt and Fleischmann (1918) observed in a 13 year old boy variations in his ability to form and differentiate conditional reflexes in direct relation to the levels of his basal metabolism serum cholesterol and other metabolic changes This and some of the other functional tests criticized above may have considerable prognostic value and clinically demonstrate alterations in the behavior of the treated subject but they are relatively nonessential for the diagnosis of myxedema

Diagnosis and Differential Diagnosis—More than four years usually elapse between the onset of the symptoms of myxedema and its recognition (unpublished data) Earlier diagnosis is important in order to avoid complications We certainly should not neglect to think of myxedema when fully developed as the characteristic body habitus the facies the striking alterations in speech and voice and a basal metabolic rate of less than —30 are salient readily detected features The peculiar personality and the body habitus should be stressed *(supra vide)* Easy fatigability and increased sensitiveness to cold are always present and should prompt the clinician to suspect myxedema immediately

It is true that the patient may consult his physician for any one or more of the symptoms that occur at any time in the course of the disease so that a correct diagnosis is not always easy Several conditions are frequently confused

1 Secondary Anemia—When secondary anemia is found in a patient who also complains of fatigue coldness and other characteristic symptoms of hypothyroidism out of proportion to those which would

have been produced by the anemia alone myxedema should always be considered If in addition some puffiness of the skin exists to simulate nephritis the clinician is truly remiss not to exclude myxedema *first*

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must be sharply differentiated if we are to avoid serious harm and even a fatal outcome in patients with the former condition The coexisting evidences of other glandular *disturbances particularly hypoadrenocorticalism* should make the clinician suspect the presence of pituitary disease If he is then still in doubt tests for disturbances in salt metabolism such as the *Wilder (Cutler Power and Wilder 1938) or Kepler* Robinson (Robinson Power and Kepler 1911) procedures will yield positive information only when the adrenal is seriously handicapped *thus supporting the presence of pituitary dysfunction with secondary* disturbances in target organs

5 *Orbital and Periorbital Swelling* —Many local causes of edema about the eyes can all be distinguished from true myxedema by the absence of myxedema and the presence of a normal basal metabolism

Prognosis *There are no authoritative data on the length of life of* the patient with untreated myxedema A 35 year old patient was slowly losing all capacity for taking care of her own bodily needs when seen *thirteen years after the onset of her untreated myxedema (McGavack* Lange and Schwimmer 1915) She responded satisfactorily to treatment as did the patient of Means (1937) whose condition had begun *fifteen years prior to receiving thyroid hormone*

When death occurs it is usually the result of some intercurrent condition Before powerful antibiotic agents were available secondary *infections were the commonest cause of death Today degenerative* processes secondary to the tissue changes of myxedema are usually responsible If myxedema continues sufficiently long slowly lethargy *coma and death may occur as a direct result of the loss of thyroid* hormone However if no complications have arisen before treatment is begun the prognosis for complete relief is good

Pathology —Atrophy of the thyroid gland is the outstanding pathological feature of spontaneously occurring myxedema in the adult Inasmuch as the majority of patients die from some complicating feature rather than as a result of the myxedema per se there is a dearth of autoptic material in which the only features are those directly traceable to the absence of thyroid secretion

The primary atrophy referred to above is usually progressive and in the fully developed case of myxedema is so complete that athyreosis usually exists The parenchyma of the gland is slowly replaced by lymphocytic infiltration and more or less widespread fibrosis An athyreotic state results in which the predominant features are an increased storage of protein and water in the intercellular spaces and a decrease in the overall metabolism of the individual cell

The histological changes described in the skin are quite characteristic of the alterations to be observed generally as a result of the loss of thyroid hormone *The epidermis is hyperkeratotic, with scattered*

atrophic areas and degenerative changes in the epidermal cells Secretory activity of the sebaceous and sweat glands is decreased which coupled with the abnormal epidermal reaction results in plugging of the hair follicles with cellular debris The consequent irritation is usually associated with a slight to moderate leucocytic infiltration about the sebaceous emunctories and the blood vessels supplying the upper part of the cutis The edema peculiar to the athyreotic state is quite pronounced in consequence of which the collagenous and elastic fibers of the true skin are separated and show mildly degenerative changes The mucinous staining property of this edema fluid is a constant and characteristic feature Indeed, an increase in mucin may be demonstrated histologically in the skin of the hypothyroid individual who shows no evidence of myxedema clinically

We have already mentioned the fact that changes in the cardiovascular system are an integral part of the picture of myxedema (see above Disturbances in the Cardiovascular System) The slight enlargement of the heart which is detected roentgenographically (Fig 46) has been ascribed to dilatation of the cardiac chambers to pericardial effusion and to interstitial edema The second of these conditions is probably the most commonly observed There are many who question the existence of an interstitial myxedema of the heart In the untreated case of long duration fibrosis due to coronary sclerosis may dominate the histological picture Attention has already been called to the increased incidence of sclerosis of the aorta (Sachs 1949) and coronary vessels and the reasons why this occurs (see Disturbances in the Cardiovascular System) Pericardial fluid is always in excess of normal but the concept frequently expressed in the past that this is the commonest cause of the clinically recognizable cardiac enlargement in the majority of cases is certainly erroneous

The skeletal structures musculature and most of the organs of the body are the seat of an interstitial edema characteristic of the myxedematous state

The close integration of the thyroid with other glands of internal secretion particularly with the pituitary the adrenals and the testes is responsible for the alterations observed in these structures Hyperplasia of the pituitary gland and thyroidectomy cells both routinely present following experimental ablation of the thyroid are commonly observed but may be entirely absent From the meager postmortem material available it appears to us that the more gradual the onset of the disease and the longer its duration prior to examination of the tissues the less characteristic the histological changes within the pituitary gland Perhaps the most constant and best sustained variation is a relative and usually an absolute increase in the chromophobic cells of that structure Benda (1946) feels that while these are colorless cells they should not be called chromophobic as that obscures their patho

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stitial edema of the vessel walls and muscle cells nor for the probable removal of some of the lipids that have infiltrated the arterial walls Moreover some considerable period of time may be necessary for the reactivation of the atrophic adrenal cortex Until that occurs glu*coneogenesis proceeds at an abnormally low rate thus failing to keep the* heart continuously supplied with glucose and the even more readily available intermediaries of carbohydrate metabolism The net result is an additional strain on the already overburdened heart which may re*sult in cardiac failure with or without coronary occlusion*

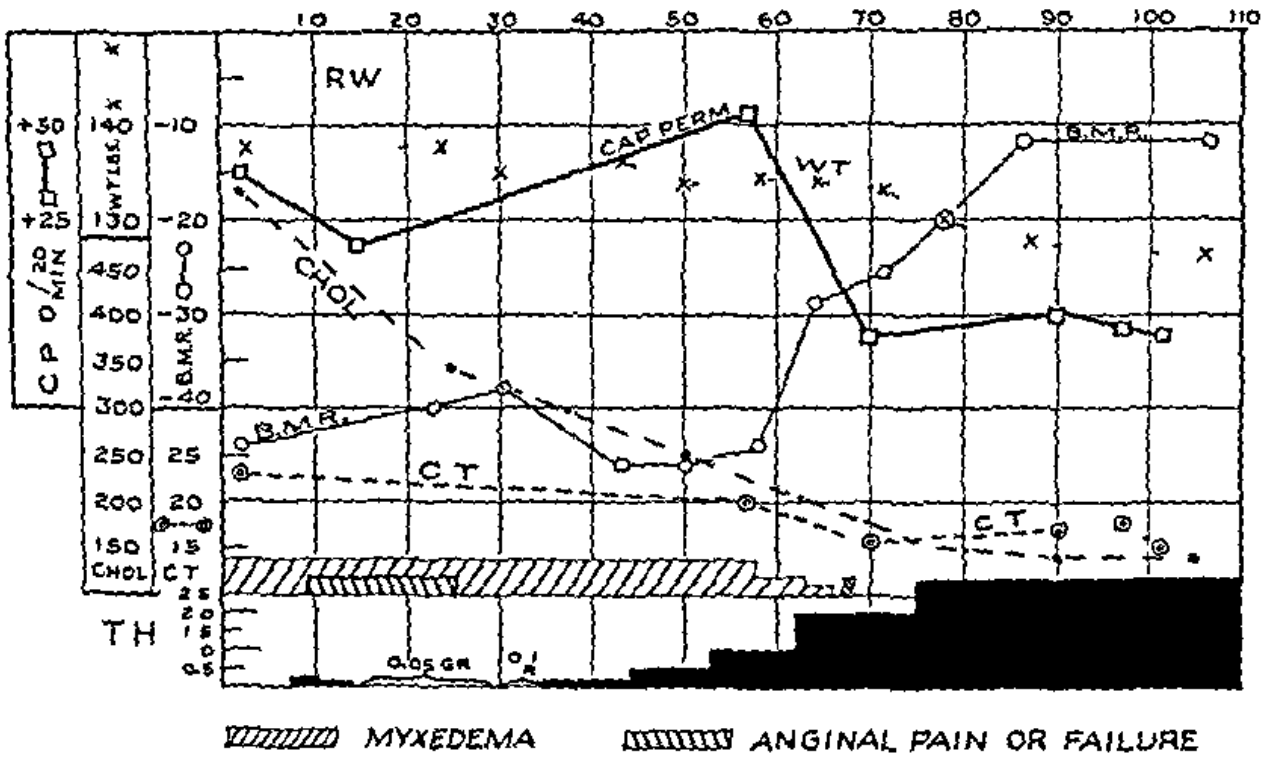


Fig 1—The influence of thyroid hormone on the anginal syndrome occurring in myxedema Disappearance after the patient's metabolic disturbances are rectified by gradually increasing doses of thyroid hormone Irrigation to diminish to the basal that 3 year-old woman whose roentgenograms and electrocardiograms are shown in Fig 16 and 1 respectively was subject to nocturnal attacks of anginal pain The preceding therapy with thyroid hormone was insufficient After days of treatment with grains of desiccated thyroid substance anginal pain returned and did not disappear until the daily dose of hormone was raised to grains With the basal metabolic rate returning to normal the patient remained free of pain while receiving 3 grains of desiccated thyroid to maintain her basal thyroid state More than this amount of hormone was tolerated without the recurrence of any cardiac symptoms whatever (After McCann Lange and Selwyn-Brown 1931)

The above mentioned disturbances can be avoided if the physician proceeds sufficiently slowly with his treatment An excellent example of this is afforded in the case of R W a 35 year old woman with an untreated myxedema of 13 years duration with anginal symptoms of 5 months' duration that disappeared after being at bed rest only to recur following the administration of 0.2 gram of desiccated thyroid substance daily for four days (Fig 51) When this dose was reduced to 0.03 grains daily the symptoms disappeared Once during successive in-

logical character. They are, in his opinion, depleted decolorized epithelial elements.

Atrophic and fibrotic changes in the cortex of the adrenal, particularly in the zona glomerulosa, are common. Special staining techniques emphasize this variation which is undoubtedly closely linked with the decreased activity that is so frequently of clinical importance in our management of the disease. This change in the glomerulosa may be associated with an alteration in the formation of desoxycorticoids (Greep and Deane, 1947) and thus secondarily with the variations in the behavior of interstitial and cellular fluid so characteristic of the myxedematous process.

In myxedema the gonads are commonly atrophic, a change which is believed, at least in part, to be mediated through alterations in the function of the anterior pituitary gland.

The other glands of internal secretion show no constant variations in appearance or function but share the burden of a generally lowered metabolism.

Treatment.—The origin of myxedema in thyroid deficiency implies a specific substitutive treatment so simple, so economical and so successful as to need little implication or comment. Means (1937) records a case successfully treated for forty four years. In view of these facts once the diagnosis is established the tendency at times has been to act upon the theory that where a little is good more is better. Most of our therapeutic difficulties have stemmed from such thinking which ignores the pathological physiology and pathology that develop in the myxedematous state. Our main objective in treatment is to rid our patient of symptoms and keep him completely symptom free on the smallest possible ration of thyroid hormone. Too vigorous treatment may precipitate cardiac or adrenal cortical failure, about both of which we have already spoken briefly (see *Disturbances in the Cardiovascular System*). If treatment is gradually applied these accidents can usually be avoided. How this is accomplished depends upon the several factors concerned in the involvement of the heart and adrenal gland. (a) In the heart narrowing of the coronary arteries results from edema and lipid infiltration of their walls, and (b) due to underfunctioning of the adrenal cortex abundant supplies of readily utilizable carbohydrates are not available. Because of the markedly lowered needs of the body as a result of the lowered metabolism in myxedema, this intrinsically damaged and extrinsically affected heart remains capable of meeting the needs of the patient with untreated myxedema. However the administration of thyroid substance raises these requirements in direct proportion to the amount given. If this is too large then coronary occlusion may occur in association with the accelerated pulse rate and increased cardiac output. In such instances time is not afforded for the resorption of the inter-

stitial edema of the vessel walls and muscle cells nor for the probable removal of some of the lipids that have infiltrated the arterial walls Moreover some considerable period of time may be necessary for the "reactivation of the atrophic adrenal cortex Until that occurs gluconeogenesis *proceeds at an abnormally low rate* thus failing to keep the heart continuously supplied with glucose and the even more readily available intermediaries of carbohydrate metabolism The net result is an additional strain on the already overburdened heart which may result in cardiac failure with or without coronary occlusion

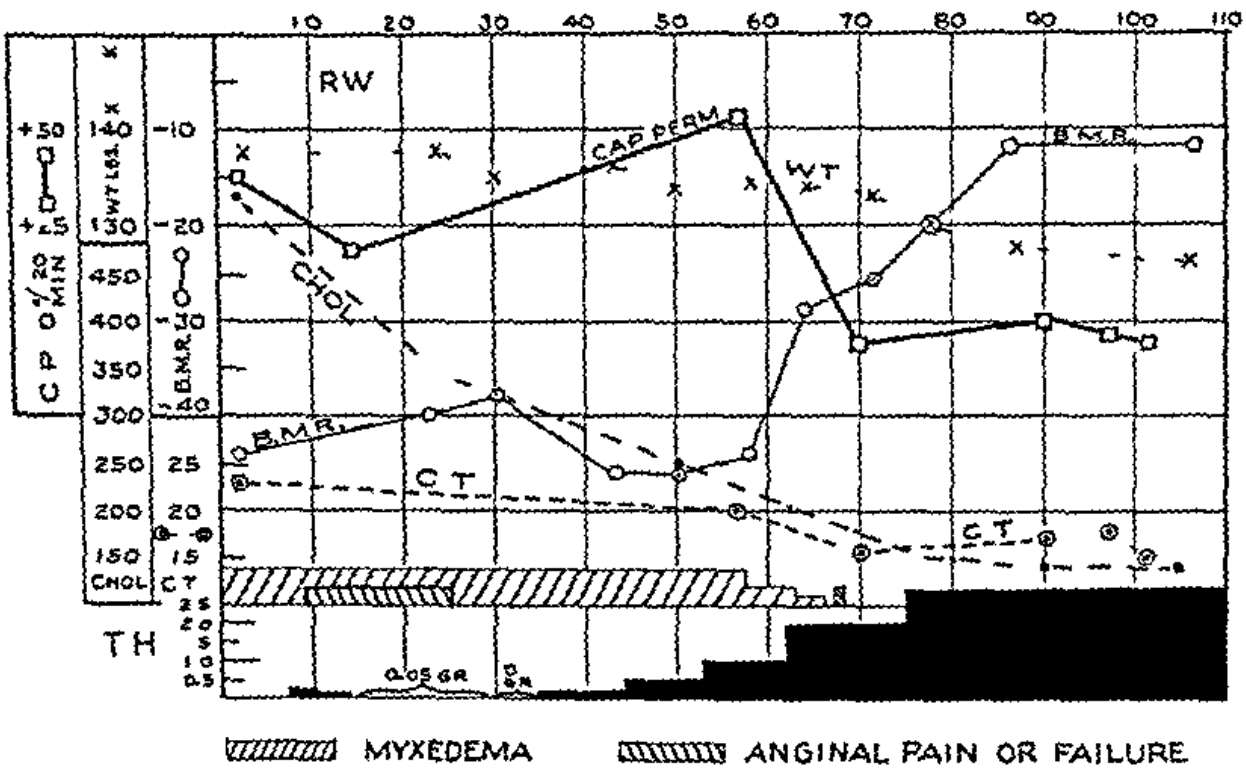


Fig. 1—The influence of thyroid hormone on the anginal syndrome occurring in myxedema and the disappearance after the pathologic disturbances are rectified by gradually increasing doses of thyroid hormone Patient admitted to the hospital this 36-year-old woman who presented angina and electrocardiographic changes shown in Figs 4b and 4c respectively was subject to occasional attacks of anginal pain The disappeared at bed rest and before therapy with thyroid hormone was instituted After five days of treatment with 0.2 grain of desiccated *thyroid substance anginal pain returned and did not disappear until the daily dose of hormone was* raised to 0.6 grain It should be noted that later after correction of the metabolic defects in her patient as the myxedematous tissues had needed 3 grains of desiccated thyroid to maintain her in a fully euthyroid state Moreover this amount of hormone was tolerated without the occurrence of any cardiac symptoms whatsoever (After McCavack Lang and Schwinmer 1931)

The above mentioned disturbances can be avoided if the physician *proceeds sufficiently slowly with his treatment* An excellent example of this is afforded in the case of R W a 35 year old woman with an untreated myxedema of 13 years duration with anginal symptoms of 5 months duration that disappeared after being at bed rest only to recur following the administration of 0.25 grain of desiccated thyroid substance daily for four days (Fig 51) When this dose was reduced to 0.05 grains daily the symptoms disappeared Once during successive in-

logical character. They are in his opinion depleted decolorized epithelial elements.

Atrophic and fibrotic changes in the cortex of the adrenal particularly in the zona glomerulosa are common. Special staining techniques emphasize this variation which is undoubtedly closely linked with the decreased activity that is so frequently of clinical importance in our management of the disease. This change in the glomerulosa may be associated with an alteration in the formation of desoxycorticoids (Greep and Deane 1947) and thus secondarily with the variations in the behavior of interstitial and cellular fluid so characteristic of the myxedematous process.

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roid substance U S P In general the scheme of Means and Lerman (1935) a variant of which is shown in Fig 12 serves as an excellent guide for determining the maintenance dose of the individual patient They found that 0 3 gram desiccated thyroid substance U S P daily will increase the basal metabolism from the initial myxedematous level to —20 per cent Symptoms of hypothyroidism will still be present When 1 0 gram is given daily few if any symptoms remain and levels for the basal metabolism will be between —20 and —10 per cent Indeed some patients do best at this level of dosage for example patient

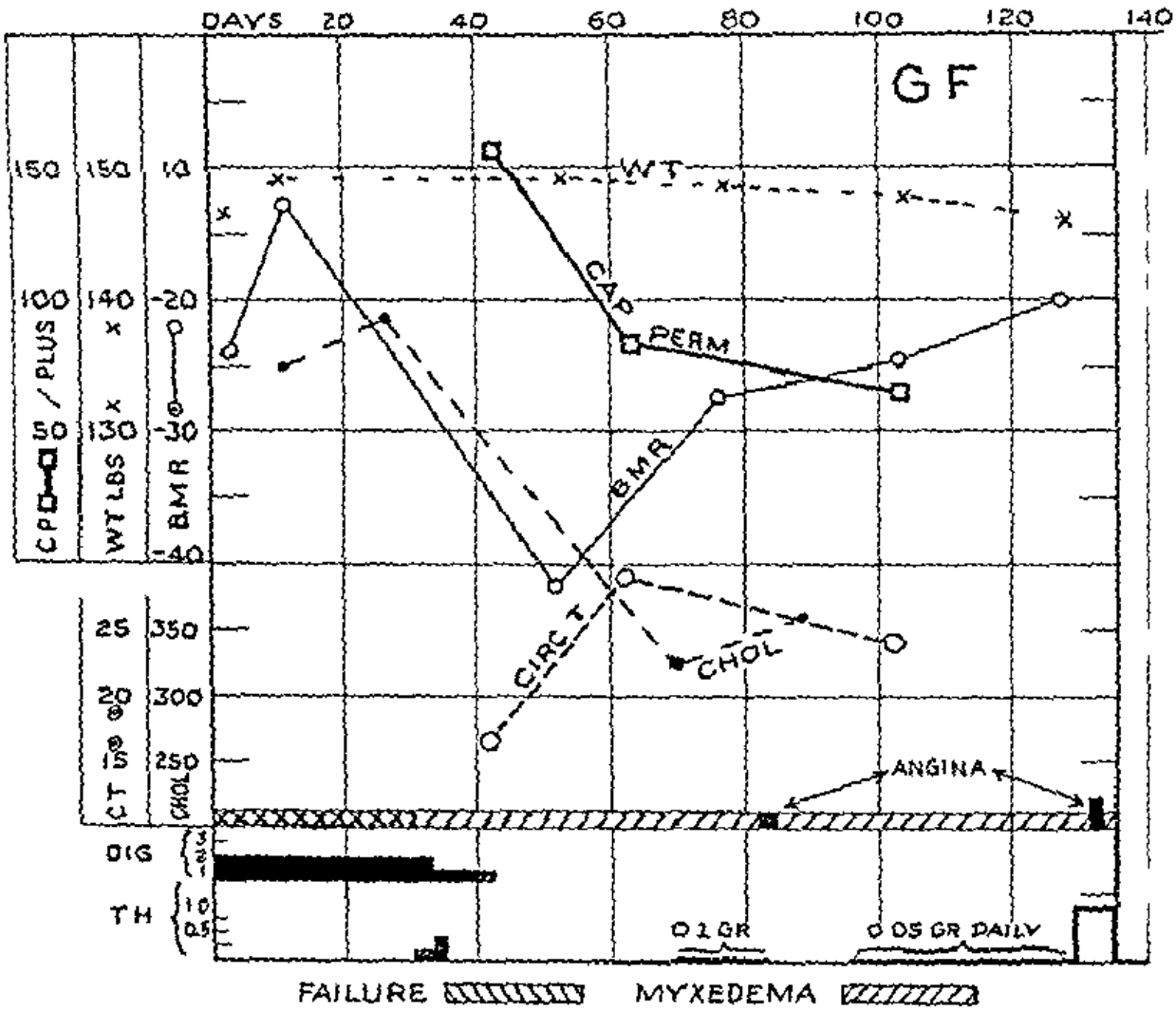


Fig —D the f t a y o clu l a lue t a uffe lar n e s in the d of d si at d thyr ti y ne Thi 63 ye ll w s who l d a l t t dtig hi l y f t t p t i wa d itt t th lo t t l t m di t b f llowi g o a y o lu a Thi sp d d t f t r ly t ip pr t ll tapp in lu t g ligh t fo th t l f tl o i t l ight ti j f lu Aft th ti t ill n s t oll l ll w r gniz d tl t n y c t of d gr t t d th) l n tal lle te w s —t s t y g l f llur to n d wl t o l g in f ie l tect ths d ul t e w g n d to \ sn pt s o u d l thi wa r duc d t 0 0 g in d ily an l n ligh t a p o u t i th myx l n tu t t wa ol d with th b si n l b lln ti ng t — 0 per ent Th t gh n t u d t ling th l f ths r d w r i d t 1 0 g ain f llowi g wi h an t t r d a l f t l y l i oc ur d (Aft r M f a k La g a d S l w t 1 t)

crease in dosage to full maintenance cardiac symptoms reappeared (Fig 51), and then only when the dose was suddenly changed from 1 to 2 grams More than three months were required to bring the basal metabolism of this individual from —11 to —12 per cent with freedom from all symptoms of thyroid insufficiency (Fig 51) The appearance of anginal pain when treatment was begun and again when a large change in dose occurred (from 1 0 to 2 0 grams) is excellent evidence that very marked adjustments occur in the circulation of the patient with myxedema who is under treatment These will be beneficial if the initial dose of hormone is small and increments of slight magnitude are made at infrequent intervals Conversely serious permanent damage even resulting in death may occur if the dose is too large or the increments too great or too frequently made Patient G I a 63 year old woman was admitted to the hospital for treatment of a coronary occlusion and right and left heart failure in the development of which myxedema undoubtedly played a contributing etiological role As soon as the cardiac failure had responded to rest in bed and therapy with digitalis her basal metabolic rate was —12 Desiccated thyroid substance 0 1 gram daily caused the return of anginal failure (Fig 52) when this dose was halved the angina disappeared and while the patient's metabolism remained low her condition generally improved steadily until the dose of thyroid was abruptly increased to 1 0 gram daily Five days thereafter a fresh coronary occlusion occurred which eventuated fatally

Because of the dangers which result from the overly enthusiastic treatment of myxedema with thyroid hormone the following rules for such therapy seem to be justified

1 In the absence of cardiac manifestations an initial daily dose of 0 25 gram of desiccated thyroid substance is administered

2 If cardiac failure either right or left exists when treatment is started an initial daily dose of 0 05 gram is employed In order to avoid an untoward reaction as little as 0 025 gram may be necessary in exceptional cases

3 The initially satisfactory daily dose shall be continued for a period of not less than three weeks longer if any evidences whatsoever of an exacerbation in the cardiac condition exist

4 The increment employed depends upon the size of the initial dose Until 0 25 gram is used daily the increase shall be not more than 0 1 gram at a time After 0 25 gram has been employed the increments are best made at the rate of 0 25 gram each until a total daily dose of 1 0 gram is reached From this point forward an increase of 0 5 gram at each change of dosage is permissible

5 The daily maintenance dose varies considerably from individual to individual and should be determined by the basal metabolic rate and the general condition of the patient The majority of patients respond well to a maintenance dose of 1 5 grams daily of desiccated thy

treatment with thyroid hormone The danger lies in its too zealous application It cannot be overemphasized that we must start with a small dose and increase the amount slowly at long intervals until all symptoms of the disease have disappeared Thereafter the patient must continue indefinitely on a maintenance dose of the hormone If the myxedema is of the dyspituitrous type then thyroid hormone must be combined with other therapy (see Dyspituitrous Myxedema Chapter XXXI)

MI (Fig 50 *A* and *B*) Rarely does any patient's requirement exceed 30 grains of desiccated thyroid substance daily

6 The maintenance dose must be continued indefinitely

7 The dosage *must be* adjusted downward if any one or more of the following manifestations is present

a Anginal distress or exacerbation of already existing bouts of precordial pain

b A persistent decrease of more than 10 mm of mercury in the systolic blood pressure

c A narrowing of the pulse pressure

d A sudden increase in pulse rate of 20 points or more

e Symptoms of either right or left sided cardiac failure

Of the preparations for the management of myxedema desiccated thyroid substance and crystalline thyroxin represent the two forms of thyroid hormone commercially obtainable It seems quite likely that artificially iodinated proteins of high potency and known strength may also be marketed soon as they are now already widely used in animal husbandry and have had limited clinical trial in man Several workers (Rocca 1916 Hamilton et al 1918 deGennes and Deltour 1918) have found artificially iodinated blood proteins highly satisfactory for managing myxedematous patients in daily doses of from 0 05 to 0 1 Gm (0 75 to 6 0 grains) The action was qualitatively little if at all different from that obtained with desiccated thyroid substance except that fewer unpleasant side effects such as palpitation and tachycardia have been noted (deGennes and Deltour 1918)

Crystalline thyroxin is rarely employed clinically as its action is inconstant when given per os and the rapid effect of intravenous administration is rarely necessary Orally ingested desiccated thyroid substance is the treatment of choice

Attempts to evaluate oral and intravenous therapy in terms of one another are practically impossible However it is usually accepted that 0 35 mg of crystalline thyroxin is the equivalent in effect of 1 5 grains of desiccated thyroid substance U S P With the exception of the product supplied by the Burroughs Wellcome & Co which is one third the strength recommended by the United States Pharmacopoeia all commercial brands of desiccated thyroid substance conform to this standard or are slightly stronger One preparation that manufactured by Parke Davis and Company is weight for weight 50 per cent stronger than the pharmacopoeial requirement Inasmuch as thyroid is a powerfully acting drug it is important to take these facts into account in the writing of prescriptions

In summary when the physician makes a diagnosis of myxedema this is tantamount to the employment of a specific thoroughly effective

Degenerative changes in other glands vary in proportion to the degree of failure in production of the hormones of the anterior pituitary that regulate them Alterations in the adrenal are probably always present but are variable in degree When they are severe thyroid medication must be undertaken with caution as in one of the cases described by the Boston group (Castleman and Hertz 1939 Means et al 1940 Lerman and Stebbins 1942) Simple atrophy is the most common and conspicuous change in the adrenals both glands being *markedly reduced in size* However routine histological examination may show no abnormalities in the arrangement or appearance of the individual cells a fact which emphasizes the secondary nature of the disturbance The gonads may undergo secondary atrophic changes with partial or complete cessation of function The parathyroid glands and the pancreas are liable to escape serious damage from the pituitary deficiency

Clinical Course —The age of the patient at the time of onset of the disease seems to influence the clinical course materially In the cases developing in childhood usually diagnosed as cretinism an easy tendency to infections particularly of the respiratory tract a more marked mental than physical retardation and excessive irritability and failure to grow following the administration of thyroid substance appear to be prominent features (Dunn 1944) Changes in the roentgenographic appearance of the sella turcica usually aid in the further differentiation of the condition from that of primary cretinism in which the initial lesion is in the thyroid

When the condition appears as a result of a pituitary disturbance occurring in adult life growth is obviously not affected and the major clinical features apart from those characteristic of adult myxedema (q v) center around disturbances in the function of the adrenal gland and the gonads Frank symptoms of severe adrenal insufficiency such as nausea vomiting abdominal cramps low blood pressure sparseness or complete absence of axillary pubic and body hair easy tendency to infections and so forth are commonly observed (Lerman and Stebbins 1942) Disturbances in the gonads may be equally striking Amenorrhea loss of libido and impotence are symptomatically significant In the female there is atrophy of the breasts vaginal mucosa and uterus and in the male the development of a eunuchoid habitus a decreased hair growth and atrophy of the testis

In therapeutic trial with desiccated thyroid substance none of the patients with pituitary myxedema respond satisfactorily Shortly after such treatment is begun nausea vomiting abdominal cramps semistupor *collapse and coma occur* (Means et al 1940 Lerman and Stebbins 1942 Riser and Corral 1946) The picture is that of adrenal insufficiency precipitated or aggravated by the increased metabolic load produced as a result of the administration of desiccated thyroid substance

Chapter XXXI

DYSPITUITROUS MYXEDEMA

Synonyms —Pituitary type of myxedema cretinous pituitarism

Incidence and Etiology —Scarcely a year passed following the classical description of acromegaly by Marie before myxedema was described in association with that condition (Hemot 1882) Of 1 319 cases of acromegaly summarized by Atkinson (1932) nine had myxedema, but in a much higher percentage there were atrophic changes within the thyroid gland and other evidences of hypothyroidism without myxedema In each instance the myxedema had followed extensive destruction of the anterior pituitary often with degenerative and cystic changes within the eosinophilic adenoma Interest in the subject was renewed by the reports of Cushman and Hertz (1939) and of Means and his associates (1940) who described a patient with Simmonds cachexia in whom the most prominent clinical features were those of myxedema The extreme aggravation of this patient's condition by therapy (thyroid hormone) uniformly effective in cases of myxedema secondary to primary thyroid failure demonstrated the necessity for recognizing a form of underfunction of the thyroid due to a lack of stimulation from the pituitary gland Means called the condition Simmonds disease masquerading as myxedema

Several subsequent reports (Lerman and Stebbins 1942 Cornell Univ Med Coll II DuBois 1941 Dunn 1941 Riser and Gavral 1946 Clinton Bennett and Kepler 1948 St George Tucker Chitwood, and Parker 1950) have served to emphasize (1) the not infrequent occurrence of pituitary myxedema (2) its origin in *any* destructive lesion of the anterior pituitary and (3) most important the dangers of vigorous therapy with desiccated thyroid substance

Pathology and Pathologic Physiology —The pathologic disturbances in the thyroid in cases of pituitary myxedema cannot be distinguished histologically from those of primary or thyroid myxedema (q v) Diffuse atrophy with almost complete disappearance of the follicular pattern is the rule Changes in the anterior pituitary gland are always present and are due to widespread destruction or disappearance of glandular elements secondary to any of a variety of lesions among which acromegaly craniopharyngioma cystic degeneration postpartum necrosis and atrophy and fibrosis of unknown etiology have been most commonly mentioned

mec is acute salt solution and idrenocortical hormones preferably watery extracts should be employed In other words the treatment should be that of the crisis of Addison s disease *If such an acute con* dition is severe as is often the case after thyroid hormone has been fed an infusion of 1 000 c c of a 2 per cent saline solution containing 5 per cent glucose and 20 c c of watery extract of the idrenal cortex is advis able If no watery extract is immediately available it is best to omit the glucose from the infusion as secondary hypoglycemia is common Sub sequent treatment for the idrenal disturbance will depend upon the pa tient s condition However it must be remembered that the primary f ult lies not with the idrenal cortex but with the f ilure of the anterior pituitary to afford it normal stimulation Ide ally, therefore adreno trophic hormone of the pituitary should be used This however is to date available only in relatively small *quantities at high cost Ierman* and Stebbins (1942) found the gonad stimulating hormone from preg nant mare s serum of value in daily doses of 20 rat units (200 Cole Saunders units) Other trophic factors of the pituitary deserve trial as if and when available Antihormone formation may interfere with the widespread application of such therapy particularly as regards the thyroid stimulating hormone but it did not seem to occur with the gonadotrophin employed by the above mentioned observer The gonadal factor of the pituitary probably improves the status of the subject through the action of hormones secondarily produced by the gonad and testis In this connection it should be emphasized that testosterone *cautiously employed* may be gradually substituted for the adrenal ther apy in either sex In women we prefer to use methyl testosterone by mouth giving 10 mg two to three times daily for 21 days out of each month starting such treatment on the third or fourth day of flow if the subject is menstruating regularly In men testosterone propionate 25 mg intramuscularly three times weekly usually gives gratifying results or for convenience an implant of from four to seven 75 mg pellets may be substituted

As soon as measures are instituted to protect the idrenal thyroid hormone may be supplied cautiously As a rule 0 25 grain is well tolerated in the beginning This should be slowly increased in much the same manner as described under the treatment of adult myxedema (Chapter XXX) until myxedema has disappeared or until some evi dence of intolerance appears As a rule 0 5 to 1 5 grains will effect a clinically satisfactory response

In summary our treatment of pituitary myxedema should be aimed at protecting the idrenal gland while substituting for the thyroid de ficiency by administering desiccated thyroid substance

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The number of pellets to be employed will vary not only with size but also with the method of manufacture The above recommendation applies only to Schering Corporation *Testosterone pellets a three month only type with which the author has had experience*

Under such circumstances it is also possible for thyroid hormone to embarrass the heart and thus lead to coronary insufficiency and thrombosis (Lerman and Stebbins 1942) a manner in which one of our own patients died

Laboratory Data—In the main, the findings are those of myxedema (q.v.) plus those of adrenocortical and gonadal deficiencies. In some instances the values for cholesterol and protein in the blood have not been elevated. It is doubtful however that this variation from their behavior in primary hypothyroidism is a reliable diagnostic feature (Lerman and Stebbins 1942). To demonstrate the presence of adrenocortical insufficiency blood levels for sodium and potassium should be done. More informative are the results of the Wilder (Cutler, Power and Wilder 1938) or Kepler (Robinson, Power and Kepler 1941) procedures for demonstrating the disturbances in electrolyte balance although the former is not without some danger. The insulin tolerance test (Fraser, Albright and Smith 1941) will show an increase in the speed with which the blood sugar falls a slow recovery and little or no response to the administration of epinephrine all indicating a lack of the diabetogenic factor of the pituitary or its adrenal components.

The 17-ketosteroids usually disappear from the urine in cases of pituitrous myxedema, whereas in myxedema of thyroid origin they are usually low in amount but not absent.

The alterations in renal function in dyspituitrous myxedema are similar to those seen in primary thyroid myxedema but in some subjects there is difficulty in concentrating the urine (Beaumont and Robertson 1913a) while others show the highest concentrations of urine during the day with a reversal of the day/night volume ratio (Miller 1916).

A low titer for urinary gonadotrophins may still further demonstrate the pituitary origin of the condition particularly when present in women of menopausal or postmenopausal age.

Diagnosis and Differential Diagnosis—The diagnosis and differential diagnosis of myxedema have already been discussed (q.v.). Therefore we need to differentiate here only that form of myxedema due to primary atrophy of the thyroid (primary myxedema) from that secondary to underfunction of the pituitary (secondary myxedema). In the latter the mental disturbances are not so great and the evidence of involvement of other glands notably the adrenal and the gonads is striking. A poor response to thyroid hormone is characteristic of the pituitary form of the disease.

Treatment—Thyroid hormone must be administered with caution in dyspituitrous myxedema as its use in customary doses may produce hypoglycemia adrenocortical crisis and possibly cardiac failure. Therefore, any treatment must afford primarily protection to the adrenal cortex while supplying the obvious thyroid deficiency. If the disturb-

Pathogenesis—At periodic intervals the normal thyroid follicle appears to go through a working cycle which we have already divided into four stages chiefly on the basis of the anatomical investigations of Williams (1937) (see Thyroid Follicle Chapter VIII) This work cycle consists essentially of a period of growth development, and functional activity followed by one of recession involution, and rest

Whenever prolonged periods of uninterrupted activity occur or involution is not fully completed even in a single follicle the background is laid for the development of a nodular goiter of one form or another *It is doubtful that we are in possession of sufficient facts at the* present time to reconstruct every step in the development of any single type of nodular goiter for a combination of factors must of necessity be concerned in each individual case However if we recognize the role of the pituitary thyrotrophic hormone the thyroid hormone iodine and certain dietary factors all of which have been given in some detail under Physiology (Section *II*) (q v) several general points may be clarified

Fundamentally the thyrotrophic hormone of the pituitary increases the size of the thyroid cell the number of cells the over all weight of the thyroid and the speed with which organic compounds of iodine (di iodotyrosine and thyroxin) are formed within the thyroid Hall (1948) accords it a position in the pathogenesis of multiple adenomata similar to that of certain carcinogens in papillomata of the skin

Thyroid hormone depresses the formation of thyrotrophic hormone by the pituitary and its action upon the thyroid and diminishes the functional capacity of the thyroid cell and follicle both directly and by way of the pituitary

Iodine without increases the capacity of the thyroid cell for the formation of thyroid hormone but if long continued hormone poor colloid collects in the follicles and the over all function of the follicle decreases while small areas may remain actually hyperplastic Large doses of iodine will depress activity of thyrotrophic hormone thus decreasing acinar cell height size and activity and causing the storage of colloid sometimes with a poor content of hormone

Cabbage goiters and thiouracil derivatives in different ways interfere with the formation of thyroid hormone thus leading to a work hypertrophy and hyperplasia of the thyroid cells

If we put the above pharmacological actions together at varying levels of dosage and in *different combinations the number of clinical* syndromes which are possible is tremendous Moreover the interaction of any two or more of these factors is not a matter of simple summation Not infrequently a reversal of action occurs as the conditions are varied For example in simple endemic goiter iodine in moderate doses increases the size of the functioning thyroid cell and decreases the volume of the acinus by effecting an extrusion of *colloid On the other hand*

Chapter XXXII

NODULAR GOITER

For many years the clinician has spoken of uni- and multinodular goiters of the toxic and nontoxic varieties respectively without any serious regard for the etiology pathogenesis or histology concerned The term nodular goiter has been used loosely to include a wide variety of disturbances of the thyroid which it has been impossible to separate from one another with any degree of accuracy and which justifiably belong together from the standpoint of the therapy indicated The same reason now holds for treating them under a single heading In addition moreover the newer knowledge of thyroid physiology as detected through the use of antithyroid compounds 'bio antagonistic' structural analogues of thyroxin radioactive iodine and radioautographic and special staining techniques has shed some light upon differences in the behavior of grossly similar nodules so that we may now begin to recognize etiological pathogenetic functional and pathological differences between them It seems premature however to become dogmatic in our discussion of the factors concerned as there appear to be many features in common Even the synonyms employed for nodular goiters are inadequate as each tends to emphasize some single feature or features of the condition to which it is applied

Synonyms—Under nodular goiters we may list adenoma toxic adenoma nontoxic adenoma cystadenoma adenoma with hemorrhage or calcification colloid goiter with nodule formation colloid goiter with cystic changes uninodular goiter multinodular goiter and so on through those types of thyroid condition in which enlargement and irregularity of the surface of the thyroid may occur

Definitions—From the synonyms above listed it is clear that we are including under the term nodular goiter a large number of etiologically pathogenetically and pathologically distinctive conditions in which the common denominator is enlargement and irregularity of the thyroid gland Because of their characteristic clinical behavior toxic nodular goiters and malignant goiters will be treated separately except in so far as either or both may enter into a discussion of the pathogenesis of this whole group of tumors

TABLE XII

SOME POSSIBLE MECHANISMS CONCERNED IN THE EVOLUTION OF SEVERAL CLINICAL CONDITIONS WHICH RESULT IN NODULAR GOITER

INITIAL CONDITION	AMOUNT PRESENT OR DEGREE OF FUNCTION OF				PROBABLE RESULTANT CONDITION
	TSH.	TH†	INTAKE OF IODINE	ADDED DIETARY FACTORS	
Simple or Endemic Goiter	Low to Normal	Normal	Low		Simple goiter (subiodic goiter) failure of involution following work hypertrophy and hyperplasia
	Low to Normal	Low	Low		Hyperthyroidism and cystic gland with hemorrhage fibrosis calcification etc
	High	*Low or Normal*	*Low*	*Calcium and selenium may intensify*	*Cystadenomas and adenomas (non* toxic nodular goiter)
	High	Low or Normal	Low	Brassicae (cabbage etc)	Cystadenoma or adenoma (non toxic nodular goiter)
	High	Low	High	With or without Brassicae	Toxic adenoma with or without complicating features (toxic nodular goiter)
Graves Disease *Untreated*	*High*	*High*	*Normal*		*Hyperplasia metaplasia subinvolution adenomatous nodules*
Resolving spontaneously *or as a result of* I_2	Normal	Normal	High or *Normal*		Subinvoluted thyroid with hyperplastic nodules of varying size (nontoxic nodular goiter adenoma)
Repeated attacks	High	High	Normal		Toxic nodular goiter
Treated with Thiouracil	High	Low	Normal		Increased hyperplasia and adenomatous change with large tall columnar cells small acini and little or no colloid (nodular goiter—adenoma)
Treated with Thiouracil	High to Normal	Low	High		Decrease in cellular proliferation (adenoma) with increase in cell id (cyst) (nodular goiter—cystadenoma)

TSH—Thyrotrophic hormone of the pituitary gland
†TH—Thyroxine

in a gland already blocked with thyroid in which the cells are very hyperplastic and no colloid is present in the form iodine depresses the cell and aids in the collection and storage of colloid by the acinus

It is clear therefore that the type of nodular goiter which is seen clinically may evolve from variations in the interaction of a number of factors the full value of each of which is probably not known However while oversimplification runs grave risk of inaccuracy it may be useful at the present time to crystallize our concepts concerning thyroid nodules In Table XII we have attempted to suggest the way in which several nodular conditions of the gland *may* be brought about

In each of the sets of circumstances postulated in Table XII the result is an interference with the normal function of the thyroid in which it attempts either successfully or unsuccessfully to cope with adverse conditions to produce its specific hormone It is often difficult indeed sometimes impossible to say where the physiological ends and the pathological begins Physical activity cold common mental stresses not in themselves overpowering and normal periods of adjustment in life such as puberty marriage the climacterium and so forth may result in temporary disturbances in the thyroid from which at least histologically it never recovers As long as such stimuli remain physiological in kind and degree their effects may be likened to the influence of pregnancy upon the virgin breast This structure never returns to its previous status histologically but is by no means looked upon as abnormal simply because it has passed through a period of vigorous activity

Just as in the breast so in the thyroid these changes due to a stress or work hypertrophy may simulate the early histological features of conditions which are commonly considered pathological This is particularly true of the thyroid which in apparently normal persons over the age of 15 years frequently shows colloid changes with nodule formation and degeneration (Schlesinger Gargill and Save 1938 Martin 1945b) Such nodules are rarely detected on physical examination and may be so small that at times they cannot be visualized by the naked eye on the cut surface of the gland Perhaps a lowered activity of the pituitary the ovary or even the adrenal during aging helps to create the background for these alterations in the thyroid gland In any event their presence indicates a gradually diminishing activity of the thyroid during declining years Moreover the larger more easily perceived nodules which sometimes appear in the apparently healthy person may represent simply an accentuation of the factors that play a normal role in senescence It is natural therefore to ask when the nodules developing in the thyroid in middle or late middle life attain a size or character which justifies their transfer from the category of degenerative lesions of advancing years to that of pathological nodular goiter"

Up to this point we have been discussing nodules in the thyroid which have been produced as a result of the efforts of the gland to respond to functional stresses of more than average magnitude The lesions which result from such conditions are usually multiple and have been well categorized by Rienhoff (1926) as involutional bodies and by Wegelin (1926) as circumscribed regenerative and compensatory new formations As a rule they are less physiologically active than the surrounding or paranodular tissue but the degree of such activity varies considerably and cannot be correlated with the histological appearance Some of them are localized occasionally single well encapsulated lesions while others are diffuse multiple enlargements merging almost imperceptibly into the normal elements of the gland Many of these nodules show only hyperplasia Frequently they become metaplastic and less commonly must be classed as truly neoplastic adenomatous tissue

The single well encapsulated nodule is likely to have a somewhat different origin in an intra uterine or embryonal disturbance It may represent a fetal rest the so called fetal epithelium of Wolfler (1883) or the mal development tissue rudiments of Kloeppel (1910) Among such lesions we must place the papillary adenomas and papillary cystadenomas which are derived from the lateral an lagen of the thyroid and without doubt are neoplastic from the beginning Other lesions in the group resemble in appearance and as far as is now known in activity the adenomas that arise in the course of thyroid disease in extra uterine life despite the fact that they represent abnormally placed rests of cells due to faulty embryonal development Some of them are thought to behave in an entirely autonomous fashion without regard for the mechanisms such as the pituitary that normally regulate the speed and direction of thyroid cellular activity Here are included the hyperfunctioning single adenomata of Cope Rawson and McArthur (1947) although there is no proof that the lesions they have described *must* arise from fetal rests

Pathology—Diffuse colloid goiter usually produces a uniformly manifest enlargement of the thyroid gland in which its size is materially increased but normal contours are maintained Nodular goiter develops when the condition is long continued without involution so that cystic areas form in between which there may appear a piling up and infolding of epithelial cells in an effort to compensate functionally for the large number of more or less inert follicles The eventual result may be a multinodular goiter in which large cystic areas are interspersed with those of hyperplasia and eventual adenoma

In subjects with diffuse hyperplastic or exophthalmic goiter the follicles are lined with a high columnar epithelium and contain little colloid As the process progresses without involution there is a tendency for infolding of the epithelium and the piling up of cell layer

This question of classification of thyroid nodules appeals to us as much more than an academically interesting problem, for upon its final solution hinges the therapy we are to employ in each individual case. More careful analyses of the data *from all types of nodular goiter* such as that recently made by Anglem and Bradford (1918) are necessary *before it can be answered fully*. Nevertheless the finding of nodules, be they micro- or macroscopic, in normally aging persons emphasizes the extreme caution with which the pathologist must proceed in labeling thyroid tissue histologically normal or abnormal. By the same token, the clinician must decide whether normalcy is to be decided on the basis of function alone. Furthermore he must appraise the local lesion in the neck not only in regard to its potentialities for becoming malignant but also in relation to possible toxicity and the functional capacity of other interrelated structures such as the pituitary, *the ovary, and the adrenal. If we accept most of these nodules* as the result of an uncompensated attempt of the thyroid to meet physiological needs in the face of overwork, then it should be possible through a correction of the underlying or basic problem or problems to encourage normal thyroid activity with a return to quiescence albeit without complete involution of the thyroid tissue. If such can be accomplished—and often it can—then the local lesion which remains in the thyroid becomes one of secondary or minor importance. Unfortunately our ability to recognize either the potentially dangerous or the assuredly harmless nodular lesion in the thyroid is not great. In any instance however, the final appraisal does not rest solely upon the finding *of a lump in the neck but also upon our knowledge of the individual as a whole* and particularly upon our understanding of his entire endocrine pattern.

The processes at which we have hinted above that result in nodular goiter may have their origin in chronic thyroiditis, subacute goiter, congenitally aberrant thyroid tissue, diffuse toxic hyperplastic goiter, fetal adenomas, and so forth.

Nodular goiters are commonest *in the endemic goitrous districts* of the world where the work of the thyroid cell is great and hypertrophy and hyperplasia are the compensating mechanisms. *In such an area* one worker found thyroid nodules in 80 per cent of *all* subjects coming to autopsy (Coller 1929). In general, the so-called adenomas arising from such glands are functionally less active than the paranodular parenchyma; they absorb less radioactive iodine and manufacture less thyroid hormone (Leblond et al. 1946; Puppel et al. 1947). However the functional capacity of adenomas may vary considerably both in endemic and nongoitrous districts (Hamilton, Soley, and Eichorn 1940; Cope, Rawson, and McArthur 1942-1946, 1947; Gross and Leblond 1947; Means 1948, 1949).

Up to this point we have been discussing nodules in the thyroid which have been produced as a result of the efforts of the gland to respond to functional stresses of more than average magnitude The lesions which result from such conditions are usually multiple and have been well categorized by Rienhoff (1926) as involutional bodies and by Wegelin (1926) as circumscribed regenerative and compensatory new formations As a rule they are less physiologically active than the surrounding or paranodular tissue but the degree of such activity varies considerably and cannot be correlated with the histological appearance Some of them are localized occasionally single well encapsulated lesions while others are diffuse multiple enlargements merging almost imperceptibly into the normal elements of the gland Many of these nodules show only hyperplasia Frequently they become metaplastic and less commonly must be classed as truly neoplastic adenomatous tissue

The single well encapsulated nodule is likely to have a somewhat different origin in an intra uterine or embryonal disturbance It may represent a fetal rest the so called fetal epithelium of Wolfler (1883) or the mal development tissue rudiments of Kloeppel (1910) Among such lesions we must place the papillary adenomas and papillary cystadenomas which are derived from the lateral anlagen of the thyroid and without doubt are neoplastic from the beginning Other lesions in the group resemble in appearance and as far as is now known in activity the adenomas that arise in the course of thyroid disease in extra uterine life despite the fact that they represent abnormally placed rests of cells due to faulty embryonal development Some of them are thought to behave in an entirely autonomous fashion without regard for the mechanisms such as the pituitary that normally regulate the speed and direction of thyroid cellular activity Here are included the hyperfunctioning single adenomata of Cope Rawson and McArthur (1947) although there is no proof that the lesions they have described *must* arise from fetal rests

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upon cell layer The adenomas thus formed may differ from the adenomas ordinarily ascribed to fetal rests' in that they are poorly encapsulated rarely contain true fetal acini often exhibit areas in which the follicles are lined with low cuboidal epithelium and in general possess more features of hyperplasia than neoplasia

The present medical therapy for toxic goiter may be a potential source of nodule formation If the basal metabolism is maintained for several weeks at or slightly below the zero point in a subject with thyrotoxicosis through the use of thiouracil or one of its closely related antithyroid compounds an obvious enlargement of the gland often occurs (McGavack Geil et al, 1945) There is experimental evidence to suggest that such a gland may become adenomatous as a result of the hypertrophy and hyperplasia induced by completely removing for too long a time the braking effect of thyroid hormone upon the anterior pituitary and its thyrotrophic hormone Two groups of investigators (Gorbman 1946 Purves and Griesbach 1947) working independently have shown that the prolonged administration of thiouracil to rats causes the development of thyroid adenomata The dosages were extremely large as compared with those used in the therapy of human hyperthyroidism In the work of Purves and Griesbach (1947) some of the adenomata eventually showed carcinomatous changes which could be arrested by stopping the drug and reactivated by resuming its administration While such an eventuality seems unlikely in the dosages used for the clinical management of exophthalmic and adenomatous goiters in the human being one instance has been reported in which an early carcinomatous lesion was found in association with diffuse toxic hyperplasia that had been treated preoperatively with thiouracil and iodine (Payne et al 1947) This may have been a coincidence In any event the length of time these antithyroid drugs have been available is still too short to pass final judgment regarding a causative role in the pathogenesis of thyroid carcinoma We can say with certainty however that the thyrotoxic gland usually becomes smaller under treatment and remains so provided the basal metabolic rate is maintained between +5 and +15 Only when the patient is overtreated do we see conditions which may simulate those obtained in the experimental animal as described above However Pemberton and Black (1948) feel that the association of exophthalmic goiter and carcinoma is such as to be accounted for on the basis of chance alone They emphasize the point that the finding of a carcinoma in the thyroid of a patient who has had radioiodine or an antithyroid compound does not imply an etiologic relationship between the drug and the malignant lesion

Conditions which we can readily admit histologically as adenomas or neoplasia may occur singly but are more frequently multiple They are encapsulated extremely variable in size light amber to reddish brown in color and soft to firm in consistency Microscopically any of a

number of changes may be observed even in a single adenoma A typically fetal arrangement may occur with the cells in diffuse masses or columns Small fetal acini with miniature lumina and no colloid or nearly mature follicles with some colloid are common In still other areas large well developed acini appear in which the epithelium may vary from a cuboidal to a high columnar type Papillary infolding is common particularly where the adenomatous condition accompanies or follows in the wake of an exophthalmic or diffuse hyperplastic goiter Histologically it is impossible to tell a toxic from a nontoxic adenoma although some recognize intra adenomatous hypertrophy with high columnar cells as a sign of toxicity Despite this intra adenomatous hypertrophy has been found in 19 per cent of adenomas without toxicity as contrasted with an incidence of such hypertrophy in about 37 per cent of the glands associated with hyperthyroidism (Johnson 1913) In many so called toxic adenomas the nodular tissue may actually be hypofunctioning while the parinodular parenchyma is hypertrophic and hyperplastic Strictly speaking the term toxic adenoma should be preserved for those nodules which show high columnar epithelium with papillary infolding and epithelial reduplication and which can be proved to be functionally active through the use of radioactive iodine or other satisfactory physiological tests (See below The Hyperfunctioning Single Adenoma of the Thyroid)

All the forms of nodular goiter about which we have been speaking are subject to degenerative changes including particularly hemorrhage cyst formation calcification malignant change and even ossification (McCaughan 1935)

In view of our present day concepts of the physiology of the thyroid gland the nature of the changes in the individual goitrous nodule that is whether predominantly colloid retention as in simple goiter or epithelial proliferation as in exophthalmic goiter depends upon a number of variables among which the nature of the dietary the intake of iodine the status of the hypophysis and the adjustment of the subject to his environment are probably the most important

Clinical Course—Our major clinical interest in nodular goiter aside from its unsightliness lies in the disabling complications which may arise (Figs 53 59) Predominant among these are pressure phenomena malignancy and thyrotoxicosis Needless to say many goiters run a wholly benign course in which the patient undergoes no serious inconvenience or danger of any kind Indeed goiters have been known to decrease in size or even to disappear after being present for years without any appreciable alteration in size shape or consistency Such reversion toward normal probably depends upon a restitution of thyroid function with satisfactory involutional changes The startling fact is that this may occur after relatively prolonged periods of nodu



A



B

Fig 53 *A* and *B* *(For l gend s e pp ite page)*



Fig 4—Ad noma w th calcifi at n and thy t c sis (C I FFAH #2 46) A 5 year old h u ewife h d fi t noti ed a lump in the lower n k s x mo ith previously while str ining to ı en a w ndo v Sh tly thereaft r she dev lop d a mild ynd me of thyrot xic sis with basal metab l rate a ou d +30 There w e no pr s u e phenomen The multin dular enlarge m nt of th l ft lobe wa l w in th n ck and i egular in ons stency Ope ative pro d re con f med th pre en of an ad n n a (6 by 4 5 by 3 cm) with me rea of hyperpla ia nd hyp t ophy and ther of deg n t e change In th ntgen g m note th soft tissu h d w show ng calcium plaque Calcifi ation of the l yngeal ca t lage not uncommon at this ag s al o p esent The t a h l shad w s normal n siz and contou The slight calcifi ati n f th t a heal ng n he e l e lon lly en n n mal ind idual o er 50 y rs of ag

larity However this is not the rule and in most subjects some remedial therapy must be considered

1 Syndromes Resulting From Pressure of the Growing Nodule Upon Surrounding Structures—Pressure phenomena result more frequently from multinodular than from uninodular goiter Usually they appear only when the goiter is very large but intratracheal (Boyd and Lathrop 1949) retrotracheal and retroesophageal extensions of rela

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Fig 53 *A* and *B*—Ad n ma of the thy id gl nd with thyr toxi o is alcification of the la yngc l nd t acheal cart l ge (L S FFAH #987 46) This 64 year ld woman wa admitted t the h p tal for ympt ms f thy otox c si and a mass in the n ck The latte was fir t n ted ight y rs p viou ly nd h d be n in sing in ly for th e yea s Th re wer no p ur phenomena the ba l m tab li r te w +60 per cent Note the light tra heal d viation without n pre on o ther m nife tati ns f p e u e No d g nerativ cha g s w r pre ent in the x sed g t This roentgen g am al o illust ates ni ly the cal ificati n of th laryngeal til g usually e n at this ge and the le c mm nly bserved calc ficati n of th t ach l lings

tively small size may give rise to alarming manifestations The more rapid the growth, the more likely the development of a mechanical or functional disturbance in surrounding structures Twenty per cent of all nodular goiters cause a displacement of the trachea (Fig 53) More than 50 per cent of the patients in whom this occurs will complain of symptoms due to the pressure of the gland upon some near by structure (Figs 51 57) The nature of the manifestations due to pressure and the relative frequency with which each occurs have already been detailed at some length in our discussion of subacute goiter (q v) and will not be repeated here



Fig —Retrosternal adenoma (OD 1 PAH #6 8 44) This was a cystadenoma completely enclosing the tracheal ring producing the symptoms In the photograph observe the forward displacement and angulation of the trachea Tracheal deviation and distensive tracheal collapse although not present in this case always have to be found in this and similar subjects

2 *Malignancy and Nodular Goiter* —Carcinoma is seen in from 1 to 7 per cent of all nodular goiters In nontoxic nodular goiter recent reports on relatively large series of cases show an incidence varying from 1 79 (Rogers, Asper and Williams 1917) to 18 4 per cent (Dailey Soley and Lindsay 1919) The lesion is a rare complication of toxic nodular goiter but there are well authenticated cases of such an asso



Fig 5f 4 1 1 B— D g n r ti g 1 o t le a l n ia cau i g p s ur ymptl s (H T MH #D13803) Thi f y old w n 1 p c t l l r lf f the t tm t f ly pnea ar l a r a j 1 the n k Tl r wer 1 yr pto s f thyr toxi osi the ba l m tabolic te w +8 The 1 w fi t 1 t d t th p of 30 y ar and h d lowly i cr a ed n i b tw n the ag of and 6 y ar A y li d n a w ghing 4 g an was r n o d at opc ation It cont ined 1 t y dilat d blood l 1 u 1 rous rg nl d and p tially o ganiz d l orrhag s and v ral lcifi d a e N t th displac n ent of tl e tra h a to the right witl ar gul t on a d c mpre sl n N ry large ll id goit rs n y b n yr1ptor tic u tll ondary deg erati ch nges occu



A



B



Fig 58.—Ca cin ma f the thyr id (D W FPMI #1 #10 80—46) Th s y ar-old w man h d ha l a s mall lu mp in th r k f bout thirty y a s whi h had ne er di turb d h r until thr e w k pri r to dmi s o wh n l e bea n to con plain of diffi ulty in swallowi g and in t milli nt sharp pain in the left low r neck ra l at t g t th left ide of h ad nd arm A hard ma s th i e of a w lnut w p lp t l low i s the n ck on th left ide A t ntativ d gnosis of car inom a w s iffi ult d fer t ely wh n this ma s (6 by 3 by 2 n) which xtended ub t rnally pro ed to b n ad a w th low grade malig a t cha ge Th roentg n gram how the ub t r l st y l s Thi ca n) l a lz s the etiol gi al r lati n hip betwe n imple n ulti od l g t r and m lignancy and l r pr ent malignant change i wh t wa probably a llin t le g lle

ciation (Pemberton 1939 Goetsch 1940b Pemberton and Lovelace 1941 Ward 1944 Cole Slaughter and Rossiter 1945 Cole Majarakis and Slaughter 1949) and in one carefully studied series of subjects 19 per cent of toxic nodular goiters showed a malignant change (Anglem and Bradford 1948) If the goiter is unnodular the incidence of malignancy is much higher having been observed in from 9 per cent (Anglem and Bradford 1948) to 21 per cent (Cole Slaughter and Rossiter 1945) of such cases It is doubtful that the incidence of cancer

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Fig A and B.—Cal ified sub t n l goit r (A N MH #130246) In thi 2 y ar old woman dy pn a nd c ugh had b n pr t for f o n ight to ten y ar wh n the ro ntgenog am s wer t k n He l rly vid nt right nd l ft id d heart failu may be tr ed in p t to th strain plac d up the heart by the pr sure f the n di stin t mass up n th t a hea and sur ou ding stru ture Alth ugh n dvanced art ios l ro is al exi t d The mo m t of the anterior m dia thi t s d l g d glut tion r ed to confl n its lation hip to th thyr id and to ul ut n h l n de n id ce t or th r lcifying tum or in thi egi n In th lat ral o ntgen g m (B) the highly lcified cond tion f the g t and its on pr on f the tr ch a ar a ily made out nd l arly Ill t ate the fa t th l n t th al but th lo tion m bility nd c n i t ncy of a int th cic golt r th in p i t t d t mini g fa t s in the n tur and verity of the p u ph n n ia th y r odu



A



B

Fig 59 *A* and *B* *(For legend see opposite page)*

in nodular goiter is as high as the figures just mentioned indicate for it is quite logical that figures obtained from any large clinic represent only those goiters that have for one reason or another attracted the attention of the patient and his family physician

In many instances of nodular goiter the thyroid enlargement is an incidental finding of long standing in a patient who has lived at least a portion of his or her life in a region of endemic goiter gives a familial history of goiter and presents neither local symptoms of pressure nor general manifestations of thyroid dysfunction It is our belief that while these patients should be periodically watched for any changes in the thyroid surgery as a prophylactic measure need not be routinely practiced On the other hand there is a second group of patients in whom goiter is the presenting complaint because of the pressure or other local symptoms which it is producing In such subjects a subtotal thyroidectomy is the only logical method of management Soley (1917) believes that neoplasm should be suspected in the course of nodular goiter when (1) the patient has never lived in an endemic goiter region (2) there is no family history of goiter (3) the thyroid enlargement appears simultaneously with symptoms of pressure and (4) the goiter shows evidence of growth (Fig 58) One might add that the younger the person developing a nodular goiter the more likely it will be to become malignant (Sloan 1930)

The above suggestions may help the physician to decide in any individual case just what therapy if any should be instituted Nevertheless it should be emphasized in all fairness that cancer is superimposed upon nodular goiter with sufficient frequency to make surgical removal a justifiable prophylactic procedure in all nodular goiters (Fig 58) and an imperative one in the uninodular type

In its earliest phases a clinical diagnosis of malignancy is well nigh impossible The condition usually occurs in a previously nodular goiter which after a long period of quiescence suddenly begins to increase in size Extreme hardness in an irregularly enlarging gland with discrete borders should suggest malignancy The gland of ligneous thyroiditis is equally hard and while at times it may show nodules usually presents a smooth surface the borders of which are outlined with some difficulty The fact that carcinoma has been reported in struma ligneosa may serve to confuse the issue (Dinsmore and Hazard 1918)

Fig 9 4 a d *B*—Thyr to ico i in a l rg n ult n l l r go t r whi h ose f m th mpl ll id g it of puberty (L D FFAH #2860-4) Enlargem nt of th thyro d wa fi st noted at t l ly (g 13 y r) fi ye r aft r which t wa de bed s nodul in ha cter T xt yn pt m w fir t app rent wh n th p ti nt was 32 yea of ge t whi h tim thyro d ctomy w s i fo m d Wh n the omp nying r ntg n gr n w taken h wa 63 yea s old a d pr nt d th cla si l ign of thy t 1 is whi h had be n p e nt f thr year De p te tl e la g l e of the ft ti u n a the devi tl n of the t a hea to the l ft and e d n of d g n ra ti e bang s (vary i g con l ten y and cal lficatl t) no pr ssure ph n m na we pre nt



A



B

Fig 3 A and B *(For legend see opposite page)*

with the development of hyperthyroidism the question of lesions within the thyroid, capable of initiating and maintaining a hyperfunctioning state of that gland certainly possesses more than academic interest to the clinician. Such lesions, while far from frequent, have been demonstrated (Cope, Rawson and McArthur, 1942; 1946; 1947; Boulle, 1949). They are unimodular, probably fetal adenomata which become functionally active and show an autonomy not dissimilar to that seen in physiologically active adenomata of the islands of Langerhans, the parathyroids and the adrenal cortex (Figs. 27 and 60).

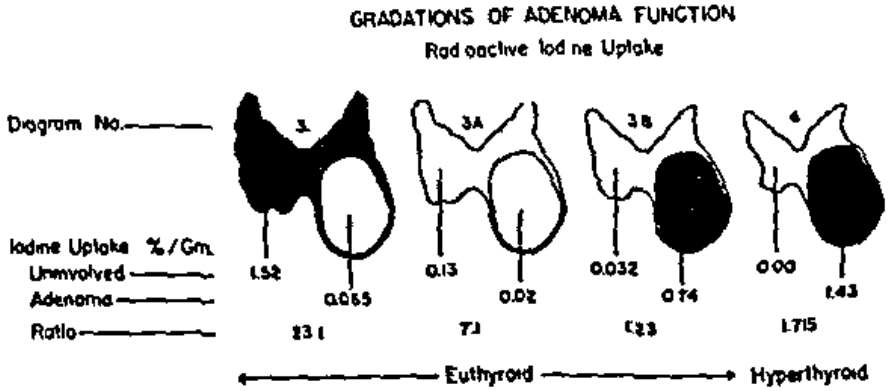


Fig. 60.—Dissociation of the function of thyroid nodules and the paranodular tissue. This figure illustrates the dissociation of the function of thyroid nodules and the surrounding thyroid follicular tissue, indicated by their respective capacities for absorbing and concentrating radioiodine. The intensity of the shading indicates the degree of avidity of the tissue for iodine. The fractional uptake of iodine is shown as per cent of administered dose per gram of thyroid substance and has been determined in each instance between the concentration of radioiodine in extracted paranodular tissue. The inhibiting effect of the functioning nodule upon the activity of the gland is clearly shown and is sufficiently great in some instances (diagram 4) to cause suppression atrophy. (After Cope, Rawson and McArthur, 1947.)

In a group of ten of these hyperfunctioning tumors, the total seen in ten years at the Massachusetts General Hospital, Cope and his associates (1942; 1946; 1947) found features which led to the conclusion that the thyrotoxicosis was due solely to the overactivity of the tumor and that such activity was not directly under the control of the usual mechanisms concerned in regulating the production of thyroid hormone. The analogy between this lesion and functionally independent islet cell adenomas of the pancreas has been based on the following observations:

1. An atrophy of disuse occurs in all thyroid tissue outside the nodule; this was present in every case and nearly complete in some.

2. Exophthalmos was seen once in ten subjects, as compared with an incidence of 50 per cent in Graves disease. Were the thyroid lesion secondary, an excessive amount of thyrotrophin would be formed with a failure of the secondarily stimulated thyroid to inactivate a portion thereof. Exophthalmos results when active or reduced forms of thyrotrophin are present in the circulation. In the unimodular lesions under discussion, the rarity of exophthalmos indicates that normal

The calcified nodules of benign adenomas may be mistaken for carcinomatous lesions but as a rule these are superimposed upon goiters with preceding cystic changes so that some portions of the tumefaction frequently remain soft The entire gland is stony hard in cancer

3 Thyrotoxicosis in Nodular Goiter—Hyperthyroidism develops in subjects with a nodular goiter in a considerable number of cases (Figs 53 54 and 59) The exact incidence is difficult to ascertain Many nodules go completely unrecognized throughout life In other instances the manifestations of thyrotoxicosis are the presenting complaints and the previously existing nodule has never been noticed by patient or friends An incidence of thyrotoxicosis in nodular goiter varying from 10 to 50 per cent can be substantiated on good authority Our own experience would support a figure nearer the lower than the upper of these two limits Nodules have usually been present in the thyroid for a number of years before the hyperthyroidism makes itself manifest (Fig 59) Cole Slaughter and Rossiter (1915) found the average duration of goiter prior to the appearance of toxicity to be nine years but this period may vary from one to twenty five or more years The tendency for toxicity to develop in nodular goiters increases as one ascends the age scale Of Coles (1915) patients with toxic nodular goiter 29 per cent were over 50 at the age of onset despite the fact that only 11 per cent of his patients with non toxic nodular goiter exceeded this age

There probably still remains some misconception regarding the portion of the goitrous thyroid from which toxicity arises We have been accustomed to speak of the toxic nodular goiter Actually, it appears that the overactivity in nodular goiters with hyperthyroidism usually resides in the paranodular tissue (Hamilton Soley and Eichorn 1940 Cope Rawson and McArthur 1942 1946 Puppel Leblond and Curtis 1947 Means 1948) and that the nodules themselves have a somewhat lowered and at times negligible activity This statement applies to most goiters of both the multi and unimodular varieties There are exceptions however most of which have been found among the unimodular type of goiter (Fig 60)

4 The Hyperfunctioning Single Adenoma of the Thyroid—The strikingly higher incidence of carcinoma in unimodular as contrasted with multinodular goiters raises the obvious question of a difference in their pathogenesis and functional significance While fetal adenomas are found in approximately 8 per cent of diffusely hyperplastic thyroid glands (Cattell 1946) they probably make up a higher percentage of the unimodular glands whether hyperthyroidism is or is not present In view of the recently demonstrated close relationship between the activity of the hypothalamus the anterior hypophysis, and the thyroid and of the primary role usually attributed to the first mentioned in connection

with the development of hyperthyroidism the question of lesions within the thyroid capable of initiating and maintaining a hyperfunctioning state of that gland certainly possesses more than academic interest to the clinician Such lesions while far from frequent have been demonstrated (Cope, Rawson and McArthur 1942 1946 1947 Roullie 1949) They are unimodular probably fetal adenomata which become functionally active and show an autonomy not dissimilar to that seen in physiologically active adenomata of the islands of Langerhans the parathyroids and the adrenal cortex (Figs 27 and 60)

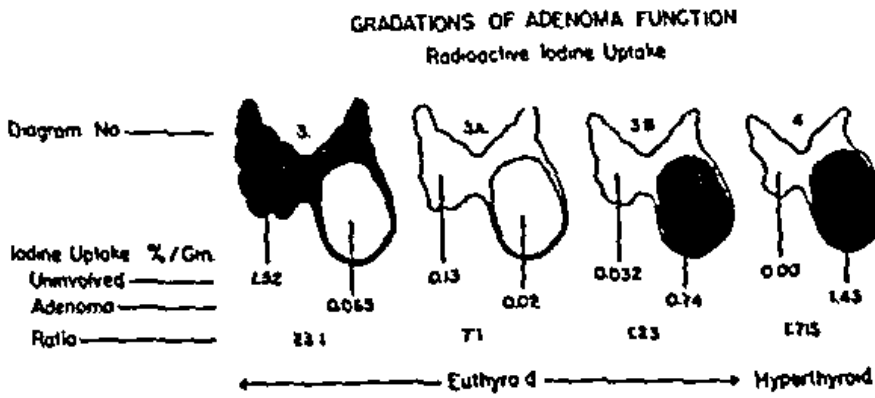


Fig 60—Dissociation of the function of thyroid nodule and the parenodular tissue This figure illustrates the dissociation of the function of thyroid nodules and the surrounding thyroid follicular tissue as indicated by their respective capacities for absorbing and concentrating radioiodine The intensity of the shading indicates the degree of activity of the tissue for iodine The actual uptake of iodine is shown as percent of administered dose per gram of thyroid substance and ratio between the concentration of radioiodine in tissue and nodular tissue The inhibiting effect of the functioning nodule upon the underlying gland is clearly shown and is sufficiently great in some instances (diagram 4) as to cause complete atrophy (After Cope Rawson and McArthur 1947)

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1 An atrophy of disuse occurs in all thyroid tissue outside the nodule this was present in every case and nearly complete in some

2 Exophthalmos was seen once in ten subjects as compared with an incidence of 30 per cent in Graves disease Were the thyroid lesion secondary an excessive amount of thyrotrophin would be formed with a failure of the secondarily stimulated thyroid to inactivate a portion thereof Exophthalmos results when active or reduced forms of thyrotrophin are present in the circulation In the unimodular lesions under discussion the rarity of exophthalmos indicates that normal

amounts of thyrotrophin are readily inactivated by the autonomously overfunctioning nodule

3 The nodule itself has been proved to be functionally overactive because (a) it is similar histologically to the parenchyma of a diffusely hyperplastic toxic thyroid gland (Wegelin's struma nodosa macro and micro follicularе) (b) it is capable of inactivating large amounts of thyrotrophin while there is a complete inability of the surrounding parenchyma to do likewise (c) it takes up 80 to 90 per cent of the tracer dose of radioactive iodine in contrast to the remainder of the gland which picks up little or none (d) like most nodular toxic goiters it responds very poorly to the use of iodine in any dose and (e) after removal there is a postoperative period of hypothyroidism due to the atrophic state of the parenchyma of the remainder of the gland From this the patient usually recovers spontaneously in a matter of several weeks even though a temporary decrease in the basal metabolic rate to – 25 may be seen

While these single well encapsulated functionally active benign adenomata are extremely rare they represent an important link in our understanding of the clinical course which thyrotoxicosis may take At the one extreme is the common type of hyperthyroidism associated with a diffusely hyperplastic gland all of which is functionally active and remains subject to normal physiologic influences such as the secretions from the anterior pituitary At the other is the lesion under consideration which alone is functional and acts like other neoplasms that is without regard for the laws which control the growth or secretory activity of the tissue from which it takes origin In its presence however the remainder of the thyroid continues to be subject to normal physiological control and as a result of the excessive hormone formed by the adenoma enters into a state of rest (Fig 60) Its disorder is secondary and the tissue is not in itself diseased (Cope et al 1947) Because the benign neoplasm acts more or less independently iodine exerts little control over the process and roentgen radiation has not been of much help in controlling toxicity

Treatment—In uninodular goiter the danger of cancer is so great that we believe these should be removed surgically as soon as discovered. Simple enucleation has long since been abandoned in favor of subtotal thyroidectomy The actual amount of thyroid tissue to leave in situ depends upon its functional status which can be judged rather accurately from the appearance of the gland at the time of operation If the nodule holds most of the tissue which is forming thyroid hormone and there is a secondary atrophy of disuse throughout the rest of the gland then very little of the atrophied but potentially normal tissue need be removed If on the other hand the paranodular tissue is hyperplastic and functionally overactive as determined by its appearance at operation and its behavior towards radioactive iodine pre

operatively then it should be attacked more vigorously and as little left as would usually be done in cases of exophthalmic goiter

Multinodular goiters which are causing pressure or have any features suggesting malignancy should be removed promptly There are those who favor the removal of all nodular goiters on the grounds that they *may later become malignant or toxic* We *no longer have need* to fear the toxic nodular goiter as it can be brought promptly and completely under control by the use of an antithyroid compound and then if desirable operated upon without danger The chance that a toxic nodular goiter will become malignant is rather slight and is variously estimated at from 0 1 to 1 9 per cent The incidence of malignancy in the nontoxic type of multinodular goiter is higher but probably not as high as is reported in the literature for many cases of nonmalignant nodular goiter never come to the attention of the physician where as most if not all with cancerous changes are medically observed Soley s (1917) advice in this regard seems to be the best middle of the road course viz to watch at periodic intervals the asymptomatic multinodular enlargement which occurs in a person raised in or living in a goitrous belt one or both of whose parents may also have had a thyroid enlargement He recommends surgery unqualifiedly only in those who present themselves to the physician with complaints relative to the thyroid

The psychological attitude of the patient toward the growth in the neck should also be a factor in our decision regarding operation Mrs A may show great concern and apprehension regarding the lump *For her removal is both good prophylaxis and also excellent psychotherapy* Miss B inquires regarding the thyroid growth at the insistence of relatives or friends and wants only reassurance that it will probably never menace her health Here a course of watchful waiting seems to be advisable in which the physician makes it clear that removal will be recommended should the nature of the lesion or the course of its activity change at any time

There are many who urge the unqualified removal of every nodular goiter coming within their surveillance Anglem and Bradford (1918) advise the removal of all nodular goiters as a prophylactic measure on the basis that the threat of malignancy or toxicity is greater than the risk of surgery Of 655 thyroidectomized patients with nodular goiter they recognized 331 in whom the operation was deemed to be prophylactic Among these there were no deaths and 17 complicating features of minor nature From the group of prophylactic operations they exclude however all patients with pressure symptoms all those with a substernal retrotracheal or intrathoracic extension and all whose goiters were 7 0 cm or more in diameter On the basis of observations in 374 patients with nontoxic nodular goiter Buckwalter Besser and Dubin (1917) take the position that subtotal thyroidectomy causes a

regression in the symptoms of a general nature of which the patient may complain. Within one to five years 59 per cent of the group they had operated upon had relief of manifestations simulating those seen in hyperthyroidism although the basal metabolic rates were and always had been normal. In those who were not subjected to surgery only 8 per cent reported comparable improvement in their general condition in a similar period of time.

It must be emphasized that many of the subjects who demand care for nontoxic multinodular goiter present themselves to the physician at or about the time of the menopause. These people are in a period of glandular adjustment in which more frequently than not at least in *our experience the thyroid disturbance is but one of several factors* demanding correction. All such cases will respond to any attention the physician may give whether on the one hand he uses psychotherapy only or on the other does a subtotal thyroidectomy. The mere fact that something is being done helps to make the discomfort of the period less tedious and more endurable. However it is our impression that those patients do best in whom we are able to appraise *fully all the factors that are poorly adjusted at this particular time*. Thus we bring to bear upon them not one set method of management but a regime which includes attention to the particular disturbances that have resulted in the thyroid condition in each individual. For example the declining function of the ovary may frequently result in overactivity of the thyroid. Thyroidectomy may decrease the production of thyroxin but it falls far short of restoring the individual to her *previously normal status as it does nothing to compensate for* the ovarian deficiency. In still another subject the adrenal may fail to compensate for the flagging activity of the gonad. *It may thus lower the working* level of the thyroid gland (see Thyroid Adrenal Relationship Chapter XIV) to a point where it compensates with a work hypertrophy and hyperplasia that result in nodule formation. Removal of the thyroid is scarcely fundamental even though sometimes necessary treatment. Crile and Dempsey (1919) expressed our feelings rather clearly when they emphasized the fallacy inherent in the recommendation that all *nodular goiters be surgically treated because of the high incidence of* malignancy. The high incidence of carcinomas of the thyroid reported by surgeons is to a large measure dependent on *the fact that the obviously* benign nodules in the thyroid are screened out by the patient or by the internist and are not seen by the surgeon. Until better statistics on the true incidence of carcinoma in adenomas of the thyroid are available it is suggested that indications for removal of nodular goiters be based on clinical judgment rather than on statistical surveys.

In summary we advise unqualifiedly the surgical removal of *all* uninodular goiters. *All* nontoxic nodular goiters *that produce any* local symptoms likewise should be removed by subtotal thyroidectomy.

Asymptomatic multinodular goiters in individuals known to have lived in a goitrous belt usually indicate a fully compensated work hypertrophy and hyperplasia of the thyroid and may be left alone unless their nature or course shows a sudden or definite change If despite a normal basal metabolism *systemic* symptoms occur which may superficially resemble those seen in hyperthyroidism they are usually not primarily of thyroid origin and should not be so treated If on the other hand thyrotoxicosis occurs the management should be that described elsewhere (see Hyperthyroidism Treatment Chapter XXXVIII) It should be pointed out here that thyroidectomy is no longer necessary as a prophylactic against the development of thyrotoxicosis in a patient with nodular goiter as the antithyroid compounds *control* the toxicity as readily in such a subject as they do in an individual whose hyperthyroidism is due to a diffusely hyperplastic gland

Chapter XXXIII

CARCINOMA OF THE THYROID GLAND

INCIDENCE

Carcinoma of the thyroid gland is a relatively rare condition comprising 0.01 per cent of all admissions to a general city hospital (McGavack 1938). During a period of ten years, it represented 2.2 and 6.6 per cent of the admissions for thyroid disease and nodular goiter, respectively (McGavack, 1938). It is difficult to state the exact incidence among goiters of all types but 2.1 per cent appears to be a fair average (Ross 1938). Among malignancies of all varieties and locations it comprises approximately one third of 1 per cent (Schreiner and Murphy 1931). It is relatively as frequent in goitrous (Coller 1929) as in nongoitrous (Clute 1931) belts.

Age and Sex.—While no age is exempt the majority of cases of malignancy of the thyroid gland are discovered between the fifth and seventh decades of life. The average age of patients in a representative series of cases (Pemberton 1939) was 52.8 years for 282 males and 48.1 years for 492 females. A little more than 2.0 per cent of all cases occur in persons under 20 years of age and Pemberton (1939) found four children less than 10 years old among 771 cases of carcinoma of the thyroid observed at the Mayo Clinic over a thirty year period. At the Lahey Clinic 2.3 per cent appeared in those under 11 years of age (Hare 1937). More recently Duffy and Fitzgerald (1950) stated that children under 18 years of age constituted 6.5 per cent of a series of 130 cases of thyroid malignancy. Fowler (1926) studied the incidence of epithelial neoplasms in people under 26 years of age and found cancer of the thyroid gland exceeded in frequency only by cancer of the stomach the colon and the ovary in the order named. It must be concluded therefore that carcinoma of the thyroid gland while usually seen in later life is a condition to be considered in the presence of thyroid tumefaction at any age.

Two thirds to three fourths of all cases of thyroid malignancy occur in females (Smith Pool and Olcott 1934 Holt 1934 Pemberton 1939). Inasmuch as women are from five to seven times as frequently affected with nodular goiter as men it is clear that the relative incidence of malignancies among nodular goiters is actually higher in men. In

deed the presence of nodular goiter in a male is full justification for its surgical removal

Duration of Previous Thyroid Pathology — Nodular goiter is the breeding ground of malignancy (Ward 1917a) Pre existing adenoma or cystadenoma had been present in seven of nine cases for 20 6 5 4 and 3 (two cases) years and 8 months respectively (McGavack 1938) Smith Pool and Olcott (1934) obtained a similar history in 38 of their 54 patients of whom 20 showed a goiter of eight or more years duration 8 of four or more years and 10 of one or more years duration Moreover they state Microscopically an adenomatous origin could definitely be traced in all but four of the 54 individuals ' The evidence is indeed overwhelming for the origin of the majority of thyroid malignancies in pre existing adenomas (Wilson 1921 Clute and Smith 1929 Coller 1929 Crile et al 1932 Shallow et al 1935 Pemberton 1939) but it must be kept in mind that the nodules of malignancy may have been malignant from the beginning (Crile Jr 1950)

CLASSIFICATION AND PATHOLOGY

Any pathological classification of malignancy of the thyroid gland is fraught with difficulties not only because many transitional forms of tumor are seen but also because many of the distinguishing features of malignancy are observed in the normal gland (Smith Pool and Olcott 1934 Portmann 1934 Lahey Hare and Warren 1940) On this basis Graham (1924) found it necessary to discard 108 of 178 cases as not malignant Errors in the opposite direction have also been made Among 97 patients who died of thyroid malignancy or its metastases Wilson (1921) found 23 glands which at the time of the first operation had been passed by the pathologist as being without suspicion of malignancy

Portmann (1934) suggests the importance of the following factors in the development and anatomic structure of the thyroid gland in connection with the different types of malignancy encountered

1 Thyroid tissue consists largely of glandular epithelial cells Hence on the basis of the laws of probability epithelial neoplasms or carcinomas should occur with proportionately greater frequency than the mesothelial neoplasms or sarcomas

2 The character of the concentric and hyperplastic development of the thyroid glandular structure predisposes to the production of localized adenomatous tumors which may undergo many kinds of degenerative changes including malignancy because of their inherent embryonic stimulus to hyperplastic growth

3 The acini of the thyroid have no basement membrane and because their cells lie in close proximity to the vessels they may readily penetrate into the circulating blood and may be quickly distributed to the different parts of the body as metastases

4 The lymphatic distribution and drainage of the thyroid cause the deeper cervical lymph nodes to be involved in certain types of malignant processes fairly

Chapter XXXIII

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Two thirds to three fourths of all cases of thyroid malignancy occur in females (Smith, Pool and Olcott 1934, Holt 1934, Pemberton 1939). Inasmuch as women are from five to seven times as frequently affected with nodular goiter as men it is clear that the relative incidence of malignancies among nodular goiters is actually higher in men. In

of 32 congenital teratomas of the thyroid reported to date. This lesion is usually found in the lateral region of the neck and interferes with delivery. If not stillborn, the infant usually dies of pressure phenomena within a few days. The case of Sutton and Gibbs (1911) was exceptional in that the child evidencing signs of interference with respiration from birth was successfully operated upon at the age of 3 months for a midline tumor the size of a golf ball, the true nature of which was only determined postoperatively.

TABLE XIII

CLASSIFICATION OF THYROID TUMORS

Benign

1. Adenoma
   - a. Embryonal
   - b. Fetal
   - c. Simple
     - (1) Hurthle cell
   - d. Colloid
2. Papillary cystadenoma
   - a. Originating from thyroid
   - b. Originating from aberrant thyroid

Malignant

Group I. Low or potential malignancy

1. Adenoma with blood vessel invasion
2. Papillary cystadenoma with blood vessel invasion
   - a. Originating from thyroid
   - b. Originating from aberrant thyroid

Group II. Moderate malignancy

1. Papillary adenocarcinoma
2. Alveolar adenocarcinoma
3. Hurthle cell adenocarcinoma

Group III. High malignancy

1. Small cell carcinoma (carcinoma simplex)
   - a. Compact type
   - b. *Diffuse type*
2. Giant cell carcinoma
3. Epidermoid carcinoma
4. Fibrosarcoma
5. Lymphoma

Let us consider the malignant tumors seriatim. Ward (1914) believes it is scarcely necessary at the present time for the surgeon or the internist to burden himself with a pathological classification. He points to the fact that papillary tumors, irrespective of their origin in adenomas, aberrant thyroid tissue or the gland proper, show the best prognosis, respond similarly to roentgen radiation and are least subject

early frequently before they can be determined clinically and the abundant intracapsular plexus permits direct extension to adjacent structures particularly to the trachea

The anaplasia heteroplasia mitoses fetal rests and other variations in the histology of the apparently normal thyroid gland make any classification of malignancies of the thyroid inadequate Despite the presence of mesothelial supporting tissue and the frequency with which sarcomas of the gland have been reported (Pemberton 1939 Ewing 1940 Jacobi and Bolker 1942 Hare 1917), it is questionable whether a neoplasm of such origin ever exists Moreover if such a possibility is conceded it is usually histologically impossible to distinguish the lesion from the more anaplastic forms of carcinoma It is therefore rather hesitantly that we include varieties of sarcoma in our classification Very recently Dean (1919) has briefly reviewed the literature in regard to lymphosarcoma of the thyroid and has described two patients with a condition meeting the criteria laid down for reticulum cell lymphosarcoma Perhaps scepticism regarding the existence of conditions arising within the stromal tissues of the thyroid should not exist but the problem of their pathological and histological recognition still remains a very difficult one

Dinsmore Dempsey and Hazard (1919) have based the diagnosis of lymphosarcoma on the massive involvement of the thyroid gland and upon the presence of the lymphocyte or the lymphoblast as the cell of infiltration They have excluded all cases in which the diagnosis was based upon the biopsy of tissue *about* the thyroid believing these may have been the result of infiltration of the gland by lymphosarcoma of a near by structure Eight cases meeting their criteria have been seen at the Cleveland Clinic over a period of twenty two years They recognize the difficulties encountered in distinguishing the lesions from those of undifferentiated carcinoma of the small cell type and struma lymphomatosa

In the present state of our knowledge that classification of thyroid tumors is most suitable which affords the pathologist adequate descriptive terms regarding the nature and degree of malignancy and the clinician information of therapeutic and prognostic value The histological classification of Clute and Warren (1931) and Warren (1941) seems most suitable in these regards and will be used here (Table XIII)

In connection with subiodic and nodular goiters some space has already been devoted to the histologically benign tumors of the thyroid except that no mention has been made of the teratomata Inasmuch as most of the subjects with such a lesion are stillborn—to our knowledge only one has survived more than a few days (Sutton and Gibbs 1911)—little needs to be said about them Pusch and Nelson (1935) collected 43 cases from the literature of which 28 were histologically proved To these should be added their own case and those of Potter (1938) Sutton and Gibbs (1941) and Munro and Waldapfel (1941) making a total

tinctly malignant features Hare (1917) is of the opinion that the cancerous condition of the thyroid found in this group has its origin in a pre existing tumor of the thyroid usually a single adenoma In contrast the remainder of the malignancies with a much shorter history and more fulminant course may arise *de novo* within the thyroid parenchyma

Commonly the metastases which affect bone more often than any other structure will appear as a benign growth or as normal thyroid tissue Even in such cases a careful search of the concomitantly-present thyroid nodule will reveal some evidences of malignancy Less frequently the metastases are histologically malignant

Clinical Course—Symptoms related to the bony metastases usually bring the patient to the physician They resemble those of other bony tumors and more particularly hypernephroma and cancer of the prostate in yielding signs from the metastases before the primary malig nant *focus is found* As in these two conditions there is a predilection for secondary growths to involve the osseous system The frequency with which various bones are involved is in the order named skull vertebræ pelvis clavicle sternum femur ribs humerus scapula and mandible These tumors grow within the bone in an expansile manner eventually eroding the bony cortex and radiographically presenting the picture of an osteolytic sarcoma or giant cell tumor Like the parent thyroid tissue these tumors are richly supplied with blood *and when sufficiently large may be pulsatile A pulsatile sternal* tumor of this nature has been observed at least nine times Emphasis has been placed upon the necessity for differentiation from aortic aneurysm and metastases secondary to hypernephroma (Crile Jr 1936)

In rare instances a bruit may be detected over bony thyroid metastases Furthermore these lesions have been said to enlarge during menstruation or pregnancy and to recede partially after the termination of either of these events Symptoms of hyperthyroidism have been reported which disappear when the metastatic tumor has been removed There is no proved case in which the hyperthyroidism could be directly ascribed to the primary tumor in the thyroid However all metastases may not function equally but if one which is physiologically active is removed a second may increase its activity to meet the demands of the body for thyroid hormone In other instances the removal of an overactive metastasis may be followed by hypothyroidism despite the fact that the thyroid gland itself has not been disturbed thus indicating that the functional level of the metastasis was high enough to suppress the work of the normally placed structure

II Papillary Adenocarcinoma

Incidence—Papillary adenocarcinomata constitute about 15 to 20 per cent of all thyroid malignancies (Smith Pool and Olcott 1931

to recurrence following surgery On this basis he divides the carcinomas of the thyroid into three groups namely papillary carcinomas malignant adenomas and all others thus stressing in descending order the therapeutic responses to be expected and the prognostic categories to be applied These statements serve to emphasize the general plan of the classification offered above which similarly relates the clinical outlook to the pathological picture

I Adenoma and Papillary Cystadenoma With Blood Vessel Invasion

Synonyms and Definitions—"Benign metastasizing goiter," metastasizing normal thyroid tissue malignant adenoma of the thyroid with bony metastases Here have been included conditions in which the tumefaction in the thyroid gland has been clinically benign but has given rise to widespread metastases particularly to bone which resemble normal or adult acinar epithelium both histologically and functionally

Incidence—Simpson (1926) observed three patients each of whom died within three years of the onset of the carcinoma despite the histological benignity of biopsied specimens He collected a total of 77 such cases from the literature Friedman was able to add an additional 28 cases in 1913 plus two of his own and others have been observed since that time (Outerbridge 1917 five cases) They are therefore not as rare as was thought at first Indeed Hare (1917) found that 108 of 240 malignant thyroid tumors that is 45 per cent belonged in this low or potentially malignant group

Two thirds to three fourths of the patients are women The majority note symptoms between 10 and 60 years of age although the enlarged thyroid may have been present for many years

Pathology and Pathogenesis—That both the initial lesion in the thyroid gland and the metastases are malignant seems now generally accepted as earlier believed by Graham (1924) and Clute and Warren (1931) In Cohnheim's case (1876) despite the histological benignity the evidences of malignancy were clear-cut namely bony metastases venous infiltration and nests of epithelial cells Graham (1924) emphasized the difficulties encountered in determining the malignancy of this group of tumors and believed the invasion of blood vessels to be one of the most important signs of malignancy in the thyroid gland His own words emphasize the point Epithelial tumors of the thyroid gland that are encapsulated and show no blood vessel invasion are benign irrespective of their microscopic picture Epithelial tumors that invade the capsule or blood stream are malignant irrespective of the microscopic picture Outerbridge (1917) believes that even though metastases have a benign histological appearance careful search will reveal a primary focus in the thyroid gland that possesses dis

Local invasiveness by way of the walls of the blood vessels is usually observed and involvement of the right side of the heart has been reported (Holt 1934)

IV Adenocarcinoma With Hurthle Cell Change

Hurthle cell tumors are relatively rare lesions of the thyroid and on that basis scarcely justify the amount of discussion which follows However their origin histological appearance and clinical features have raised so many questions regarding the nature and function of various thyroid structures that separate treatment seems warranted

Pathology and Pathogenesis—Clinically Hurthle cell tumors behave like adenomas or adenocarcinomas but represent a histologically characteristic pattern not shared by other thyroid lesions in either of these categories The primary cell is a large polyhedral eosinophilic granular chromatin rich structure 15 to 20 microns in diameter Its nuclei are eccentrically placed contain many threads and clumps of chromatin possess a prominent nucleolus and measure 6 to 8 microns across There is a close resemblance between these cells and similar ones found in the liver and in the adrenal cortex (Langhans 1907) These cells are compactly arranged in small alveoli so that they give to the tissue *a solid appearance The tumor as a whole may be discrete and* well encapsulated or diffuse and invasive

Three distinct theories regarding the origin of the cells making up these tumors have been well summarized in several good reviews (Wilensky and Kaufman 1938 Martin and Elkin 1939 Morrow 1945 Steiner 1948)

1 Hurthle (1894) used the term parafollicular thyroid cell and considered it a normal structural element of the median anlage of the thyroid gland Despite the fact that neoplasms containing this cell bear his name he described only the peculiar cell and never any tumor formation

2 Getzowa (1907) advanced the hypothesis that these cells and the tumors arising from them belong embryologically to the ultimobranchial bodies or lateral anlagen of the thyroid She based this theory on the fact that the individual cells looked very much like those of the parathyroid in one stage of their development

3 Langhans (1907) advanced the hypothesis that these tumors arise from normally or ectopically located parathyroid cells

Irrespective of their origin present concepts (Wilensky and Kaufman 1938 Martin and Elkin 1939) lead to the conclusion that the tumors of this type may be grouped with other adenomas or adenocarcinomas of the thyroid Therefore we speak not of

Pemberton 1939 Hare 1917) The age and sex grouping differ little from those of other carcinomas of the thyroid

Pathology and Pathogenesis—Papillary adenocarcinomas of the thyroid commonly arise from either of the lateral or fourth anlagen The lack of thyroid secreting cells arising from these structures (Marine 1937) probably accounts for the absence of a history of hyperthyroidism in these cases A portion of the pre existing adenoma may sometimes be discernible in sections through these tumors Histologically, we may divide them into two groups those with papillary projections and those with small acini filled with irregularly shaped large cell masses

Clinical Course—Frequently there is a history of a long standing thyroid tumor which has recently begun to grow However the entire course may be asymptomatic and the malignant nature of the condition not be recognized until postmortem examination is performed The malignancy is of grade 1 or grade 2 Metastases occur late usually by way of capsular invasion and lymphatic spread Therefore 70 to 80 per cent of the metastatic lesions are found in the regional lymph nodes About one fifth of the cases develop secondary growths in the lungs while the skull pelvic bones breast and mediastinum are less frequently involved

III Alveolar Adenocarcinoma

Incidence—From 20 to 25 per cent of all thyroid carcinomas are of this type No age is immune but people between the ages of 35 and 50 years are most frequently affected

Pathology and Pathogenesis—These tumors probably arise directly from the parenchyma of the thyroid and rarely from a pre existing adenoma There is therefore a wide range of variation in their microscopic appearance In some there is little to suggest a normal thyroid architecture while in others alveoli are well developed and contain colloid We may see any variant from solid embryonal tumors to the adult alveolar structure showing cystic degeneration with or without calcification and other secondary changes Metastases occur by way of the blood stream and the lymphatics

Clinical Course—Local signs of pressure are usually present Weakness and loss of weight are late general symptoms A history of hyperthyroidism prior to the onset of clinical phenomena has been reported (Speese and Brown 1921 Crile et al 1932 McGavack 1938) A sudden onset and relatively rapid course are characteristic The cervical lymph nodes are secondarily involved in 50 per cent of the cases and the lungs in at least one third

Dinsmore and Hicken 1934 Pemberton 1939 Lahey Hare and Warren 1940 Ewing 1940 Jacobi and Bolker 1942 Hare 1947) That sarcoma of the gland ever exists however seems extremely doubtful (Smith Pool and Olcott 1934 Ewing 1940) It is not too difficult to recognize the epithelial nature of the cells of the compact type while on histological evidence alone *the diffuse type* of lesion may be readily mistaken for Hashimoto's disease Its lack of radiosensitivity is characteristic and aids materially in making a differential diagnosis clinically Indeed only one instance of radiosensitivity has been described in a tumor of the compact type (Haagensen, 1931)

Both types of small round cell carcinoma metastasize early and widely *both by the blood stream and the lymphatics* Any organ or tissue of the body may be involved Most commonly affected in a descending order of frequency are the regional lymph nodes lungs mediastinum spine ribs and axillary nodes

Clinical Course—Small round cell carcinoma is the most rapidly evolving uniformly fatal and therapeutically resistant of the thyroid carcinomata

VI Giant Cell Carcinoma

This is a true histological type of thyroid carcinoma which may or may not arise in pre existing adenoma and which shows a rapid fatal clinical course much like that of small round cell carcinoma *However it usually affects those of an older age group* (55 to 65 years)

VII Epidermoid Carcinoma

Epidermoid carcinoma arises from the epithelium of the thyroglossal duct It probably constitutes 1 to 2 per cent of all thyroid *malignancies Clear cut differentiation from branchiogenic cysts* and from primary laryngeal and esophageal tumors is difficult both clinically and pathologically The condition is usually seen in people over 60 years of age and runs a uniformly fatal course within one to two years

CLINICAL PICTURE

The early recognition of carcinoma of the thyroid gland is extremely difficult It has been suggested that we suspect new growth in the thyroid gland if (1) a nodule appears in a person who has never lived in an area of endemic goiter (2) *there is no goiter in the family* (3) the pressure symptoms and goiter occur simultaneously or nearly so and (4) the goiter shows evidence of increasing in size after a long period of quiescence (Soley 1947 Dailey Soley and Lindsay 1949) Shall we routinely operate upon people who fall into one of the cate

Hurthle cell tumors but of adenomas with Hurthle cell change or adenocarcinomas with Hurthle cell change Such a classification seems all the more logical as these tumors cannot be distinguished clinically from those arising from fetal adenomatous rests (Martin and Elkin, 1939)

Clinical Picture—Twenty four cases of Hurthle cell tumor were collected from the literature and summarized in detail by Morrow in 1915 to which should now be added those of Wilensky and Kaufman (1938) Reimann (1943) Hazard and Ingle (1947) Bakay (1948) and Lennox (1948) More than half of these have proved to be histologically malignant At one time or another at least a third have been associated with hyperthyroidism On physical examination the tumor mass in the neck resembles that of other nodular goiters Most of the tumors have been described in patients between the ages of 30 and 60 although the condition has also been seen in infants (Morrow 1915) The ratio of sex incidence is female to male is 5 to 1 The clinical course and treatment of the lesion are similar to that for other thyroid adenomata both benign and malignant In other words early complete surgical removal should be practiced It is our belief that the prognosis of the malignant Hurthle cell tumor is better than that of other carcinomas of the thyroid Certainly the clinical data and the concept that the oxyphilic cell of the Hurthle cell tumor is a degenerating structure lend support to such a view

V Small Round Cell Carcinoma

Incidence—Approximately 20 to 25 per cent of thyroid carcinomas are of the small round cell type They usually appear after the age of 50 and are almost as frequently seen in men as in women

Pathology and Pathogenesis—The histological appearance of these tumors tends more to confuse than to clarify the question of their origin Two types may be recognized (a) *The compact type which can sometimes be traced to a pre existing fetal adenoma* The small round cells have a tendency to form small acini fetal in appearance which tend to invade the entire gland and its blood vessels (b) *The diffuse type which cannot be traced to a pre existing adenoma* In this type the round cells resemble lymphocytes and show no tendency to form acini However they invade the entire gland and blood vessels as readily and completely as do the growths of the compact type

Histologically the picture may suggest sarcoma Several workers have included sarcoma among the tumors to be found in the thyroid gland (Smith Pool and Olcott 1931 Portmann 1934

degree of malignancy. Their distribution in various tissues of the body is given in Table XIV. *Evidence of metastases may be delayed for* periods up to ten years after the removal of the primary tumor (Horn et al. 1947). It is now well recognized that functionally active metastases occur (Keston et al. 1942; Friedman 1943; Frantz et al. 1944; Leiter et al. 1946; Seidlin et al. 1946; Cope 1947; Smedal and Salzman 1948). The lower the grade of malignancy is the more closely the growth of the metastases simulates that of normal acinar tissue and the greater the tendency for physiological activity. When hyperthyroidism occurs as a result of such lesions it responds as readily to thiouracil (Leiter et al. 1946) or radioactive iodine (Keston et al. 1942; Seidlin et al. 1946) as does the normally situated toxic gland.

TABLE XIV

LOCATION AND FREQUENCY OF METASTASES FROM CARCINOMA OF THE THYROID GLAND

GROUP	NUMBER	PER CENT OF	
		TOTAL	THOSE WITH METASTASES
Total	1,453	100	
Metastases	479	33	100
Metastases to the			
(a) Cervical lymph nodes	319	23	67
(b) Lungs, pleura, and mediastinum	266	18	55
(c) Bones†	128	9	26
(d) Liver	56	4	12
(e) Kidney	30	2	6
(f) Brain	21	1	4
(g) All other‡	46	3	10

Compiled from data of Clute and Smith (1928), Stout (1938), Dunphy and Hellman (1934), Thalhardt (1934), Shallow, Lemon, and Sealy (1938), McCormack (1938), and Pemberton (1939).

†The skull and spine are the most frequent sites.

‡The number in any one location is less than 1 per cent of the total number of cases and less than 3 per cent of those in which metastases were demonstrated. Site includes the breast, axilla, mediastinum, pleura, adrenals, and skin.

THE THYROID AS THE SITE OF SECONDARY CARCINOMA

The thyroid gland is a rare site of metastases from primary malignant foci elsewhere in the body. The infrequency with which such lesions are seen has been ascribed mainly to three things: (1) the rich arterial blood supply inhibiting the lodgment of emboli; (2) the high oxygen and iodine content; and (3) the filtering action of the lungs.

gories stressed by Soley (1917) The frequency with which we should find early cancerous lesions would undoubtedly increase tremendously and our number of cures of this disease would rise accordingly However even with such cure a fair proportion of thyroid carcinomata will probably remain undiagnosed preoperatively As the lesions progress the early asymptomatic stages give way to an increasingly characteristic picture

The patient is usually between the ages of 15 and 65 years There is a relatively rapid enlargement of a goiter which has usually been present for a long time without any apparent alteration in its size, shape or consistency Its surface becomes more irregular and stony hard Simultaneously pressure symptoms appear representing encroachment upon the larynx pharynx hypopharynx or esophagus *Common among these are hoarseness and dyspnea With involvement* of the nerves pain is manifest commonly auricular and postauricular and may precede any other evidence of pressure Fixation to surrounding structures is a very late event Hemoptysis occurs only if there is ulceration of some one of the adjacent mucous membranes In the more slowly growing and less malignant tumors it may be present for as much as two years before its real cause is recognized (Grimes and Bell 1918) Dyspnea may progress to stridor and stridor to choking so that death can occur by asphyxiation if therapy is delayed too long

The old concept that hyperthyroidism and carcinoma never occur in the same individual is fallacious but the association is probably governed by the laws of chance and lacks any cause effect relationship (*Pemberton and Black 1918*) *The actual incidence is small* probably not exceeding 0 1 per cent although reported at 1 per cent by one group of investigators (Cole Majors and Slaughter 1919) In any event the association has been reported by a sufficient number of workers to leave little doubt about its existence (Pemberton 1939 Goetsch 1940a Moore et al 1941 Cole Slaughter and Rossiter 1915 Wood 1917a b Pemberton and Black 1918) It is the present belief that such carcinomata arise in small often microscopic adenomata and not in the diffusely hypertrophied and hyperplastic tissue that has given rise to the hyperthyroidism (*Goetsch 1940a Pemberton and Black* 1918) On the other hand a pre existing adenoma has not been demonstrated *in some cases* In these it has been suggested that the adenoma has been destroyed by the cancerous growth The carcinomas of this origin usually grow slowly exhibit a low grade of malignancy and may have been present before any evidence of hyperthyroidism appeared

As a general rule metastases occur relatively late in the course of thyroid carcinoma although enlargement of the Delphian node may be an early useful clinical sign (Cope Dobyns Hamlin and Hopkirk 1949) The rapidity of appearance of metastases varies *directly* with the

degree of malignancy Their distribution in various tissues of the body is given in Table XIV Evidence of metastases may be delayed for periods up to ten years after the removal of the primary tumor (Horn et al 1947) It is now well recognized that functionally active metastases occur (Keston et al 1942 Friedman 1943 Krantz et al 1944 Leiter et al 1946 Seidlin et al 1946 Cope 1947 Smedal and Salzman 1948) The lower the grade of malignancy is the more closely the growth of the metastases simulates that of normal adult tissue and the greater the tendency for physiological activity When hyperthyroidism occurs as a result of such lesions it responds as readily to thiouracil (Leiter et al 1946) or radioactive iodine (Keston et al 1942 Seidlin et al 1946) as does the normally situated toxic gland

TABLE XIV

LOCATION AND FREQUENCY OF METASTASES FROM CARCINOMA OF THE THYROID GLAND

GROUP	NUMBER	PER CENT OF	
		TOTAL	THOSE WITH METASTASES
Total	1 453	100	
Metastases	479	33	100
Metastases to the			
(a) Cervical lymph nodes	319	23	67
(b) Lungs pleura and mediastinum	266	18	55
(c) Bones†	128	9	26
(d) Liver	56	4	12
(e) Kidney	30	2	6
(f) Brain	21	1	4
(g) All other‡	46	3	10

Compiled from the data of Clute and Smith (1928) Stout (1939) Dinsmore and Hiken (1944) Fishardt (1944) Shallow Lemmon and Sealy (1945) McGuack (1948) and Pemberton (1949)

†The skull and spine are the most frequent sites

‡The number in any one location is less than that of the total number of cases and in more than 3 per cent of those in whom search was made it included the base axillary rim pleura trachea pancreas pituitary gland

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Not less than 125 instances of metastases in the thyroid are on record (Willis 1931 Mayo and Schlicke 1911, McKnight 1916 Linton et al 1916 Boys 1917 Denton and McClintock 1919) and it is quite likely this number would be increased were the thyroid carefully examined at every autopsy Hypernephromata (Linton et al 1916 Boys 1917 Denton and McClintock 1919) gonadal malignant tumors (Pusch and Nelson 1935 Rawin 1937 Livingston 1939 McKnight 1916) and malignancies of the large bowel (Rankin and Fortune 1936 Mayo and Schlicke 1911) are among the primary sites most frequently responsible for secondary thyroid growths In some of these the thyroid was noticeably enlarged, and, in several instances was operated upon as the seat of primary pathology Those cases in which a goiter can be recognized clinically hold most interest for the clinician as he must always consider the possibility of a metastatic lesion in patients who have been previously operated upon for a malignant growth

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In the advanced or moderately advanced case of malignancy of the thyroid gland the diagnosis should offer little difficulty as some or all of the following will be apparent (1) recent enlargement of a pre existing goiter or a suddenly appearing goiter (2) pressure phenomena especially dyspnea or dysphagia (3) hoarseness, (4) hardness and nodularity of the goiter and (5) loss of mobility of the thyroid enlargement We have already stressed the points which should make us suspect cancer of the thyroid early goiter appearing in a person not living in an area of endemicity, absence of a history of goiter in the family evidences of pressure or pain occurring simultaneously with the appearance of the thyroid enlargement and sudden growth in a previously quiescent nodular gland

The uptake and excretion of radioactive iodine may lead one to suspect and later find functioning metastases (Chapter XVI) but other laboratory procedures—even the sedimentation rate—may prove to have little or no value early Biopsy which is certainly inferior to surgical intervention may fail to demonstrate early the cancerous tissue which is later proved to be present

Features of the differential diagnosis have been discussed in the sections on Thyroiditis (Chapter XXVI) Subiodic Goiter (Chapter XXVIII) and Nodular Goiter (Chapter XXXII) Some further comments, however may be applicable

If the lesion is of the "benign metastasizing" type, then confusion will arise with

(a) *Hypernephroma* In this condition as in benign metastasizing goiter the bony lesions may produce symptoms before the seat of the primary focus is suspected Indeed metastasis to the thyroid gland

has been operated upon in the belief that a primary thyroid lesion existed (McKnight 1946) However as a rule some manifestations of urinary dysfunction—dysuria or hematuria—will be present In the later stages the pulsatile nature of the bony metastasis from a thyroid cancer may be diagnostic In hypernephroma the sedimentation rate is usually elevated a secondary anemia of considerable degree may be present and evidences of malignant cachexia appear earlier than in the confusing goitrous state

(b) *Prostatic carcinoma* Bony lesions which may be indistinguishable from those of benign metastasizing goiter except that they are neither pulsatile nor as rapidly eroding may bring the patient to the physician in the absence of symptoms or signs pointing to the prostatic condition Discovery of an elevated serum acid phosphatase may be the only finding which leads to the correct diagnosis

If the degree of malignancy is greater than that seen in "benign metastasizing goiter," then attention is usually focused upon the local condition in the neck and the differential diagnosis involves all the tumefactions which may occur in that area

(a) *Midline tumors* which include aberrant thyroid glands and thyroglossal cysts will rarely be confused with cancer of the thyroid as the latter seldom occupies a midline position

(b) *Lipomas* may appear in any portion of the neck but their mobility smooth discrete contour and soft consistency should preclude any diagnostic difficulty

(c) *Lateral tumors* of the neck may offer considerable difficulty in their differentiation and quite frequently the true nature of the lesion will not be recognized until the pathologist's report is at hand However tumors arising in the thyroid gland proper will rise and fall during deglutition This physical sign is not shared by any other lesion in the neck with the exception of fibroma of the esophagus which is however a very rare condition and much more deeply situated Lateral aberrant thyroid tumors may be single or multiple benign or malignant and usually lie in close relationship to the sternocleidomastoid muscle It is often impossible to distinguish them clinically from the tumefactions of Hodgkin's disease lymphosarcoma branchial cysts tuberculous lymph nodes dermoid cysts carotid body tumors parathyroid tumors or neurofibromas Some of the hints useful in differentiating these various lesions have already been given (Chapter XXVI Chapter XXVIII Chapter XXXII) It should be re emphasized here that a preoperative diagnosis of thyroid cancer can never be made with certainty particularly early when there is most to be gained by surgical removal

PROGNOSIS

An inordinately long survival of the patient with apparently dormant malignant tissue is probably more frequently seen in cancer of the thyroid than in any other type of malignancy" (Wood 1917a). The prognosis varies as the histological type of the lesion and the stage of development at the time treatment is instituted. In relation to these two factors Cattell (1916) found that the probability of cure varied from 17 per cent in the most severe forms to 80 per cent in the least malignant.

The papilliferous types of tumor offer the best prognosis, of Horns (Horn et al. 1917) patients in these groups 60 per cent were alive and well at the end of ten years. The same workers observed that of those cases in which the true nature of the thyroid lesion was discovered only after histological examination 75 per cent were still alive ten years later.

In the presence of recognizable metastases the prognosis becomes less favorable although very prolonged periods of survival have been described.

TREATMENT

The problem of treating cancer of the thyroid is inseparably linked with the management of nodular goiters.

a **Prophylactic Treatment**.—Three types of nodular goiter should be surgically treated as soon as they are recognized: (1) solitary or unimodular goiters, (2) all nodular goiters in the male, and (3) nodular goiters in children under 15 years old. From 12 to 21 per cent of unimodular goiters have been reported to become malignant. Wood (1917b) observed that cancer appeared in approximately 17 per cent of the men he had encountered with any type of nodular goiter. In a study of nodular goiter in children living in an endemic goitrous district Kennedy (1940) demonstrated malignant degeneration in 19 per cent. The incidence of cancer in these three types of nodular goiter seems reason enough for their removal prophylactically.

The type of operation for nodular goiter becomes important in preventing malignancy. Simple enucleation of the nodules as formerly practiced is inadequate as small focal potentially malignant areas may be thus overlooked. Subtotal thyroidectomy should be employed in all operations upon nodular goiters that are removed prophylactically.

b **Active Treatment**.—

1. *Surgery*.—In the presence of clinically demonstrable malignancy not only complete thyroidectomy but also block dissection of the tissues of the neck on the homolateral side may be indicated. The actual procedure in any given case will depend upon the local conditions found and the presence or absence of demonstrable metastases (see Section IV on surgery of the thyroid).

Roentgen Radiation.—It is difficult to evaluate fully the use of
ntgen radiation in the treatment of thyroid malignancy as the sur
l time in cancer of the thyroid particularly of the papilliform types
nite prolonged, irrespective of therapy Moreover roentgen radia
has seldom been employed alone but usually in conjunction with
gical procedure

The papillary types of tumor respond best to the roentgen ray while
undifferentiated small round cell carcinomas and the epidermoid
ons are almost completely radioresistant

It seems wise to employ roentgen radiation in all patients in whom
re is doubt about the complete removal of all malignant tissue The
lly recurrent nodules do not respond well to x ray and are probably
approached by secondary operations Graham (1937) has shown
these nodules are tumor thrombi in the proximal venous stump
y resist irradiation because of the surrounding venous capsule and
ause they are usually not papilliferous

In view of the unpleasant symptoms which may attend the use of
ntgen radiation it is probably best not to use it in those instances
which the malignant lesion is well circumscribed within the capsule
he adenoma from which it originates

Radioactive Iodine.—This form of therapy is only adaptable
he cases in which the cancerous tissue is capable of picking up iodine
other words the cells of the lesion must be functionally active Early
eriences with tracer doses of radioiodine failed to show any ap
reciable collection of iodine by the tumor growth (Hamilton Soley
Trichorn 1940) It is now clear that in general the primary growth
he thyroid is less functionally active than its metastases Further
re the lower the grade of malignancy the better the pickup of iodine
consequently the more effective the radioiodine Metastases of
nign metastasizing goiter have been completely controlled by its
and the more radioresistant but functionally active adenocar
oma is have been held in check by repeated doses (Seidlin Marinelli
Oshry 1946 Frantz Larsen and Jaretzki 1950 Kour and Peterson
0) In the past many of the metastases have been relatively in
ssible to external radiation When behaving functionally like the
mal thyroid cell they can now be reached by radioiodine sometimes
sufficient quantity to accomplish their complete destruction Hy
hyroidism may follow the use of relatively large doses of radioiodine
ployed for this purpose Further details of diagnosis and therapy
h radioactive iodine have been discussed in Chapter XVII

PROGNOSIS

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disease Parry's disease Flajani's disease primary hyperplastic goiter) with or without exophthalmos (2) *Plummer's disease (toxic adenoma* adenomatous goiter with hyperfunction toxic nodular goiter) (3) mixed forms intermediate between groups *1* and *2* and (4) thyrotoxicosis arising in the course of thyroiditis

The names and the synonyms used above are to some extent self explanatory As a rule eponyms are undesirable Toxic hyperplasia might be a satisfactory pathological synonym for Graves disease but such a change is also seen in so called adenomatous goiter Exophthalmic goiter is a good descriptive term but exophthalmos may or may not be present in Graves' disease the incidence varying remarkably with the geographical location For instance approximately 10 per cent of all cases of Graves disease on the west coast of the United States show exophthalmos while a majority of those in the eastern United States present this sign and in certain parts of Europe it is rare to see the disease without it

To use the term toxic adenoma instead of Plummer's disease is to imply that this condition always arises in true neoplastic tissue In actuality the origin of the condition is the same as for nodular goiter that is so called toxic adenomas may arise from pre existing simple goiters pre existing Graves disease fetal adenomas thyroiditis and so forth

Most authorities accept the fact that fetal adenomas make up 5 per cent of all nodular goiters There is however grave doubt as to whether or not true embryonic rests of an adenomatous type arise from the median anlage of the thyroid gland (Graham 1941) Graham's belief is that all adenomas take origin from the fully developed so called adult type of follicular epithelium in a manner identical with the development of neoplasms in other secretory organs By inference carcinomas arising from embryonic thyroglossal duct rests and papillary adenocarcinomas of the lateral anlage of the gland are excluded from this concept

Inasmuch as there are many intermediate forms which fall neither conclusively into the Graves or the Plummer's type of hyperthyroidism intermediate forms must be recognized However, because the management and prognosis of these two forms of hyperthyroidism are to some extent different it is well for the clinician to make the distinction wherever possible even though the two syndromes probably are varying phases or stages of the same condition

At this point a few comparisons between Graves and Plummer's types may help to distinguish them moreover further discussion will then apply equally to both except where otherwise specifically noted Toxic symptoms in patients with Plummer's syndrome usually appear a number of years after the nodular goiter has been noticed In the majority of instances of Graves disease thyrotoxic manifestations may

Chapter XXXIV

HYPERTHYROIDISM I DEFINITION, CLASSIFICATION, AND PATHOLOGY

Synonyms —Toxic goiter thyrotoxicosis

Definitions and Classification —*The term hyperthyroidism is used* here to indicate overactivity of the thyroid gland or perhaps more correctly an abnormal increase in the secretion of thyroid hormone It therefore includes all the conditions in which this may occur Neither this nor any other word covers completely all the features that must be included For example the term hyperthyroidism is certainly incorrect if some of the toxic symptoms are due not to an oversecretion but to a qualitative change in the thyroid hormone In such a case thyrotoxicosis might be a better term However there is no conclusive evidence that any of the toxic conditions arising secondary to disease of the thyroid gland are due to a qualitative change in the hormone of the thyroid On the contrary *it has been possible to reduplicate experimentally* in the human being every clinical manifestation of thyrotoxicosis by the use of excessive doses of the normally formed thyroid hormone (Rogers *1917* Skrause and Riggs *1918*) We realize that there is greatest divergence of opinion regarding so called cardiotoxic goiter and its origin In such cases the thyrotoxicosis manifests itself almost entirely through symptoms related to the cardiovascular system Even here we are strongly inclined to agree with Thompson (1943) and with Lahey and his associates (1943) all of whom emphasize that the cardiotoxic type of goiter represents the response of a peculiar or particular constitution to excessive amounts of thyroid hormone rather than a condition arising from some specific factor within the thyroid gland Raab (1945) relates these findings to an interplay between the adrenal cortex and the thyroid and thus lays the basis for a glandular diathesis Indeed one of the fundamental postulates concerning the origin of thyrotoxicosis envisages a peculiar type of psychosomatic background There seems to be therefore no sound reason for assuming that the toxic symptoms *must represent* an alteration of qualitative type in the activity of the thyroid gland on the contrary there is a wealth of evidence to show that the changes are quantitative only

As above *indicated the term hyperthyroidism* will include (1) Graves' disease (exophthalmic goiter toxic hyperplasia Basedow s

The familial tendency may represent (a) damage to the child in utero because of a thyroid disturbance in the mother (b) environmental conditions particularly mineral deficiencies (iodine) and excesses (calcium) and goitrogenic foods (rutabaga cabbage carrots peanuts peaches and so forth) (c) hereditary factors of a recessive type (Bartels 1941 Martin 1945) or (d) a constitution in which the thyroid function is disturbed through emotional upsets or psychic trauma (Rundle 1941 Means 1944) of insufficient intensity to cause a reaction in the normal subject However the stigmata of this constitutional diathesis are not very sharply delineated For instance they do not occur in a peculiar type of body build for we see the disease in all patterns of bodily configuration even in the obese short stocky well extroverted individual

Juvenile Hyperthyroidism —Probably less than 3 per cent of all cases of exophthalmic goiter occur in children under 16 years of age Seven of 373 patients observed by Olesen and Schiødt (1948) were under 15 years of age The condition is extremely rare before the age of 5 years but is not unknown in the newborn (White 1912 Sweet 1928 Bram 1933 Elliott 1935 Schwartz 1945 Margetts 1950) Most of the cases in children have been observed between the twelfth and fourteenth years of life Clinically juvenile hyperthyroidism resembles the adult type It is easy however to overlook the early stages as the nervousness and hyperirritability are frequently mistaken for a normal pattern of childish behavior

Methods of handling thyrotoxicosis in the child have been widely debated *Prior to the advent of goitrogenic or antithyrotoxic drugs* surgery offered the only real solution Today it is probably better to control the toxic state medically while simultaneously correcting any underlying factors clearly playing a causative or accessory role in the production of the hyperthyroidism If the goiter is nodular operation should be performed as soon as the child is properly prepared

Pathogenesis —The bulk of available evidence confirms the accuracy of the conclusions drawn by Means (1943 1944 1949) by Rawson and his associates (1943) and by Heinbecker (1949) relative to the pathogenesis of toxic goiter This concept has been inferred in our exposition of the physiology of the thyroid gland and is schematically illustrated in Fig 5 It appears that a neurohormonal mechanism is involved in which nervous impulses of markedly increased frequency and intensity pass by way of the hypothalamus to stimulate the anterior pituitary gland to an increased output of thyrotrophic or thyroid stimulating hormone Thus the activity of the thyroid cells is augmented with an overproduction and release of thyroid hormone The excess of thyroid hormone sets up characteristic secondary effects throughout the body However the suppressive effect of thyroid hormone upon the production of thyro

precede any noticeable enlargement of the gland The onset is rapid and fulminant in the latter condition and slow and insidious in the former The goiter of toxic adenoma is nodular and asymmetrical while in Graves disease the thyroid usually appears as a diffuse symmetrical tumefaction commonly associated with thrill and bruit Changes in the eyes are rarely present in toxic adenoma but are common in the diffuse type of hyperplastic goiter Graves' disease affects younger people predominantly those in the third and fourth decades of life while patients with Plummer's syndrome are more often attacked in the fourth and fifth decades In both conditions the sex incidence is the same In classical exophthalmic goiter or Graves disease the hyperthyroidism is associated with a diffuse hyperplasia of the gland and in toxic nodular goiter with a frankly roughened irregular thyroid gland in which adenomatous changes have taken place

Distribution and Incidence —As no race is exempt hyperthyroidism is seen in all parts of the world it occurs most frequently in areas of endemic goiter There are no extensive studies of the actual incidence or relative severity of thyrotoxicosis in different races However the disease as occurring in southern Negroes is at least twice as severe as the condition among the white people of the same region (Boyce 1910 Mayes and Romano 1940) Variations in distribution between the sexes are striking when goitrous areas are compared with nongoitrous districts In the latter the ratio of female to male varies from 10 1 to 70 1 whereas in goitrous districts the number of affected males increases and in areas of greatest endemicity the ratio approaches unity

Graves' disease usually produces symptoms in the third and fourth decades and toxic adenoma in the fourth and fifth decades of life although no age is spared (Olesen and Schiødt 1918 Seed and Lindsay 1919) In general the younger the individual at the age of onset the greater tendency there is toward the exophthalmic type

A familial tendency to hyperthyroidism has been shown We have observed one family reported by Eckes Glasser and Mersheimer (1943) in which six instances of goiter three of which were thyrotoxic occurred in a single family More recently Jackson (1919) reported 12 instances of goiter in a family neither raised nor living in an endemic goiter belt five of which were associated with hyperthyrodism Rundle (1941) was able to find a familial history of Graves disease in more than 20 per cent of his patients Moolten and Bruger (1942) have made a comprehensive survey of the subject of juvenile hyperthyroidism They doubt that the correct incidence of a familial history can be obtained from existing data but their analysis of the literature indicates that Atkinson's (1939) figure 18 8 per cent is too low Reports of hyperthyroidism in similar (Neff 1932 Fife 1940) and dissimilar (Bowers 1918) twins are on record

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trophic hormone by the anterior pituitary is not sufficient to cope with and neutralize the vigorous nervous stimulation received from the hypothalamus The net result is a maintained overactivity of the thyroid gland with the development of a diffuse toxic goiter of the Graves type

The concept above mentioned can certainly account for the majority of cases of thyrotoxicosis of the exophthalmic type and for most of those of the so called nodular type However it leaves unexplained cases like that reported by Spence (1947) in which Graves disease developed in a 23 year old woman with pituitary infantilism In such a case one has to assume that *thyrotrophic activity of the pituitary* was preserved or that the presence of factors other than those in the pituitary were capable of precipitating the overactivity of the thyroid For instance it is well known that both the adrenal and the gonad affect thyroid activity It must also be recalled that the thyroid is capable of a certain degree of autonomous action when completely released from pituitary control There is one type of thyrotoxicosis in which this autonomy is complete namely the hyperfunctioning single adenoma the behavior of which has been so fully analyzed by Cope and his associates (1947) However with the exception of these relatively rare conditions it seems fair to say that thyrotoxicosis of the Graves variety is precipitated by an imbalance or a maladjustment of a mechanism in which the hypothalamus the pituitary and the thyroid are reciprocally involved

Such bandying of words does not however suggest just why the pituitary is bombarded by an excess of impulses from the hypothalamus As a general rule we have ascribed these to emotional or psychic disturbances or in a loose way to nervous tension Thus far we have rarely found Graves' disease without a concomitant history compatible *with such a concept However other factors must* also be important for were nervous tension the sole predisposing factor then the countries torn by war or threats of war should have been found to have a markedly increased incidence of hyperthyroidism That this was not the case in World War *II* is attested by *the analysis of data gathered* in Finland (Bistrom 1948) and in Belgium (Basteme 1947) which in both instances not only failed to show an increase in the incidence of Graves disease but actually revealed a decrease for the war years Both of the workers quoted suggested the possible role of *altered diet* While Meulengracht (1945) found an increase in hyperthyroidism in Denmark between 1932 and 1942 he felt that this was in no way related to the stress of war for two reasons it was already well under way before the war began and no similar increase occurred between *1914 and 1918* when conditions were equally bad He suggests the epidemic nature of the increase and feels that some as yet unrecognized infectious agent may be capable of upsetting the regulatory mechanisms by which thyroid function is normally controlled

In summary Graves disease is usually precipitated by some disturbance in the normal regulation of thyroid activity, commonly through an increase in hypothalamic activity with secondary overstimulation of the anterior pituitary gland A smaller number of cases are due to the unbridled activity of the thyroid or a portion of the thyroid which begins to act autonomously Emotional stress psychic trauma infection and constitutional inferiority are among the conditions which may produce hyperthyroidism by unbalancing normal physiological processes

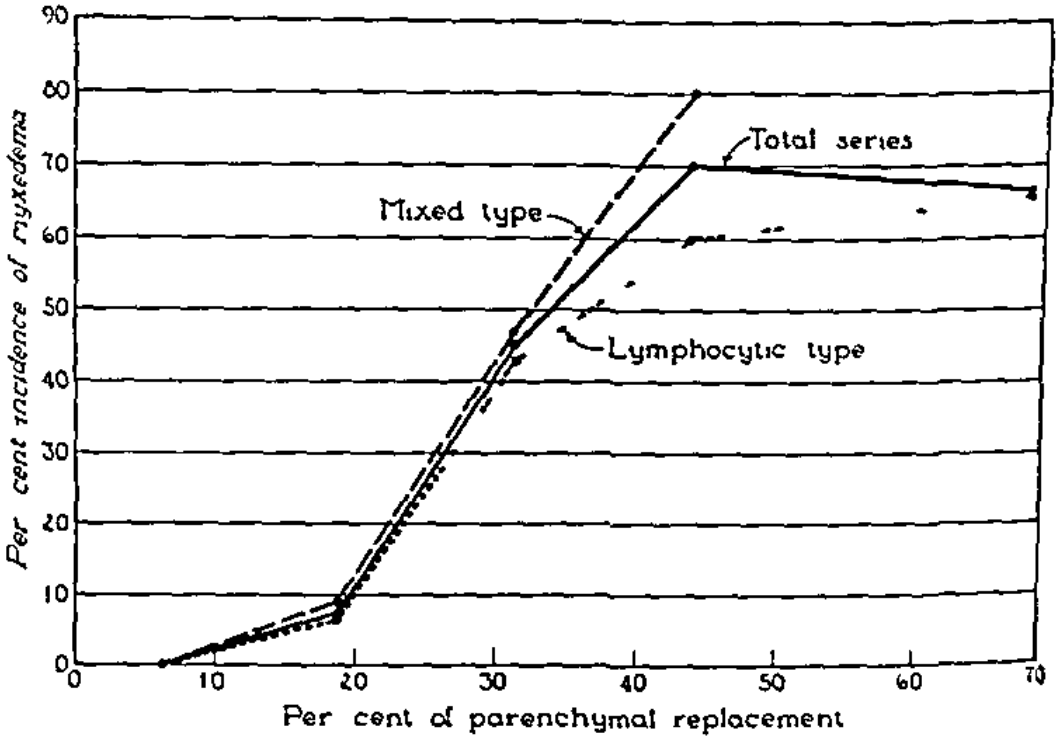
Pathology and Pathological Physiology —The thyroid hormone acts upon every organ and tissue in the body Therefore pathological alterations in hyperthyroidism are widely distributed and may best be discussed by considering changes in the various tissues seriatim

a Thyroid Gland—Secondary to hyperthyroidism there is no pathognomonic pathological picture in the thyroid gland The gland may be of any size and of any shape Indeed too often the physician is misled by a gland of normal size and contour It should be emphasized that this is not an infrequent occurrence one worker having observed a normal or small gland at operation in 8 1 per cent of all thyroidectomies for hyperthyroidism (Foss 1918)

While nearly every type of histological variation may be present in the gland which is toxic identical changes can also be demonstrated in completely nontoxic thyroids (Graham 1911) Hypertrophy and hyperplasia are the earliest commonest and undoubtedly the most fundamental of the cellular mutations produced by thyrotoxicosis It is believed that hypertrophy and hyperplasia constitute a direct and proportionate index to the degree of the depletion of stored iodine within the gland (Graham 1911) These processes will therefore be observed not only in hyperthyroidism but also in any condition such as cretinism endemic goiter and hypothyroidism in which there is an interference with the storage and release of organic iodine

Following the initial hypertrophy and hyperplasia seen in exophthalmic goiter there appear both lymphocytic and fibrous tissue replacement of the parenchyma These vary considerably in degree from patient to patient but are rarely entirely absent The recent study of Whitesell and Black (1949) has lent added significance to their presence These workers selected 86 of approximately 600 thyroids removed for thyrotoxicosis in an effort to correlate the degree of fibrocytic and lymphocytic replacement with the clinical picture observed before and after operative therapy They divided their cases into two groups (1) those with a lymphocytic replacement only and (2) those with a mixed lymphocytic and fibrocytic deposition of tissue The magnitude of the changes in all of these patients prompted these observers to make a pathological diagnosis of exophthalmic goiter with thyroiditis In the glands studied from 6 to 70 per cent of the parenchyma was replaced by the lymphocytes or lymphocytes and fibrous tissue

Some important correlations were developed by Whitesell and Black between the pathological findings and the clinical course of the condition The patients with the mixed or fibrolymphocytic reaction were older than those exhibiting the lymphocytic response only In corresponding age groups the glands of women showed greater replacement than those of men The greater the degree of infiltration was the lower the incidence of auricular fibrillation the more depressed the basal metabolic rate the greater the tendency to postoperative myxedema and the more marked and progressive the exophthalmos



Postoperative incidence of myxedema in exophthalmic goiter as related to the type and degree of parenchymal replacement by lymphocytes and fibrous tissue Mixed type is meant the group in which lymphocytic infiltration and fibrous tissue reaction were both prominent (After Whitesell and Black 1919)

In the accompanying chart is shown the incidence of postoperative myxedema in relation to the type and degree of replacement It will be noted that the mixed type of lesion was associated with a higher incidence of myxedema in relation to the amount of thyroid tissue lost Approximately 80 per cent of the subjects with a mixed lesion developed postoperative myxedema when 40 per cent or more of the parenchyma was involved while under similar conditions approximately 60 per cent of the lymphocytic type became hypothyroid following surgical procedure In passing it may be well to emphasize that the types of pathological change noted in the chart are present albeit in a lesser degree, in a majority of all cases of exophthalmic goiter

In hyperthyroidism there is enlargement and elongation of the thyroid cell with an increase in its use of iodine and in its production of colloid all resulting in a diffuse uniform enlargement of the gland There is a tendency for spontaneous remissions and intermissions each of which leaves in its wake some residual pathology already discussed in the comments on nodular goiter If repeated sufficiently often such episodes give rise at first to mixed types of thyrotoxicosis in which hyperplastic and adenomatous changes exist side by side Finally a predominantly nodular toxic goiter is apparent

If the work hypertrophy and hyperplasia continue for a sufficiently long time eventually a state of exhaustion occurs There ieini atrophy Then lining cells lose all normal cytological characteristics and appear waxy hyperchromatic and pyknotic (Graham 1941) The parenchyma of the gland is partially replaced by fibrous tissue proliferation

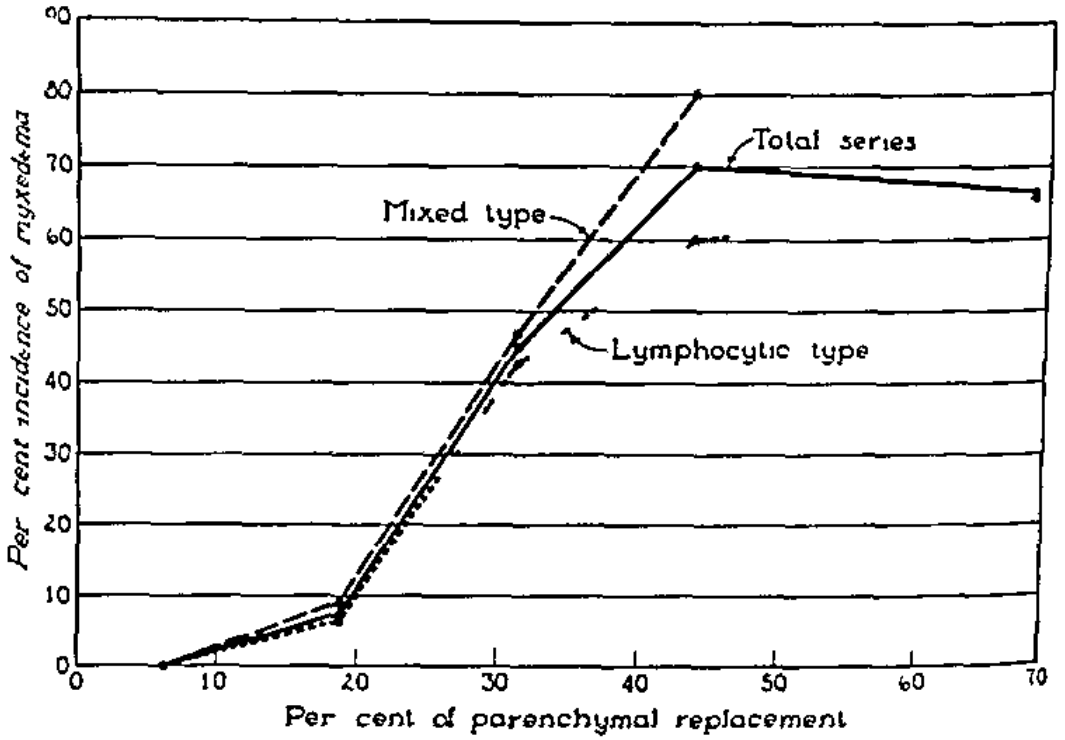
The nature and extent of these histological changes vary directly with the functional state eventually attained If the majority of the gland is replaced by fibrous tissue hypothyroidism may supervene If the damage is not so widespread and leaves a *functionally* normal gland then it may be inferred that the hyperthyroidism has receded spontaneously If on the other hand the *histology* of the gland is not restored to normal as the hyperthyroidism disappears then the cycle of hypertrophy hyperplasia and involution produces a colloid goiter of a fully compensated type Such a sequence of events has been compared with that occurring when the virginal breast goes through the changes incident to childbearing Both before and after such an event the structure of the mammae is physiological but the anatomy is different So it is with the thyroid before and after the ordeal of physiological strain in which hypertrophy hyperplasia and involution follow one another in orderly fashion

Graham (1941) believes that the development of adenomas is more closely related to the proliferative phase of goiter than to its involutional phase thus adenomas of the thyroid gland arise as in other glandular tissues and behave in a similar manner There is little doubt that in many instances some of the adenomatous cells retain a thyroidal function and undergo qualitative cyclical changes similar to those in the normal portions of the gland

Whether adenomas are toxic or nontoxic is not apparent from their anatomical appearance They are subject to all the degenerative processes mentioned under Nodular Goiter (Chapter XXXII) and are the breeding ground for a majority of the carcinomas of the thyroid gland

b Pituitary—The pituitary is hyperactive in hyperthyroidism although it has not been easy to demonstrate gross anatomical changes in that structure (Holst 1935 Means 1937) Hyperemia has been found in patients dying of exophthalmic goiter (Hamig 1897 Pettaval

Some important correlations were developed by Whitesell and Black between the pathological findings and the clinical course of the condition. The patients with the mixed or fibrolymphocytic reaction were older than those exhibiting the lymphocytic response only. In corresponding age groups the glands of women showed greater replacement than those of men. The greater the degree of infiltration was the lower the incidence of muscular fibrillation, the more depressed the basal metabolic rate, the greater the tendency to postoperative myxedema, and the more marked and progressive the exophthalmos.



Postoperative incidence of myxedema in exophthalmic goiter as related to the type and degree of parenchymal replacement by lymphocytes and fibrous tissue. By mixed type is meant the group in which lymphocytic infiltration and fibrous tissue are both prominent features. (After Whitesell and Black, 1943.)

In the accompanying chart is shown the incidence of postoperative *myxedema in relation to the type and degree of replacement*. It will be noted that the mixed type of lesion was associated with a higher incidence of myxedema in relation to the amount of thyroid tissue lost. Approximately 80 per cent of the subjects with a mixed lesion developed postoperative myxedema when 10 per cent or more of the parenchyma was involved, while under similar conditions approximately 60 per cent of the lymphocytic type became hypothyroid following surgical procedure. In passing it may be well to emphasize that the types of pathological change noted in the chart are present, albeit in a lesser degree, in a majority of all cases of exophthalmic goiter.

e Spleen—In at least one third of the cases of exophthalmic goiter the spleen is moderately enlarged weights of 150 to 250 grams having been commonly reported

f Adrenal—That the activity of the adrenal cortex and medulla and the function of the thyroid are closely allied, there is no doubt (Chapter XIV) There is a mass of conflicting clinical and experimental data however in relation to the anatomical changes which take place in the adrenal as a result of hyperthyroidism Small normal and large adrenals have been described in patients dying of hyperthyroidism The functional zones particularly the glomerulosa have been mentioned as enlarged and widened or atrophied and narrow The interpretation of these and many other similar statements in the literature demands our study of adrenal activity in direct relationship to two distinct phases of hyperthyroidism

(Hyperthyroidism may exist for long periods of time even at high intensity in a compensated phase without impairing the general health The appetite remains good no weight is lost muscular strength is not strikingly diminished and fatigability is mild hyperkinesis in thought and action is predominant Under such conditions the process within the adrenal cortex will be mainly one of hypertrophy and hyperplasia *in which a thickening and hyperactivity of the zona glomerulosa* occur with an increase in its lipoid content

(When the general health becomes impaired in hyperthyroidism the patient may be said to be in a decompensated phase) When this happens excessive appetite gives way to anorexia sometimes of severe degree (Loss of weight is rapid and extreme Hepatic function may be impaired) Fatigue and loss of muscular strength become prominent symptoms of incapacitating magnitude Finally exhaustion of the adrenal cortex may take place with associated signs of adrenal insufficiency and in rare instances readily recognized Addison's disease appears

'From a study of the Wilder chloride depletion test in 40 hyperthyroid patients Bartels and his associates (1940) came to the conclusion that underfunction of the adrenal cortex plays no causative role in the production of thyrotoxicosis) They were equally convinced however that hyperthyroidism places a strain upon that structure eventually damaging its secretory capacity and accounting for the increased *urinary excretion of chlorides* While *they never considered these* alterations in the function of the adrenal gland sufficient to play any important role in directing the trend of therapy other workers (Richardson 1939) have observed striking improvement following the administration of adrenal cortical extract a fact which we have repeatedly corroborated) The advent of hyperthyroidism has been found to aggravate a potential or already existing state of hypocorticoadrenalism (Gitman et al 1943 Perera and Parker 1943 Moehlig 1943) The

1812, Khrustleff 1913 Rautmann 1921) The fever polyuria polydipsia insomnia glycosuria high blood pressure, alterations in fat metabolism and the decrease in growth in preadolescent subjects may all be due to involvement in this area (Moehlig 1913) The hyperthyroidism of acromegaly possesses all these clinical features (Saint Milco 1917) except the *disturbances in growth/ It is clear therefore that the* hyperthyroidism of acromegaly is not unlike that which occurs in the *absence of a primary pituitary change)*

A number of histological changes have been observed in the pituitary in subjects dying from exophthalmic goiter (Benda 1900 Kraus 1911 Berblinger 1932) and in small laboratory animals who have been fed large doses of thyroid hormone (Severinghaus Smelser, and Clark 1934) The basophiles are increased in number and size, many castration cells are present There is hypertrophy of the eosinophilic elements *all of which stain more brilliantly than normally The Golgi* apparatus of these cells is enlarged and mitochondrial elements of the cytoplasm are increased Changes in the eosinophiles are diametrically opposite to those seen following thyroidectomy When the anterior pituitary enlarges, this is due chiefly to the hyperplasia of its chromophilic elements particularly the acidophils (Tarner 1896 Khrustaleff, 1913 Merklen and Aron 1933) Obviously chromophobic cells are less in evidence than normally

*(*The hypothalamus probably shares in these pituitary changes In*deed the nervous phenomena associated with hyperthyroidism may* arise from changes in this area (Moehlig 1913) The tremor the headache *and the state could be thus developed The normally high iodine* content of this portion of the brain and of the pituitary is thought to have significance in relation to hyperthyroidism (*Moehlig 1913) McClendon* and his associates (1918) believe that such levels have an inhibitory function tending to prevent the release of thyrotrophin

c Parathyroid—Despite the rather striking disturbances in the metabolism of calcium and phosphorus (q v) there is no anatomical or *histologic al evidence of changes in the parathyroid gland* in patients dying with hyperthyroidism when ordinary fixing and staining techniques are used

d Thymus and Lymphoid Tissues—The thymus is usually increased in size in patients with Graves disease the percentages actually reported varying from 50 (Means 1937) to 95 (Cappelle and Boyer 1913) in autopsied cases

(Enlargement *of the lymph glands is commonly* associated with exophthalmic goiter The tonsils Peyer s patches in the small intestine and the cervical and *thoracic lymph nodes are all hypertrophied* to a degree which many workers believe bears a direct relationship to the intensity of the disease process)

g Mammary Gland—Hypertrophy of the mammae is commonly seen in patients with hyperthyroidism and frank cases of gyneco mastia in the male have been described (Moehlig 1943)

h Gonads—Changes in the sex glands and their function are frequent accompaniments of (Moehlig 1943) and may even cause hyperthyroidism (Hoet and Lederer 1949)

The ovaries may be very small and atrophic with a diminution in the number of primordial follicles and a tendency to cystic degenera tion among those which are developing The testes have shown no consistent structural alteration It has been suggested that loss of function and atrophy of the testicle usually accompany severe hyper-thyroidism However in exceptional cases particularly those associ ated with malignant exophthalmos a hyperactivity is found

(Functionally increased sexual desire and activity are common early manifestations of hyperthyroidism)(These are superseded by hypoactivity as the thyroid process becomes more severe)(Almost any disturbance of menstruation may develop either amenorrhea or menorrhagia appearing early in the disease) Hypermenorrhea is per haps *the most common early alteration but this may rapidly give* way to some other type of disturbance and many cases may show complete amenorrhea (Chapter XIV) Dysmenorrhea is not as com monly observed as in hypothyroidism but does occur

Rusfeldt s (1949) analysis of the menstrual histories of 340 women who underwent thyroidectomy is enlightening Menstrual disorders were prevalent in the older subjects but all menopausal subjects were excluded from the study (Irregularity of menstruation was found in 31 per cent of those with a diffuse toxic goiter) in 21 per cent with a nodular toxic goiter and in about 10 per cent with a nontoxic goiter) Of those with some abnormality of menstruation hypomenorrhea occurred in 51 per cent oligohypomenorrhea in 31 per cent and oligo menorrhea in 18 per cent The relationship of the menstrual disturb ance to the thyrotoxic state was confirmed through relief afforded by thyroidectomy)

i Pancreas—The functional relationship between the pancreas and the thyroid in exophthalmic goiter is well illustrated in the data compiled by Regan and Wilder (1940) They found that the incidence of diabetes mellitus in exophthalmic goiter was 1 7 per cent or the same as for the population at large However the occurrence of diabetes in toxic adenomatous goiter was a little over three times this figure (5 6 per cent) *Therefore it would appear that long standing* changes of a toxic nature in the thyroid gland markedly increase the tendency to diabetes A hyperactive thyroid gland places an added load upon the pancreas When the hyperthyroidism is controlled the consequent diabetic state may disappear provided of course that no permanent damage has developed in the islands of Langerhans

negative nitrogen balance produced by feeding thyroxin to normal and adrenalectomized dogs is decreased following the administration of adrenocortical hormone (Koehlsche and Kendall, 1935) A similar effect undoubtedly occurs in man

On histological examination a variety of disturbances in the adrenal have been described Perhaps the commonest of these is some decrease in the thickness of the zona glomerulosa The amount of lipoid is usually decreased These are the alterations one would expect to find post mortem in a subject dying of hyperthyroidism

No constant changes in the medulla of the adrenal have been observed despite the fact that many of the nervous phenomena of hyperthyroidism may be mediated through it It is not uncommon for an elevated metabolism (up to +10 per cent) and signs of hyperthyroidism to accompany so called benign or functionally active tumors of the chromaffin cells (pheochromocytomas) Indeed several cases are on record in which the diagnosis of hyperthyroidism had been made before the true nature of the condition was discovered (Rabin 1929 Esperson and Dahl-Iversen[Case 1] 1946 Foote et al 1948) In two of these no examination of the thyroid was made but in Rabins case no histological alterations were demonstrable However an asymptomatic colloid type of goiter has been found in a subject who sought relief for manifestations due to pheochromocytoma (Hedinger 1911) In one of the above cases diabetes mellitus also existed and was thought to confirm the diagnosis of thyrotoxicosis (Foote et al 1948) In another methylthiouracil proved of considerable value for controlling the symptoms of the pheochromocytoma and enabled the clinician better to prepare him for surgical intervention (Esperson and Dahl Iversen 1946)

Conversely it appears that thyroid hormone is capable of increasing the sensitiveness of nervous tissue to adrenergic stimuli (Raab 1944b Hoffmann et al 1947) The fact that these functional changes in the medulla are not reflected pathologically in hyperthyroidism may be merely that our methods of study still lack sufficient delicacy Radioactive isotopes newer staining technics and observation of isolated living tissue may soon throw further light on these problems (Reiss Forsham and Thorn, 1949)

When adrenal function is disturbed in hyperthyroidism secondary alterations occur in the anterior pituitary gland These may be related to the formation of pigment and to changes in the hematopoietic system

While much of the collected data has not been thoroughly correlated there is definite reason to believe that a close association does exist between the levels of thyroid and adrenal medullocortical activity in Graves' disease similar in kind to that known to exist in health but different in intensity

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If diabetes has been aggravated by hyperthyroidism treatment for the latter sometimes improves the former

No characteristic pattern of pathological changes has been recorded in the pancreatic tissue of patients with fatal exophthalmic goiter

j Kidneys—Hyperemia of the kidney is commonly found in patients dying from hyperthyroidism There are sometimes degenerative changes in the renal tubules (Moehlig 1913) In experimental animals thyrotoxicosis has caused an increase in the weight of the kidney Clinically diuresis is common in patients with thyrotoxicosis and alterations in glomerular flow and filtration rate may occur (see Hyperthyroidism Laboratory Diagnosis Chapter XXXVI)

l Heart—No pathological changes of a constant nature are observed in the hearts of fatal cases of exophthalmic goiter Perhaps a slight microscopically discernible fibrosis is the most constant lesion (see Complications of Hyperthyroidism Cardiac Failure Chapter XXXVII)

l Muscles—A certain degree of myasthenia is expected in exophthalmic goiter Skeletal muscle suffers most The muscle cell undergoes atrophy fatty infiltration vacuolization nuclear degeneration and loss of striation Any muscle or group of muscles may be affected and in any single subject all muscles are not equally involved

A number of theories have arisen as to the cause for the muscular weakness The majority of workers feel that thymic hyperplasia may be responsible (Schumacher and Roth 1912) for it has been shown experimentally that thyroid hypertrophy and hyperplasia follow the feeding of thymic extracts and desiccated thymus gland (Kjerulf Jensen 1917) Indeed the association of myasthenia gravis and exophthalmic goiter in the same patient has been observed (Thorn and Tierney 1941 Kowallis et al 1941 1942) Kowallis and his associates (1941) stated that there were 14 recorded cases of this association including four of their own

Muscular atrophy with fibrillary twitchings simulating progressive muscular dystrophy has been reported in 11 patients (Bartels and Pizer 1941) The positive relationship between the atrophy and the disease was shown by the complete disappearance of symptoms and histological changes following the control of the hyperthyroidism in Bartels case

In five of 16 cases of familial periodic paralysis Hildebrand and Kepler (1941) found a coexistent exophthalmic goiter Thyroidectomy completely relieved both conditions in all five of these cases The relation of symptoms to the serum concentration of potassium was similar to that seen in uncomplicated forms of the familial disease

m Liver—(See also Action of Thyroid Hormone on the Liver Chapter XIII) In patients dying as a result of exophthalmic goiter

pathological changes in the liver of two main types have been described (a) acute and subacute disturbances in which epithelial structures suffer primarily fatty degeneration and necrosis may be followed by acute hepatitis or yellow atrophy and (b) alterations first affecting the blood vessels and connective tissues of the liver in which sclerotic or fibrosing periportal changes are predominant In general the more severe the hyperthyroidism the greater is the tendency for hepatic involvement although hepatosplenomegaly in moderately toxic cases receding after thyroidectomy has been described (Wallerstein and Walker 1949) Weller (1933) found pathological evidence of such damage in more than 50 per cent of the subjects he examined Schmidt Walsh and Chesky (1941) using the hippuric acid test demonstrated a disturbance of hepatic function in more than 50 per cent of their cases

So many types of pathological change have been described that the injury to the liver must be looked upon as nonspecific rather than as a fundamental integral part of the anatomical picture of uncomplicated thyrotoxicosis In other words the liver is secondarily altered by the tremendous strain placed upon it through the increased metabolic needs of the individual The sequence of events is well defined The excessive amounts of circulating thyroid hormone quickly mobilize all available glycogen Gluconeogenesis is at first increased but later in the more toxic patients with some degree of adrenal cortical exhaustion it is depressed with a lowering or complete loss of its reserves of glycogen

When such depletion is fully developed the liver becomes unusually vulnerable to attack by any of a number of superimposed stimuli such as infections toxins or drugs The intralobular patchily and peripherally distributed hepatitis described by Weller (1933) the circulatory failure and periportal fibrosis of Haban (1933 1935) the cirrhosis of the liver mentioned by Marine and Lenhart (1911) the sclerosis demonstrated by Rossle (1933) and the acute and subacute fatty and necrotic changes observed by Beaver and Pemberton (1933)—all represent changes which are a secondary rather than a primary part of the clinical picture of thyrotoxicosis

In view of the rather extensive use of thiouracil and closely allied derivatives in the treatment of thyrotoxicosis the danger of hepatic damage from such drugs must be considered (Sloan and Shorr 1944 Gargill and Lesses 1945 Muether and Anderson 1945 Van Winkle et al 1946 Moore 1946 Rezek 1947) As Rezek (1947) emphasizes it is impossible to tell whether the antithyroid compound had anything to do with the jaundice in any of the cases above cited for no tests of hepatic function were done prior to its administration in any instance However in most of the patients the thiouracil was not believed to be the primary cause of the jaundice (Muether and Anderson 1945

Rezek 1917 Sloan 1918) In retrospect Sloan (1918) states that the case reported previously (Sloan and Shorr 1944) proved to have a virus hepatitis apparently unrelated to both the thyrotoxicosis and the use of thiouracil Far from causing a hepatitis thiouracil appears to have protected the liver against cirrhotic changes ordinarily induced by dietary deficiency (Gyorgy and Goldblatt 1943) This effect is probably accomplished by way of its suppression of thyroxin formation which leads to lowered metabolic requirements particularly as concerns methionine Therefore if we are careful to maintain a high protein intake thiouracil should prove beneficial rather than harmful to the liver in all cases of thyrotoxicosis

Chapter XXXV

HYPERTHYROIDISM II CLINICAL MANIFESTATIONS

Precipitating Factors—Psychic trauma or emotional stress acting in a subject with a susceptible constitution is commonly the exciting or immediate stimulus which leads to hyperthyroidism In the Plummer form of the disease such a factor is apparent in approximately 10 per cent of the cases while it is demonstrable in more than 90 per cent of the individuals with Graves disease It is as though the constitution were the dynamite and the psychic or emotional stress the match, which lights the fuse leading to the explosion While stresses of a purely physical nature such as an acute infection or overexercise may at times touch off the dynamite (Means 1937) the detonating spark is much more likely to be some psychic insult or emotional disturbance connected with an acute infection puberty marriage pregnancy the climacterium or a change in environment or occupation

Onset—The onset of Graves disease more commonly is sudden and fulminant sometimes appearing within a few hours following severe nervous or mental upset while that of Plummer's syndrome is gradual and insidious

Any one of the classical manifestations of hyperthyroidism may be the first to appear in a particular case and no one of them is pathognomonic (Table XV) In the order of their frequency the more commonly observed initial symptoms may be weakness increased appetite palpitation nervousness irritability intolerance of heat and shortness of breath Among the more unusual early manifestations of thyrotoxicosis are menstrual disturbances usually amenorrhea or oligomenorrhea diarrhea angina pectoris urinary frequency a psychosis or evidences of some complicating condition such as diabetes mellitus normochromic macrocytic anemia or cardiac failure

In some instances family or friends notice a change in the patient before he has become aware of any unpleasant subjective phenomena This is more commonly true of men than of women Tremors a prominence of the eyeballs a loss of weight and hyperkinesis rank high among such manifestations

Course—The severity of the hyperthyroidism varies tremendously from patient to patient and often in the same patient from time to time

It is clear therefore that the disease may run an extremely variable course A fulminant full blown picture may be attained in a remarkably short space of time In such patients a fatal outcome is the rule if treatment is not prompt and vigorous In the majority of instances however there is a tendency for the disease to be self limiting Indeed patients with hypothyroidism occasionally give an unmistakable history of previously active hyperthyroidism In such subjects an exhaustion of the thyroid cells has undoubtedly occurred In still other cases a low grade hyperthyroid state may wax and wane in intensity for many years Such patients are chronically toxic but may not consider themselves sufficiently sick to consult a physician In still other subjects complete remissions may alternate with bouts of activity which often appear suddenly and without definitive cause Such spontaneous remissions and relapses are much more common in exophthalmic goiter

TABLE XV

CLINICAL FINDINGS IN 234 THYROTOXIC PATIENTS TREATED WITH THIOURACIL OR A CLOSELY ALLIED COMPOUND

	INITIALLY PRESENT	NOT MENTIONED	FIRST TO DISAPPEAR*	ABSENT AFTER TREATMENT
Symptoms				
Nervousness	234	0	10	221†
Apprehension	181	42	90	179
Palpitation	138	40	43	123
Insomnia	114	78	30	112
Voracious appetite	139	65	10	124
Anorexia	30	67	1	30
Weakness	78	147	0	74
Diarrhea	20	0	0	20
Signs				
Sweating	200	22	0	200
Pulse above 100	163	0	0	147
Systolic B P above 150 mm Hg	150	0	28	108
Pulse pressure greater than diastolic pressure	74	0	0	38
Loss of weight	223	0	42	223
Enlarged thyroid	193	0	0	41‡
Exophthalmos	106	0	0	44‡
Fibrillation	61	0	0	47

Numbers refer to patients

In some instances the symptoms were relieved to disappear simultaneously or nearly so

†In many instances the attendant nervousness was due in part to a hyperactive syndrome when this was true both sedative and antithyroid therapy were necessary to relieve the nervous condition

‡Decreased only

than in toxic adenoma Some observers believe that the hyperthyroidism which recurs or persists after thyroidectomy represents merely a failure to remove sufficient tissue at operation (Lahey and Clute 1926 Thompson Morris and Thompson 1930 Scott 1937 Cattell and Morgan 1939 Berlin and Gargill 1939) While there are many exceptions to such a generalization it emphasizes the care which should be exercised in the performance of subtotal thyroidectomy Nevertheless it must not be forgotten that there is a peculiar personality underlying all cases of thyrotoxicosis which also needs constant and judicious treatment

While spontaneous remissions occur as above mentioned it is not the thyroid which becomes exhausted in the majority of cases The vital organs and major functions of the rest of the body are more likely to suffer For instance crisis often acute in onset is probably due to failure of hepatic activity Until the advent of thiouracil and its derivatives such crises were the commonest single cause of death postoperatively

Several atypical forms of hyperthyroidism have been described (McCullagh 1941) for which the clinician should be constantly on the alert Thyrotoxicosis may masquerade as an eye condition as heart disease as a joint disturbance or as some infectious process such as tonsilitis cholecystitis or pyelitis Hare and Richey (1946) have emphasized the point that an exaggerated state of muscular weakness and general debility may lead to such a degree of disinterest resignation and apathy as to cloud completely the underlying hyperthyroid state and necessitate differentiation from such conditions as anorexia nervosa Simmonds cachexia and wasting infectious processes

Zondek (1946) has used the term mixed thyroidism to describe subjects who show some features commonly seen in hypothyroidism along with others which are usually representative of an overactive gland Here obesity may persist despite typical features of thyrotoxicosis or the patient may present the features of a myxedematous subject together with exophthalmos tremor nervous excitability and tachycardia or a low basal metabolism and hypercholesterolemia may go hand in hand with the clinical picture of thyroid overactivity Zondek's classification of these subjects is somewhat confused but makes clear that thyrotoxicosis is often difficult to recognize and represents a disturbance in which the nervous system and all the glands of internal secretion may be involved thus creating a multifaceted picture that requires carefully elaborated therapy which takes cognizance of every abnormal feature Simple suppression of thyroid activity is not enough

Hyperthyroidism may be self induced by the use of massive doses of thyroid hormone over prolonged periods of time (Thompson 1917 Goldfinger 1946 Rogers 1917 Skanse and Riggs 1918) Thompson's patient with a manic depressive psychosis developed a clinical picture

indistinguishable from Graves disease after using desiccated thyroid substance for one and a half years in daily doses varying from 60 to 120 grains

Systemic Review.—We may turn with profit from these generalizations regarding the extremes of variation seen in hyperthyroidism to a consideration of specific factors which may be disturbed

1 *Nutritional Status*.—The nutritional state of patients varies considerably with hyperthyroidism About 4 per cent of our patients have been obese As a rule if the appetite is well maintained very little loss of weight occurs Prognosis is at its worst in the individual with anorexia and a rapid loss of flesh

2 *Nervous and Mental Symptoms*.—The nervous and mental symptoms vary little in kind but much in degree Heightened irritability is the keynote and makes the patient appear restless and ill at ease Responses to external stimuli are excessive This hyperkinesis is associated with a general tendency for bodily hyperactivity and emotional instability The patient may weep without apparent cause A trifling annoyance may anger him greatly Sudden noise may cause profuse clammy perspiration palpitation and anxiety Examples of this hyperexcitability and hyperirritability can be multiplied indefinitely

Profound mental and physical asthenia and fatigability accompany the hyperkinetic state It is as though the organism were stimulated beyond its capacity to endure It is little wonder that such patients frequently feel a hopeless inadequacy toward their environment which sometimes ends in a mental state of frustration and futility regarding life itself Manic depressive disturbances indistinguishable from true psychoses are not uncommon However when caused by the hyperthyroidism they disappear following appropriate therapy

Phobias of one form or another are probably the most common presenting symptom in the fully developed case of Graves disease This feature is less common in the toxic subject with toxic nodular goiter Ricarra and Nelson (1917) found phobias in all of 115 subjects with thyrotoxicosis and observed their disappearance in every instance following treatment for the thyroid condition This emphasizes the importance of caution in distinguishing hyperthyroidism from readily confusing conditions such as neurocirculatory asthenia anxiety neuroses and certain types of hypochondriasis (see Differential Diagnosis Chapter XXXVII) Lidz and Whitehorn (1949) trace these psychiatric problems to disturbances in childhood particularly to overcompensation against unwantedness

The fine tremor so characteristic of hyperthyroidism is best observed in the hands and tongue It is most successfully demonstrated by having the patient hold the arms slightly bent at the elbows with the fingers spread wide apart The pads of the palm of the examiner's

hand are then placed gently but firmly against the ends of the fingers of the patient In this way a tremor which cannot be visualized is readily palpable



Fig 61 —Facial expression in Graves disease The staring eyes of untreated Graves disease are responsible for the red or anxious look Note that here as in a large number of subjects with Graves disease the ophthalmos is not bilaterally symmetrical



Fig 6 —Classic nodular goiter with thyrotoxicosis (FEFAH # 418 4) This 6 year-old woman developed a nodular goiter at the age of 4 years and thyrotoxicosis six months prior to the taking of this photograph Note the anxious frightened expression the lymphatic edema and the nodule in the neck Exophthalmos of a type readily observed on inspection is present Instances of bilaterally unsymmetrical exophthalmos type of the disease

In addition to the tremor the tongue may show some tendency to atrophy often appearing smooth and fiery red These trophic changes are sometimes caused by a relative or absolute avitaminosis while in other instances they accompany an achlorhydria or hypochlorhydria

In thyrotoxicosis the deep tendon reflexes are usually quadrilaterally exaggerated No abnormal reflexes appear

3 The Face and Eyes—Characteristically the individual with thyrotoxicosis has a scared look an anxious expression or in the extreme a facies of terror (Figs 61 62 and 63) When the general



Fig 63—Bilateral exophthalmos and retraction of the eyelids in a case of toxic adenoma of the thyroid (IT FEAH 44) This patient's bilateral exophthalmos was +66 per cent with corresponding to extension and fixation At a +9 per cent at the time the accompanying photograph was taken Exophthalmos was halved by treatment and was bilaterally the same (+ 3 mm) Prior to therapy both eyes appeared the same with much more sclera uncovered than is noted in the accompanying figure Therefore this staring which was marked before treatment was due more to upper lid retraction than to proptosis some retraction still remains in the right eye It is not uncommon to find stare and proptosis thus dissociated

nutritional condition is good the face may be flushed whereas it is wrinkled and drawn when emaciation is severe and has occurred rapidly

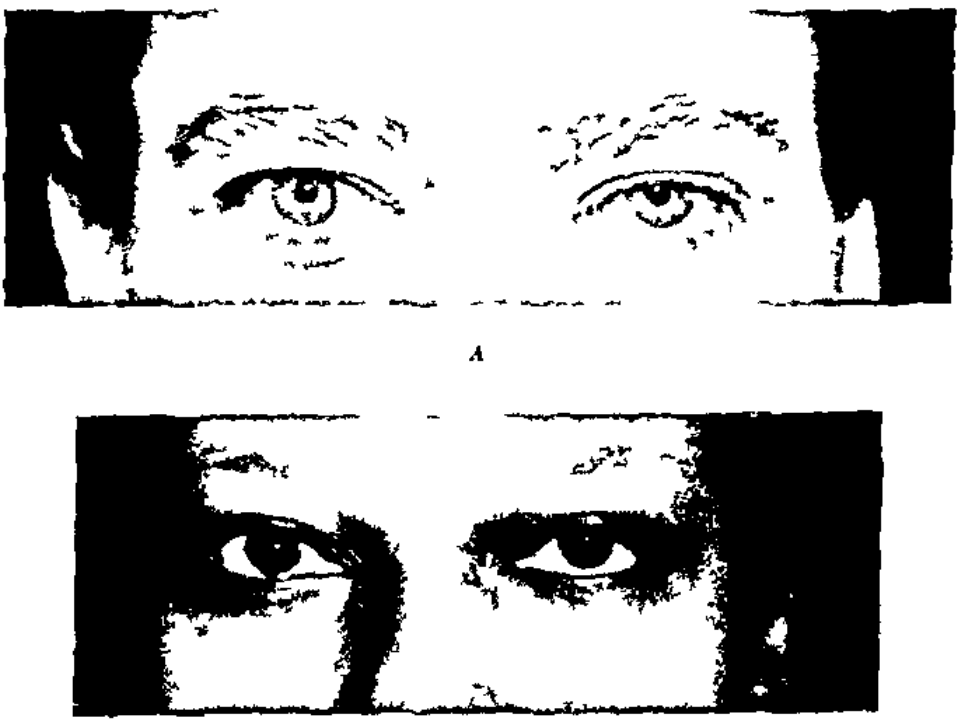
Much of the alteration in facial expression is due to the disturbances in and about the eyes Prominence of the eyeballs or exophthalmos a widening of the palpebral fissures (Stellwag's sign) infrequent blinking (Stellwag's sign) a lag of the lid when the orbit is rotated downward (von Graefe's sign) difficulty in focusing or converging the eyes on a near object (Moebius' sign) the appearance of the sclera between the iris and the lower lid when the gaze is directed horizontally (von Koller's sign) (Fig 61 *A* and *B*) and inability to wrinkle the forehead on looking upward (*Joffroy's sign*) are the signs most commonly observed and always diagnostically significant Edema of the lids (Basedow's sign) is sometimes present and indicates a tendency on the part of the hyperthyroid subject to retain extra amounts of fluid (Bartlett 1940) Retraction of the *levatores palpebrarum* is common in hyperthyroidism rare in other types of exophthalmos (Dinsmore and Ruedemann 1941) More than one half of the cases of acute toxic goiter (Eden and Trotter 1942) show this sign which disappears as soon as the thyrotoxic state is controlled This retraction is subject to hormonal influence from the thyroid and the anterior pituitary (Eden and Trotter 1942)

The ophthalmic signs of hyperthyroidism are commonly bilateral However they are often more striking in one eye than in the other and are occasionally confined entirely to one side Sometimes unilateral exophthalmos is an early and only sign of Graves disease (Kisner and Mahoney 1947 Devine 1947) The degree of proptosis is commonly more marked in one eye than in the other (Figs 61 62 and 63) At least two factors are concerned in its development (a) weakness of the external orbital muscles and (b) the retraction of the levators of the eyelids *Difficulty in convergence* more marked on one side than on the other may add to the observed asymmetry

Less common ophthalmic findings in hyperthyroidism include corneal dystrophies keratitis transitory glaucoma and the ophthalmoplegias Ruedemann (1941) comments upon the frequency with which paralysis of one or more eye muscles occurs and notes that there is no direct relationship between the incidence of paralysis and the severity of the thyrotoxicosis This type of lesion must be sharply distinguished from the inability to move the eyeballs which is present in malignant exophthalmos The latter is due not to paralysis of nerves but to the edema increased tension and marked fibrosis within the orbital fossa (see Ophthalmopathic Graves Disease Chapter XXXIV)

Inasmuch as the eye signs above mentioned have always been stressed in connection with thyrotoxicosis it seems advisable to empha

size the point that many of them may also occur in other conditions For instance, one observer (Jackson, 1919) reported lid lag in approximately one third of all cases of peptic ulcer in one seventh of his patients with nontoxic goiter, and in normal people He found the condition in 10 per cent of 600 patients selected at random who had neither thyrotoxicosis nor peptic ulcer in both of which conditions one notes that the incidence was considerably higher In other words, there is no pathognomonic ophthalmic sign of thyrotoxicosis, each clinical manifestation must be taken into consideration in conjunction with all the others if we are not to be led astray in the matter of diagnosis



A

B

Fig 64 *A* and *B*—Von Kolle sign Two subjects with thyrotoxicosis of the Graves type who have no exophthalmos but present a positive von Kolle's sign—sclera showing between the iris and the lower lid when the gaze is directed horizontally This is one of the earliest signs to appear in thyrotoxicosis and while not pathognomonic is extremely useful in confirming the diagnosis in early or borderline cases

4 Neck—Goiter is present in the majority of patients with hyperthyroidism The enlargement is usually smooth and diffuse in the exophthalmic type with a thrill detected on palpation in one third of the subjects and a bruit heard during auscultation over the gland in two thirds to three fourths of all patients with a maximum intensity normally over the superior pole of the lateral lobes (Lian Welti and Debedas, 1919) In the toxic nodular goiter the surface is irregular and one portion of the gland is more affected than another (Fig 65) Thrill and bruit are rarely elicited

Any of the pressure symptoms already described under thyroiditis may be observed in hyperthyroidism and occur more commonly in nodular than in diffuse goiters. Aphonia and hoarseness are the commonest symptoms denoting pressure from an overlying adenomatous gland.



A *B*

C *D*

Fig. 6. *A*, *B*, *C* and *D*.—A typical case of thyroid adenoma with a dull area in the neck which can be palpated as a lobe. In the neck held in a slightly extended position or viewed *from the side* as in *A* and *B* are views of a patient with toxic nodular goiter and *C* and *D* those of one with a multinodular colloid goiter. Typical signs are absent in both cases.

5 Skin and Its Appendages—The skin of the hyperthyroid patient is smooth soft moist hot and flushed The combination of heat and moisture is highly significant diagnostically Conversely, a cold hand dry or moist almost excludes hyperfunction of the thyroid (Means 1937) The instability of the vasomotor system gives rise to flushes of heat to various parts of the body Together with the heightened activity of the sweat glands they plainly point to an increased metabolism of the skin and its appendages



Fig 66—Vitiligo in hyperthyroidism (A H MH #1 13 4) Large irregular patches were spread widely over the entire body surface of the hyperplastic Negro woman whose thyroid colloid was depleted with pigmentary changes Negligible was palpable but the basal metabolic rate was +8 Serum cholesterol was 100 mg per 100 cc Subjective symptoms and physical signs were in accordance with the above laboratory data

An increase in pigmentation occurs in from a fifth to a fourth of the patients with hyperthyroidism vitiliginous patches are not uncommon (Fig 66) Moehlig (1913) believes that such pigmentary disturbances can be accounted for on the basis of involvement of the diencephalic hypophyseal system This pigmentation lies in the deeper layers of the epidermis In addition small isolated colonies of pigment have been observed in the corium particularly in the region of the blood vessels (Farner 1896)

Due to the excessive activity of the sebaceous glands and the richness of the dermic vascular bed acne of the face and chest are often present and sometimes troublesome in hyperthyroidism

In the less severe cases of hyperthyroidism there is an increase in the growth of hair and excessive oiliness of the scalp In the more severe cases, alopecia occurs

In our experience the concavity and separation of the nails described by Plummer (1918) is relatively common and quite characteristic when present (Fig 67) When of high degree it appears to be connected with disturbances in gonadal function

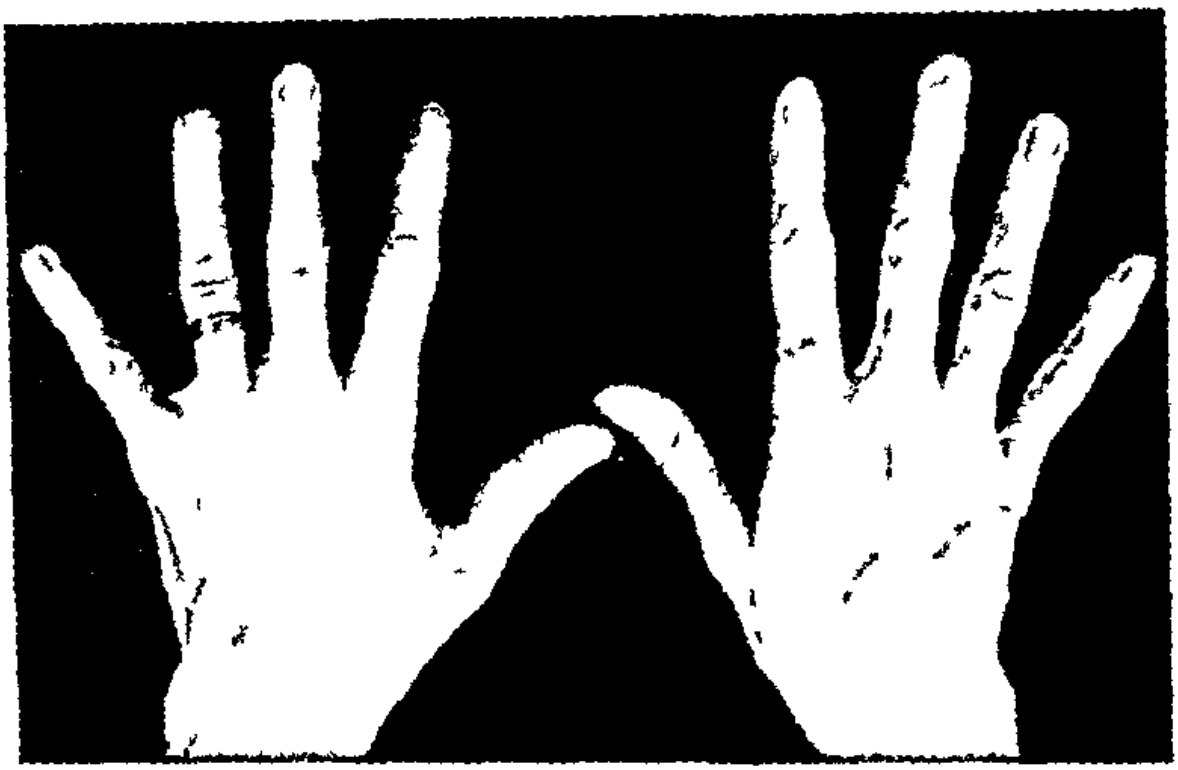


Fig 67—Disturbance of the nails in thyrotoxicosis (S M FFAH #10 6 48) This 49 year old woman had had repeated attacks of hyperthyroidism for fifteen years not altered materially by a thyroidectomy performed at that time Her symptoms controlled by antithyroid compounds with temporary relapses for three years prior to the taking of the accompanying figure Note the clubbing the pitting and the separation of the majority of the nails from the nail bed No pooling of the nails was present The patient complained that he could never keep his nails long

On the basis of experiments in animals Abelin (1940) ascribed all the chemical changes in the skin of hyperthyroid subjects to hypermetabolism and to disturbances in heat regulation

The high incidence of thyrotoxicosis in pseudoxanthoma elasticum justifies a consideration of that disease in connection with the skin manifestations of hyperthyroidism Revell and Carey (1948) have emphasized the systemic nature of the condition in their rather exhaustive review of approximately 150 cases reported to date The cutaneous

lesions are symmetrically located discrete and usually circumscribed and are commonly found in the larger flexor folds of the skin, especially the neck axillae and inguinal regions Their saffron or orange color is suggestive of a xanthoma hence the name They vary in size from that of a pinhead to that of a pea and are joined to each other in a network of trabeculations along the natural folds of the skin The skin becomes increasingly inelastic and when stretched does not readily resume its normal shape Atrophy appears late The condition is due to a loss of elastic fibers in the subcutaneous tissues and is associated with characteristic changes in the eyes and in the vascular structures throughout the body While at the present time it is looked upon as a recessive and irregularly dominant Mendelian trait (Revell and Carey 1918) it seems possible that a common etiology exists for it and certain types of thyrotoxicosis The action of thyrotrophin may be involved in its pathogenesis

6 Muscles —Pathological changes in the muscles in thyrotoxicosis (q v) and alterations in creatine metabolism in that disease (q v) are indicative of the muscular weakness which may at times be profound and often out of proportion to the degree of apparent thyroid activity A classification of the myopathies seen in thyrotoxicosis has been made by Starling and his associates (1938) (1) exophthalmic ophthalmoplegia (2) thyrotoxic myopathy—(a) acute thyrotoxic myopathy (b) thyrotoxic periodic paralysis (c) chronic thyrotoxic myopathy and (3) myasthenia gravis and thyrotoxicosis To this classification might be added dystrophia myotonica with thyrotoxicosis (Boshes Terry and Jessup 1946) although hypothyroidism has been as frequently described in this disease

Exophthalmic ophthalmoplegia represents merely part of a generalized process in which changes in fat and connective tissues are fundamental (Pochin 1944 Rundle and Pochin 1944 Dobyns 1946a b c) In this condition stored fat is mobilized and replaced by a somewhat translucent gelatinous material There are edema and thickening of the fibrous tissue septa of the fat pads generally and of other fatty tissues The fatty and connective tissues become edematous early and are invaded by large numbers of polymorphonuclear leucocytes, lymphocytes and tissue macrophages During this phase the polymorphonuclear leucocytes and macrophages are filled with tiny droplets of fat Later there is an increase in connective tissue formation Muscles do not escape striations of both cardiac and skeletal muscle are lost and many tiny droplets of fat arrange themselves in the cells along the lines of cross striations Edema and new cellular elements are also present in the muscle Clinically the only muscular imbalance may be found in the eye For this reason it was formerly thought that the condition was a localized process (Starling et al 1938 Brain and Turnbull 1938) It is now clear that the paralysis of the orbital muscles

is secondary to the marked increase in post and periorbital fluid and tissue with a striking increase in the amount of fat present (Rundle and Pochin 1944) This eventually interferes with muscular activity which is already abnormal due to the fatty changes and edema and to the stretching occasioned by the proptotic position of the eyeball The condition is usually seen in patients with mild hyperthyroidism in those with medically controlled hyperthyroidism (Fig 68) or in those who have had thyroidectomy Paralysis is always confined to the external ocular muscles because of the factors just mentioned The palsies do not respond to treatment with Prostigmine and are frequently made worse by thyroidectomy We have seen them develop in the course of treatment of the thyrotoxicosis with antithyroid compounds of the thiouracil type (Fig 68)

Acute thyrotoxic myopathy first recognized by Heuer in 1916 is a rare condition simulating myasthenia gravis of the bulbar type It is a rapidly progressive myasthenia involving not only the ocular muscles the tongue the palate and the muscles of respiration and deglutition but also those of the extremities From the time of Heuer's description in 1916 until the report of the case by Sheldon and Walker in 1946 all cases had ended fatally in from one to several weeks after onset Laurent (1944) observed improvement in the muscular condition of two subjects through the use of Prostigmine Thorn and Eder (1946) had a similar experience and suggested that the condition is not a separate clinical entity but represents the association of myasthenia gravis of the bulbar type and thyrotoxicosis However the remarkable recovery of the patient described by Sheldon and Walker (1946) in whom Prostigmine could be discontinued five months after subtotal thyroidectomy emphasizes the etiological role of the thyroid This successful outcome shows that there is an acute thyrotoxic myopathy which closely simulates myasthenia gravis even in its response to Prostigmine but is not identical with it since thyroidectomy has repeatedly failed to relieve myasthenia gravis with a coincident thyrotoxicosis (Editorial Lancet 1946)

Thyrotoxic periodic paralysis is a condition readily distinguished from chronic thyrotoxic myopathy and occurs in conjunction with familial periodic paralysis In this condition the muscles appear normal the attacks of muscular weakness occur periodically between which the patient is asymptomatic and serum potassium is abnormally low Five of 16 of Hildebrand and Kepler's cases of familial periodic paralysis suffered from a coexisting Graves disease (1941) In all five of these thyroidectomy was followed by a complete remission of symptoms (Dunlap and Kepler 1931 Hildebrand and Kepler 1941) Others have noted that thyroidectomy relieves the severity and frequency of the attacks without causing them to disappear (Morrison and

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Levy 1932) Control of attacks has also been reported following treatment with propylthiouracil (Seed 1947)

The incidence of thyrotoxicosis in patients with familial periodic paralysis appears to be too high to be explained by chance alone but the pathogenetic basis for such a relationship still remains obscure

Chronic thyrotoxic myopathy in its extreme form is difficult to distinguish from myasthenia gravis except by thyroidectomy which effects a complete cure in the thyrotoxic cases but does not help appreciably those with a true myasthenia gravis Some degree of disturbance in muscular metabolism associated with weakness is the rule in hyperthyroidism so that in all its forms from the mildest to the most severe chronic thyrotoxic myopathy is the most important muscular condition associated with thyrotoxicosis Symmetrically distributed atrophy of severe degree may affect any group of muscles but most frequently appears in the shoulder and pelvic girdles Thorn and Eder (1946) on the basis of five reported cases and an analysis of others in the literature reconstruct a general picture for the disease The average age at onset is somewhat greater than that found for all subjects with hyperthyroidism A higher percentage of men than women with thyrotoxicosis show evidence of this myopathy In mild form the symptoms may have been present for long periods of time but the patient usually states that severe manifestations have been present for from two to several months prior to the first visit to the clinician Weakness and fatigability are the outstanding manifestations and may be sufficiently severe to confine the patient to bed In the male testicular atrophy occurs Fibrillary twitchings have been seen in some patients Bulbar involvement has been reported Indeed while the shoulder girdle is most frequently and severely affected there is no muscular structure that may not be involved Evidences of thyrotoxicosis may be slight and less frequently are classical Prostigmine may or may not be of use in relieving the symptoms

The excretion of 17 ketosteroids has been diminished in all subjects upon whom it has been determined (Thorn and Eder 1946) The creatinuria is not materially different from that of other hyperthyroid patients nor do the severity of the myopathy and the amount of the creatine excretion vary directly Cardiac disturbances are common and the circulation time shows the shortening characteristic of other forms of hyperthyroidism Incidentally this finding may be of some value in distinguishing Addison's disease as the myograms in the two conditions may be remarkably similar with an absence in both of the muscular potentiation normally present during stimulation (Swank and Bergner 1948 Sanderson and Adey 1949)

Relief of the thyrotoxicosis either by antithyroid compounds or thyroidectomy has been followed by dramatic improvement in all subjects and complete relief in the majority In male subjects the



Fig 68 *A B C* and *D*—Exophthalmic ophthalmoplegia (A.A MH #134 47) Thi 38 year old N gro v o a w s fir t een for a n oder t ly s e type of (ra s dl ase wl ich had b en p esent fo nine month It w lly c ntrolled with p opylthi uracil but he de eloped the ocular palsie shortly after th toxicity was relieve l The photogiaphs sh w her ttempting t look far to the right *(A)* far to the left *(B)* down *(C)* and up *(D)* It is lea that there l a weakne s f the right superior obliq e and right superior rectu n u les The co dition lowly returned to normal over a period of ix months during which time he r nain d controll d on small maintenance do es of the antithyroid compound in conjunction with daily minim doses of Lugol s solution

In hyperthyroidism the apical heart tones are loud and abrupt systolic murmurs are common and diastolic murmurs may occasionally be heard All bruits disappear when the hyperthyroidism responds to treatment thus demonstrating their purely functional nature

A disturbed rhythm is the commonest evidence pointing to a cardiac complication in hyperthyroidism Simple tachycardia is most frequently observed Its severity varies directly with that of the intoxication Auricular fibrillation usually paroxysmal but frequently persistent is the second arrhythmia in importance and auricular flutter is a distressing third Recently (Goodwin 1919) attention has again been called to the rapidity with which antithyroid compounds control these irregularities

TABLE XVI

PULSE BLOOD PRESSURE AND FIBRILLATION IN 78 THYROTOXIC PATIENTS TREATED WITH THIOURACIL

	NO CASE	
	BEFORE TREATMENT	AFTER TREATMENT
Pulse above 100	52	4
Systolic B P above 150	30*	8*
Cardiac Load (Pulse Pressure — Diastolic Pressure)		
Below 0 5	5	20
Bet 0 5 and 1 0	38	42
Above 1 0	26	7
Fibrillation† in		
Hyperplasia	10	2
Adenoma	8	1

In luded 3 pat nts th known hype ten i card al v scular di ea
†In ch group hythm reverted to n mal in 6 w thout using d tali

Anginal pain sometimes accompanies thyrotoxicosis Cardiac failure represents a severe complication (see Complications Chapter XXXVII) In all forms of thyroid intoxication but particularly in Graves disease the systolic blood pressure is increased with a concomitant rise in pulse pressure (Table XVI) Both pulse rate and pulse pressure are more markedly affected in women than in men

Mechanism of the cardiac disturbances in toxic goiter Disturbances of the heart due to thyroid overactivity may be spoken of as thyrocardiac disease Lahey and his associates (1943) have defined

addition of testosterone therapy has materially added to the sense of well being and has brought about full restitution of muscular strength if not already achieved by medication directed to the thyroid gland

Postmortem examination in one of Thorn and Eder's (1916) patients who had marked myopathy and mild thyrotoxicosis revealed atrophy with fatty infiltration of the muscles There was loss of cross striation, an infiltration of lymphocytes and fibrous tissue replacement of the muscle cells The zona glomerulosa of the adrenal cortex was atrophied The thyroid was hyperplastic

On the basis of the low excretion of 17 ketosteroids the atrophy of the adrenal cortex and the testicular atrophy, it seems justifiable to postulate as Thorn and Eder (1916) have done that the myopathy results from a combination of thyrotoxicosis and steroid hormone deficiency On the basis of their study of creatine metabolism in these individuals and in others with thyrotoxicosis they further suggest that the defect in creatine metabolism may be one in the direction of failure to maintain adequate synthesis to meet the abnormal demands

Myasthenia gravis and thyrotoxicosis are a rare combination but occur with sufficient frequency to represent more than simple coincidence It is very difficult to distinguish the combination from a chronic thyrotoxic myopathy as the clinical pictures are indistinguishable and both may be relieved temporarily by Prostigmine

Thyroidectomy or antithyroid medication of the thymectomized type sometimes improves but rarely cures myasthenia gravis Indeed Eaton (1917) believes the ultimate prognosis is not materially altered by such measures whereas Thorn and Eder (1916) saw dramatic relief but not complete cure following the employment of either of them It seems difficult to make a sharp distinction between myasthenia gravis with thyrotoxicosis and chronic thyrotoxic myopathy In all doubtful cases therefore it is advisable to manage the condition as though it were the latter condition Prostigmine should be administered as necessary and thyroid overactivity even though seemingly mild should be controlled by appropriate medical or surgical measures

7 *Cardiovascular Manifestations*—Palpitation and tachycardia are the commonest manifestations of circulatory disturbances in hyperthyroidism The heartbeat is so vigorous that it causes the entire precordium to vibrate with each cardiac impulse Scherf and Boyd (1916) have aptly spoken of the hypermotility of the heart A similar phenomenon is sometimes seen in subjects with arteriosclerosis and in those with a cor bovinum but rarely is it more marked in degree than in hyperthyroidism Because of the violence of the pulsation the heart is often described as enlarged although neither percussion nor teleoroentgenography confirms this

plished by shunting blood from the interior reserve depots such as the subpapillary layer of the skin spleen liver and lungs

When there is a considerable increase in the production of heat in hyperthyroidism an increase in blood volume occurs (Keeton 1944 Volpe and Zanmm 1948) which further aids in maintaining the peripheral blood flow and thus increases the dissipation of heat by convection from the body surface This increment in blood volume places further work upon the heart which responds by an increase in heart rate an increased filling of the cardiac chambers and a consequent increment in the output of blood per minute Keeton (1944) has called attention to the fact that this increase in cardiac output is greater (in hyperthyroidism) at the same oxygen consumption than it is in work He therefore stresses the point already made by others that the hyperthyroid heart is hyperactive and that there are other factors than the demand for the transport of extra heat operative

There has been much speculation regarding the nature of these other factors Neuroadrenal mechanisms seem to deserve most consideration Hoffmann and his associates (1947) have demonstrated the fact that the sensitivity of the adrenergic accelerator fibers to the heart is markedly increased by an excess of thyroid hormone thus increasing the responses normally to be expected from the increase in metabolism which thyroxin simultaneously produces Raab (1943 1945) has attacked the problem from another viewpoint He has shown that an increased production of epinephrine like substances (that is certain catechols) will produce myocardial hypertrophy and dilatation associated with arrhythmia and myocardial degeneration These disturbances are unduly accentuated by the administration of thyroxin It therefore seems probable that the hyperreactivity of the heart in thyrotoxicosis—clinically manifested by a diffuse pulsation of the left chest sharp loud apical heart sounds visible and vigorous pulsations in peripheral arteries with a wide pulse pressure—is caused at least in part by the interreaction between the thyroid and the adrenal gland

Other factors which appear to play a role in the development of the cardiac problems of the hyperthyroid patient include age sex duration of the thyrotoxic state and the coexistence of cardiovascular disease In analyzing the data from 103 cardiacs among a group of 810 cases of hyperthyroidism Griswold and Keating (1949) noted that those with auricular fibrillation or failure or both were on the average ten years older than the patients without signs or symptoms of cardiac involvement The heart was more often affected in men than in women The longer the duration of the thyrotoxic state the higher was the percentage of cardiac complication Cardiovascular disease of nonthyroid origin was more frequently observed among thyrocardiac patients than among other subjects with hyperthyroidism

a thyrocardiac as one in whom 'the heart complications seem to be definitely attributable to the overactive thyroid" In other words, a 'thyrocardiac has a condition precipitated by hyperthyroidism and relieved by its cure By definition the primary cardiac deficiency associated with hyperthyroidism is a reversible one (Cornell Univ Med Coll 1941 III Lahey, Hurxthal, and Driscoll, 1943 Gordan Soley and Chamberlain, 1941) Eventually, permanent damage can be done by thyrotoxicosis even the course of previously existing organic disease may be markedly hastened Should depletion of cardiac reserve continue sufficiently long cardiac failure is bound to ensue

It has been claimed by some authorities that a specific autocoid of the thyroid or some altered portion of its secretion has a direct toxic effect upon the heart (see Thyroid Hormone Action on the Heart and Circulation Chapter XIII) (Meyer and Marine, 1942) It seems more logical to postulate that the disturbances within the heart due to hyperthyroidism actually represent physiological exhaustion resulting from the tremendous increase in cardiac load and a deficiency in certain metabolites essential to maintaining the efficiency of the cardiac muscle fibers In other words alterations in the physiology of the circulation in thyrotoxicosis are largely the result of overwork and undernutrition So called thyrotoxic heart disease is the end result of these abnormalities imposed by an excess of thyroid hormone There is no need to postulate the presence of pre existing cardiac damage (Rogers 1917 Skanse and Riggs 1918) although the constitutionally underprivileged cardiovascular tree may suffer most (Thompson 1913 Lahey et al, 1913 Griswold and Keating 1919)

A primary result of the overactivity of the thyroid is the increased metabolism with an increased expenditure of energy and a corresponding rise in the amount of heat produced In the process of eliminating this extra heat the circulatory apparatus responds by (1) an increase in peripheral blood flow which bears a linear relationship to the rise in the basal metabolic rate (Keeton et al 1941 Stewart and Evans 1942) (2) an increase in blood volume (Gibson and Harris 1939) associated with a marked increment in the volume of extracellular fluid (Cachera Lamotte Darmis and Raynaud 1949) and (3) an increase in cardiac rate and output of blood per minute (Keeton 1941)

Keeton and his associates (1941) have shown that the peripheral flow of blood may be increased sevenfold in normal subjects exposed to a hot moist environment as compared to the peripheral movement of blood under comfortable conditions In the hyperthyroid subject the extra production of heat has a similar effect upon the peripheral flow of blood Quantitatively the additional calories formed closely parallel the degree to which the basal metabolism is raised (Stewart and Evans 1942) This increase in peripheral blood flow is accom

In summary it may be said that the tremendously increased physiological load placed upon the heart by thyrotoxicosis and the relative undernutrition present result primarily in a variety of functional disturbances which disappear completely when the thyrotoxicosis is adequately treated However if the stresses are sufficiently long continued irremediable myocardial damage and cardiac failure may ensue (See Complications of Hyperthyroidism Chapter XXXVII)

8 *Gastrointestinal Manifestations* —The appetite is usually increased early in the thyrotoxic state and may result in a caloric intake sufficiently high to prevent any serious loss of weight In the more severely ill patients anorexia appears and may be associated with nausea and vomiting the latter at times so severe as to dominate the entire picture (Lopez Hence and Ortega 1918) Irrespective of other symptoms loss of appetite and gastric distress are always poor prognostic signs

Achlorhydria is found in about one third to one half of the cases of hyperthyroidism The higher the metabolic rate and the more severe and long standing the anemia the more marked is the decrease in gastric acidity (Lerman and Means 1932b Plaut et al 1917)

While both constipation and diarrhea occur in connection with thyrotoxicosis the latter appears more frequently The achlorhydria and a disturbed equilibrium of the autonomic nervous system are probably responsible The rate of rhythmic contraction of the intestine is markedly increased both in hyperthyroid patients and in normal subjects fed thyroid hormone (Althausen 1939 Althausen and Stockholm 1938 Brown et al 1941 Castleton and Alvarez 1941)

Brown and his associates (1941) have well summarized the gastrointestinal changes characteristic of hyperthyroidism (1) an increased incidence of achlorhydria (2) increased prominence of gastric rugae (3) an increase in the rapidity with which the stomach starts to empty (of questionable significance) (4) a delay in gastric emptying (increased gastric emptying time) (5) increased small intestinal tone with an abnormal pattern (6) increased small intestinal motility (decreased time to cecum) (7) increased large intestinal tone and (8) increased large intestinal motility

The hepatic manifestations of hyperthyroidism are discussed elsewhere (see Thyroid Hormone Action on the Liver Chapter XIII and Hyperthyroidism Pathology Liver Chapter XXXIV)

While the increased production of heat occasioned by an excess of thyroxin in hyperthyroidism is adding to the burden which the heart must carry, *undernutrition is decreasing* its capacity for work Some years ago Plummer and Boothby (1922) showed that the cost of doing work is greater in the hyperthyroid than in the normal subject Keeton (1941) calculates that a subject with severe hyperthyroidism may have an expenditure of energy equivalent to 6 000 or 7 000 calories daily It is difficult to furnish this amount of energy to a normal person through the usual channels, and exceedingly more troublesome to administer the necessary quantity of food to the hyperthyroid subject whose appetite is usually decreased and all of whose functions are easily fatigued Therefore, unless he is carefully instructed and constantly encouraged the patient's wholly inadequate caloric intake leads to *semistarvation This starvation may eventually cause* (a) a negative nitrogen balance and an increase in the excretion of creatine (Keeton 1941) (b) depletion of the glycogen reserves of the cardiac musculature (Berk and Goldburgh *1941* Moses *1941*) (c) avitaminosis (Berk and Goldburgh 1941 Likoff and Levine 1943) and (d) a relative ischemia caused directly and indirectly by the increased cardiac activity in association with the lack of readily available glycogen (Andrus, 1932 Moses 1941)

Vitamin B deficiency which readily occurs in hyperthyroidism increases the cardiac damage (Himwich et al, 1932 Raab 1943 Lishoff and Hershberg 1945) Conversely yeast has been shown to protect hyperthyroid rats from the development of cardiac failure (Lishoff and Hershberg 1945)

The increasing activity of the cardiac muscle makes it exceptionally *vulnerable to the inadequacies we have mentioned* so that it is particularly prone to develop arrhythmia and failure

While crisis (see Complications of Hyperthyroidism Chapter XXXVII) is commonly looked upon as an hepatic or an *hepatorenal* problem it seems quite likely that cardiac failure on a functional basis does occur in conjunction with it (Foss et al 1939)

While undergoing operative cure for their hyperthyroidism 21 of 31 individuals *believed to be entirely free of organic heart disease* at the time of operation developed cardiac failure (Likoff and Levine 1943) This led to the conclusion that thyrotoxicosis not infrequently is the sole cause of congestive *heart failure* There is *no variation* in the size of the heart of the thyrocardiac patient unless fibrillation chronic passive congestion or some organic heart disease is present (Levene and Miller *1942*) Unfortunately such *complications occur all too frequently* as nearly 50 per cent of all fatal cases of hyperthyroidism show an enlarged heart (Kepler and Barnes 1932) Fifteen per cent had right sided failure due entirely to the thyroid *condition* (Foss et al 1939)

In summary it may be said that the tremendously increased physiological load placed upon the heart by thyrotoxicosis and the relative undernutrition present result primarily in a variety of functional disturbances which disappear completely when the thyrotoxicosis is adequately treated However if the stresses are sufficiently long continued irremediable myocardial damage and cardiac failure may ensue (See Complications of Hyperthyroidism Chapter XXXVII)

8 Gastrointestinal Manifestations —The appetite is usually increased early in the thyrotoxic state and may result in a caloric intake sufficiently high to prevent any serious loss of weight In the more severely ill patients anorexia appears and may be associated with nausea and vomiting the latter at times so severe as to dominate the entire picture (Lopez Heree and Ortega 1948) Irrespective of other symptoms loss of appetite and gastric distress are always poor prognostic signs

Achlorhydria is found in about one third to one half of the cases of hyperthyroidism The higher the metabolic rate and the more severe and long standing the anemia the more marked is the decrease in gastric acidity (Lerman and Means 1932b Pla et al 1947)

While both constipation and diarrhea occur in connection with thyrotoxicosis the latter appears more frequently The achlorhydria and a disturbed equilibrium of the autonomic nervous system are probably responsible The rate of rhythmic contraction of the intestine is markedly increased both in hyperthyroid patients and in normal subjects fed thyroid hormone (Althausen 1939 Althausen and Stockholm 1938 Brown et al 1941 Castleton and Alvarez 1941)

Brown and his associates (1941) have well summarized the gastrointestinal changes characteristic of hyperthyroidism (1) an increased incidence of achlorhydria (2) increased prominence of gastric rugae (3) an increase in the rapidity with which the stomach starts to empty (of questionable significance) (4) a delay in gastric emptying (increased gastric emptying time) (5) increased small intestinal tone with an abnormal pattern (6) increased small intestinal motility (decreased time to cecum) (7) increased large intestinal tone and (8) increased large intestinal motility

The hepatic manifestations of hyperthyroidism are discussed elsewhere (see Thyroid Hormone Action on the Liver Chapter XIII and Hyperthyroidism Pathology Liver Chapter XXXIV)

Chapter XXXVI

HYPERTHYROIDISM III LABORATORY DIAGNOSIS

In the *diagnosis of hyperthyroidism nothing will take the place of* clinical judgment Of all the tests employed in confirming the diagnosis the basal metabolic rate and the levels for protein bound iodine in the blood are the most reliable There is however, no infallible or pathognomonic laboratory test The following determinations will be useful

1 **Basal Metabolic Rate** —This is the most reliable laboratory procedure commonly used in the diagnosis of hyperthyroidism No case of thyrotoxicosis develops without an increase in basal metabolic rate Values between —10 and +15 per cent are usually considered normal The metabolism before and after the appearance of hyperthyroidism must be taken into account in evaluating the result in each individual case for severe thyrotoxicosis has been present with a +10 basal metabolic rate in patients whose previous rates ranged from —10 to —20 (Bartels and Bell 1917)

Along with the increased basal metabolism in toxic goiter there is an increase in total metabolism In general we speak of mild thyrotoxicosis in patients whose basal metabolic rates range from +15 to +30 Moderately severe cases show figures between +30 and +50 per cent The most toxic forms of the disease are accompanied by increases of metabolism above +50 but rarely do they exceed +100 per cent

Cardiac output and circulation time are necessarily altered by the elevated metabolism in an effort to meet the excessive demands of the tissues for oxygen A normal person responds to effort by an increase in the per minute volume output of the heart and a decrease in circulation time The changes in these however, are not quite so great proportionately as the increase in total metabolism produced by the subject's muscular activity In hyperthyroidism on the other hand the increase in minute volume of blood flow and the decrease in circulation time are proportionately more marked than the increase in total metabolism occasioned by the effort showing that the thyrotoxic individual functions at a disadvantage The importance of this additional load upon the heart cannot be overestimated clinically It undoubtedly accounts for the frequency with which cardiac complications are encountered

An increase in the basal metabolic rate may occur in a number of states totally unrelated to hyperthyroidism such as hyperpituitarism malignant hypertension hyperadrenocorticalism leukemia infectious diseases drug intoxications (e g dinitrophenol poisoning) and so forth

2 **Estimation of Liver Function** —Because all metabolic activity is increased in hyperthyroidism more than one of the manifold functions of the liver may be involved Of the many tests devised for appraising hepatic activity we shall discuss those with which we have had personal experience and which we feel may materially aid in detecting early dysfunction of the liver in patients with hyperthyroidism

a Hippuric Acid Formation —This test measures the ability of the liver to manufacture and combine glycine with ingested benzoic acid to form hippuric acid The oral and intravenous methods of performing this test are considered equally valid by most investigators Most of our experience has been with the intravenous test performed in the following way one and seventy seven hundredths grams (1 77 Gm) of sodium benzoate are injected intravenously and the urine is collected for one hour following the injection Hippuric acid in the urine is then determined by the method of Griffith (1926) The normal amount of hippuric acid formed and excreted varies from 0 7 to 0 95 Gm Some hyperthyroid patients showing no gross evidences of hepatic dysfunction may give a positive test (Haines et al 1939 Schmidt et al 1941 Bartels 1938 Probstein and Londe 1940 Snell and Plunkett 1936) A positive inverse correlation exists between the output of hippuric acid and the retention of bromsulfalein (Haines et al 1939) that is the hippuric acid output is reduced in nearly all cases failing to eliminate bromsulfalein promptly

No mathematical correlation can be made between the height of the basal metabolic rate and the decreased formation and excretion of hippuric acid from sodium benzoate Nevertheless the more prolonged the thyrotoxicosis the more frequent are its remissions and exacerbations and the more profound the loss of weight the less the capacity of the liver to transform benzoate into hippuric acid The actual level of basal metabolism is less important for rather severe grades of liver damage can occur when this is only moderately elevated The excretion of benzoyl glucuronate (Snapper and Saltzman 1917) may eventually prove to be a more sensitive test than that we have just described but we have had no experience with it

b Proteins of the Blood Serum or Plasma —The total protein of the blood serum is usually decreased in hyperthyroidism This reduction affects chiefly the albumin fraction which is relatively and absolutely low Using the Tiselius method for determining electrophoretic

tions By this method Lewis and McCullagh (1913 1914) found the proteins of normal plasma to be distributed as follows albumin 60 to 65 per cent alpha globulins 6 to 8 5 per cent beta globulins, 11 to 16 per cent gamma globulins 9 to 15 per cent fibrinogen 3 to 7 per cent with albumin globulin ratios varying from 1 75 to 2 30 In hyperthyroidism the albumin fraction was definitely reduced with an increase in the alpha globulin fraction to twice that normally seen Occasionally there is an associated increase in fibrinogen (Stern and Reiner 1946)

It is generally agreed that a decrease in the ability of the liver to form albumin accounts for the hypoproteinemia of hyperthyroidism (Lewis and McCullagh 1913 1914 Schmidt et al 1941 Bartlett 1942 Beaver and Pemberton 1943 Maddock et al 1937 McIver 1942 Stern and Reiner 1946) In conjunction with this hypoproteinemia a decrease in the volume of circulating blood may occur (Chiu and Lundem 1948) despite the fact that this is ordinarily increased in the severely toxic subject (Gibson and Harris 1939)

Within several months after successful thyroidectomy or successful irradiation therapy the plasma protein returns to normal However in cases which develop a progressive exophthalmos after treatment the electrophoretic pattern is abnormal with a particularly low concentration of albumin (Stern and Reiner 1946) This leads to the conclusion that the low values for serum albumin ordinarily seen in the thyrotoxic state are not due to thyroid hormonal activity but to the effects of excessive amounts of inactivated thyrotrophic hormone of the pituitary In normal rats however suppression of the thyroid did not result in a lowered albumin as large doses of thiouracil produced an increase in the plasma content of total protein globulin and non protein nitrogen but no significant change in albumin (Leathem and Seeley 1947) This may have been due to the short duration of the experiments

c Serum Cholesterol—Serum cholesterol decreases in the majority of subjects who have hyperthyroidism (Brøchner Mortensen and Möller 1940 1941 Kaufmann and Wall 1941 Drill and Shaffer 1943) The change is not striking as averaged values for any series of patients usually fall well within normal limits (McGavack and Dreiter 1945 Peters and Man 1950) Nevertheless the trend under treatment is unmistakable in the individual patient (Fig 69) Low normal values are present before therapy accompanying which a steady rise occurs as the hyperthyroidism is controlled After control is established the behavior of cholesterol is erratic and usually varies within the limits of normal

Absolutely low values for serum cholesterol that is values of 100 mg per 100 c c or less with a decrease in esterification are found only in cases with severe damage to the liver or in those who are in crisis Therefore such alterations in the blood cholesterol are prognostically

unfavorable In men (Peeler et al 1949) and in women no correlation has been established between the absolute values for the blood cholesterol and the basal metabolic rate nor between the blood cholesterol and serum precipitable iodine (Peters and Man, 1950) although values for the former may be elevated when the latter is 4 micrograms per 100 c c or less

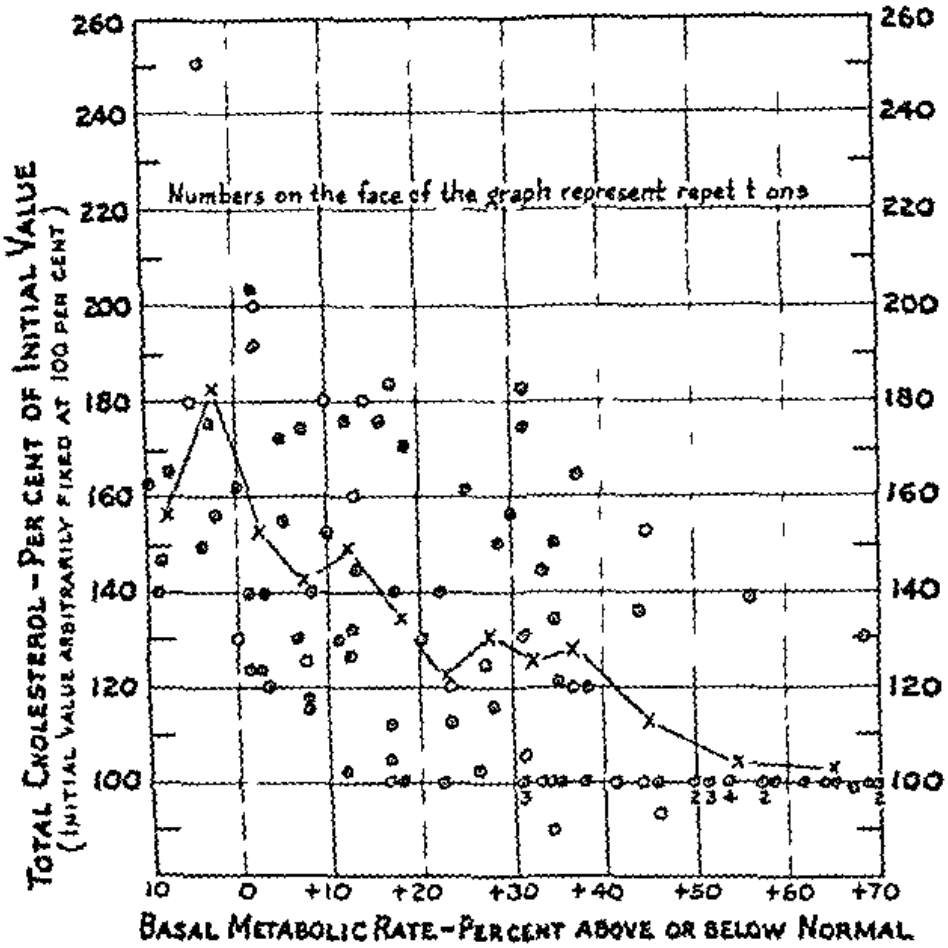


Fig 79—The effect of serum cholesterol in hyperthyroidism under treatment with thiouracil The chart shows the averaged plotting charts for serum cholesterol in 31 patients while undergoing treatment with thiouracil In each instance the absolute figure for the pretreatment level was arbitrarily fixed at 100 per cent and all subsequent changes recorded as a percentage variation from that point (After McCash and Brekter 1944)

In women there has been found an increase in the values for cholesterol in the blood commensurate with increasing age

d Serum Phosphatase—When the liver is damaged in hyperthyroidism changes in the value for serum alkaline phosphatase closely parallel the bromsulfalein retention (Drill and Shaffer 1943) Alterations in phosphorus and calcium metabolism may increase the amount of alkaline phosphatase present (Nothmann 1911)

In evaluating the results of a determination of the blood protein bound iodine it must be remembered that the ingestion of any inorganic iodine preparation will influence the results for 18 hours thereafter or more (Petit, Starr, and Chaney, 1949, Man and Peters 1950) Organic compounds of iodine will affect the results for *much longer periods of* time For instance elevated levels for blood protein bound iodine have been observed for as long as three months following cholecystography and *for more than a year in instances in which the iodized oil* has been introduced into the lung or subarachnoid space (Petit Starr and Chaney 1949 Jakob and Wachsmann 1949)

Increasing age is associated with a decrease in serum precipitable iodine in men which shows a reasonable degree of correlation with the diminishing basal metabolism (Kountz Chieffi and Katz 1949) No such associations could be detected in women

In connection with a study of the protein bound fraction of blood iodine it is interesting to note that a single dose of 6.3 grams of thyroid hormone (Proloid) raised the serum value to 40.9 gamma per 100 c c without producing a change in the basal metabolic rate or any thyrotoxic manifestations (Robbins and Man, 1949) This is in sharp contrast with the influence of much smaller doses used over longer periods of time (see Thyrotoxicosis Factitia Chapter XXXVII)

7 **Blood Count** —Variations in the erythrocyte count in hyperthyroidism are not striking Contrary to reports of anemia in the earlier literature high counts are frequently obtained (Boenheim Schwimmer and McGavack 1945) Pernicious anemia and hyperthyroidism have been observed in the same patient but the association is no greater than that to be expected from the operation of chance alone (Boenheim Schwimmer and McGavack 1945)

In hyperthyroidism the total white blood count is usually normal A relative lymphocytosis is the rule (McCullagh and Dunlap 1932) *Hertz and Lerman (1932) using supravital staining techniques* have demonstrated a relative and absolute increase in monocytes It is clear from the above that both relative and absolute lymphocytosis and monocytosis are the only two characteristic morphological changes in the blood of patients suffering from hyperthyroidism (Table XVII)

8 **Calcium and Phosphorus Balance** —

a Levels in the Blood Serum - In hyperthyroidism McCullagh (1928) Aub and his associates (1929) Puppel (1911) and Gross (1911) found *no change in the serum calcium* and phosphorus However there is later evidence for a slight but definite lowering of the values for both serum calcium and phosphorus particularly for the former (Robertson 1911b 1912) The figures of Robertson are shown in Table XVIII while the variations from normal are not great they may be of some value in appraising the thyrotoxic state of certain patients *It is im*

TABLE XVII

DATA FROM BLOOD COUNTS IN 104 PATIENTS WITH THYROTOXICOSIS UNDER TREATMENT WITH THIOURACIL

	LEUKOPENIA (<5,000 CELLS/CU MM)			RELATIVE GRANULOCYTOPENIA (POLYS < 60%)		
	NO CASES	WEEK OF APPEARANCE		NO CASES	WEEK OF APPEARANCE	
		RANGE	AVERAGE		RANGE	AVERAGE
Pretreatment	7	—	—	8	—	—
Appearing and disappearing during treatment	15	1 to 7	3.1	17	1 to 16	3.9
Reaction necessitated stopping drug	4	1.5 to 6	3.7	4	1.5 to 6	3.6

TABLE XVIII

SERUM CALCIUM AND INORGANIC PHOSPHORUS IN THYROID DISEASE

CONDITION	SERUM (MG PER 100 C.C.)				PRODUCT OF Ca X P	CORRESPONDING B.M.R.
	CALCIUM		*INORGANIC PHOSPHORUS*			
	RANGE	MEAN	RANGE	MEAN		
Normal controls	*9.9–11.1*	*10.39*	*3.1–4.8*	*3.83*	*39.8*	*– 8*
Untreated thyrotoxicosis	9.1–10.8	9.71	0–3.5	3.14	30.8	+ 6
Thyrotoxicosis after subtotal thyroidectomy	9.8–11.2	10.59	3.–4.1	3.74	39.3	– 7
Untreated myxedema	9.8–11.2	10.51	3.5–4.5	3.93	41.3	–35
Treated myxedema	9.0–10.6	9.85	3.8–4.7	4.29	41.6	+ .

Taken from the data of Rawson (1941–1942) which gives the variation in the product of calcium and inorganic phosphorus as highly significant in thyrotoxic

portant to stress the necessity for simultaneously determining serum protein so that we may evaluate properly the figures for calcium and phosphorus according to nomograms such as that of Peters and Eiserson (1929) which derives from the formula Total Ca(mg/100 c c) = —0 255 P (inorganic in mg/100 c c) +0 566 Prot (per cent) +7

b Urinary and Fecal Excretion of Calcium and Phosphorus—There is a marked increase in both the urinary and the fecal excretion of calcium in thyrotoxicosis (Williams and Morgan 1910 Puppel et al 1912 1913, 1915 Aub et al, 1929 Albright et al 1929 Albright and Ellsworth, 1929 Beaumont et al 1910 Robertson 1911b, 1912 Puppel 1911 Gross 1911) the output of calcium sometimes reaching seven times normal (Albright et al 1929) Despite this tremendous mobilization of calcium and the consequent negative balance metastatic calcium deposits similar to those seen in hyperparathyroidism do not occur Puppel (1911) believes this is due to the fact that there is no increase in the levels for serum calcium in thyrotoxicosis In fact they are often slightly lower than normal (Robertson 1911b 1912) The calcium drain in hyperthyroidism is tremendous and eventually gives rise to marked decalcification and osteoporosis rarely so severe as to cause bone cysts and fractures (Boenheim 1916)

c Decalcification and Osteoporosis—Kummer (1917) was apparently the first to draw attention to the occurrence of osteoporosis in thyrotoxicosis Since that time many workers have studied the phenomenon Several good recent discussions are available (Puppel Klassen and Curtis 1939 Beaumont et al 1910 Williams and Morgan 1910 Brunner 1910 Bodenheimer and Barcham 1912 Puppel et al 1915) The demineralization of the skeleton is often greater in thyrotoxicosis than in hyperparathyroidism (Aub 1937) and is frequently demonstrable roentgenographically (Beaumont et al 1910 Williams and Morgan 1910, Brunner 1910 Bodenheimer and Barcham 1912) Any bone may be affected (Williams and Morgan 1910) but lesions appear earliest in the small flat bones and the spine and latest in the long bones (Bodenheimer and Barcham 1912) Unlike the bony disturbances of von Recklinghausen's disease those found in hyperthyroidism respond readily to the feeding of calcium in quantities sufficient to change the negative balance to a positive one (Puppel Klassen and Curtis 1939 Beaumont et al 1910 Puppel et al 1915)

In 1929 Aub and his associates showed that calcium depletion in hyperthyroidism was dependent upon three principal factors (1) the duration of the disease (2) the rate of calcium loss, and (3) the daily calcium intake Bony complications will depend upon all three of these factors but particularly upon the daily intake of calcium Therefore the experiences of individual physicians will vary widely Means (1937) while observing demineralization in roentgenograms 'frequently' has never seen clinical symptoms arising from it On the

other hand ten of Brunner's (1910) 22 patients were osteomalacic 22 per cent of the 110 patients reported by Golden and Abbott (1933) showed decalcification radiographically while four of 22 patients intensively studied by Williams and Morgan (1910) developed pathological fractures Morgan (1912) has described osteoporosis in conjunction with myopathy postoperative ophthalmoplegia and avitaminosis in hyperthyroidism Of five cases reported by Plummer and his associates (1928) two had pathological fractures and at necropsy in all of these cases the ribs were very friable and readily crushed between the fingers Osteodystrophia fibrosa cystica has been described in juvenile hyperthyroidism (Jacobs 1913) and the association of fibrous dysplasia of bone in association with hyperthyroidism in children has been reported (Lichtenstein and Jaffe 1942) *If roentgenograms of several bones were consistently made in every case of hyperthyroidism it seems quite likely that osteoporotic changes could be demonstrated in nearly 50 per cent*

Of all the factors concerned in the development of the demineralization a low intake of calcium has been proved to be the most important Therefore geographic and sociologic conditions as well as habits of eating can often be positively related to its appearance Should routine roentgen ray examinations of the skull spine, or long bones show demineralization the necessity for calcium therapy is stressed Its administration both therapeutically and prophylactically may prevent serious complications and hasten recovery from the thyrotoxic state

9 **Electrocardiogram**—The electrocardiogram of the thyrotoxic patient does not show any change which is pathognomonic Other causes for heart disease must be ruled out in interpreting the electrocardiogram Thyrotoxicosis may aggravate previously existing organic heart disease a fact to bear in mind when interpreting electrocardiograms from such patients (Maher and Sattler 1936)

In a relatively large series of cases Gordan Soley and Chamberlain (1944) observed the following electrocardiographic variations in the order of frequency given (1) sinus tachycardia (2) various abnormalities of the T wave of which low amplitude and notching were the most common (3) auricular fibrillation (4) partial auriculoventricular block and (5) in rare instances auricular flutter The incidence of these findings was the same in those subjects under 40 and in those who were over 40 suggesting that they were not due to the vascular changes of aging The further relationship of these conditions to hyperthyroidism was confirmed by their tendency to disappear following appropriate treatment A shift in the direction of the ventricular gradient has been ascribed to myocardial strain (Talley and Hyman 1918) Periods of a prolonged PR interval alternating with paroxysmal auricular fibrillation without organic heart

disease have been observed (Altschule, 1945). Ventricular fibrillation has also been reported (Boone 1945). In addition to the disturbances in rhythm Scherf and Boyd (1946) emphasize the high T waves and slight depression of the S-I segments seen in cases of thyrotoxicosis. However since these are not always present they suggest that these alterations arise from complications and from involvement of other glands.

10 Circulation Time.—The circulation time is usually shortened in cases of hyperthyroidism. This determination is particularly useful in detecting thyroid disease complicated by cardiac failure. Because technical faults are inherent in all the variations used for determining circulation time and because many nonthyroid conditions are associated with shorter than normal values this test must not be employed as a substitute for clinical evaluation or as a replacement for other more reliable laboratory analyses. Attempt has been made to employ the *circulation time as a criterion for ascertaining the best time to operate* such a practice is to be discouraged as the circulation time may still be short when the patient is ready for surgery or may yield normal values before the patient is fully prepared.

The speedy mobilization of radioactive sodium from the tissues of the extremities in thyrotoxicosis probably represents one effect of the rapid circulation time and the heightened metabolism (Cooper Fillmer Shea and Dennis 1949).

11 Collection of Radioiodine by the Thyroid.—In thyrotoxic patients the accumulation of iodine by the thyroid gland is much greater than in normal individuals. This added capacity for iodine can be measured diagnostically with radioactive iodine in tracer doses. The actual percentage of iodine taken up by the thyroid varies considerably from subject to subject as it depends to a major degree upon the amount of hyperplasia and hypertrophy present. There is therefore considerable overlapping of values among normal borderline thyrotoxic and mildly thyrotoxic subjects. For this reason the simple calculation of iodine uptake in hyperthyroidism may have extremely limited value (Quimby and McCune 1948).

A modification of the above procedure has been suggested by Stanley and Astwood (1948) which accentuates the differences between persons with normal thyroid glands and those with hyperthyroidism. This is predicated upon a difference in the behavior of the normal and of the hyperplastic glands, respectively, to the administration of a single dose of an antithyroid compound *followed at an appropriate interval* by a large dose of potassium thiocyanate or iodine.

Several now well recognized facts represent the basis of the test.

(1) The administration of an antithyroid compound causes in addition to a thyroid enlargement, a diminution in the concentration of iodide and prevents its conversion to diiodotyrosine and thyroxin.

(ii) After treatment with thiouracil or an antithyroid compound of the same physiological group the actual quantity of iodine in the gland is related directly to the intake of iodine In other words if the iodine intake is greatly increased large concentrations appear and remain in the gland but this iodine is not protein bound If little or no iodine is fed under such circumstances the total iodine of the gland drops to very low levels and the organic forms almost completely disappear

(iii) After depletion of its iodine store by thiouracil the gland so blocked is capable of trapping large amounts of iodine temporarily even 30 times normal (VanderLaan and VanderLaan 1947) which remains in the uncombined or iodide form This entrapped iodide is spontaneously discharged from the gland so that about one half is lost in five to six hours and most of the remainder in an additional 18 hours

(iv) Potassium thiocyanate not only prevents the uptake of iodide by the normal and the hyperplastic gland but also causes a rapid discharge of the iodide accumulated while such glands were under the influence of a thiouracil derivative

(v) The more hyperplastic the thyroid gland the greater is its iodide concentrating space or the capacity of the compartment for the collection of iodide and the greater the amount of such material absorbed in a given space of time A large iodide space develops under two conditions In animals and man whose thyroids are made hyperplastic by prolonged antithyroid treatment and in hyperthyroidism (Stanley and Astwood 1948)

(vi) When the normal or hyperplastic gland is blocked by an antithyroid compound of the thiouracil type a maximum concentration of radioactive iodine is achieved rapidly (within one to two hours) and its loss is markedly enhanced by the use of thiocyanate or large doses of potassium iodide

(vii) A thyrotoxic gland is more difficult to block with a thiouracil derivative than the normal gland

(viii) Protein bound radioactive iodine does not leave the gland readily under the influence of thiocyanate or iodine

From these data the following conclusions can be drawn

(a) A single dose of an antithyroid compound may increase the uptake of radioactive iodine in the hyperplastic thyrotoxic gland to a greater degree than in the normal gland

(b) The loss of this large accumulation of radioiodine is more rapid and precipitous from the thyrotoxic blocked gland than from the normal blocked gland following the administration of a single dose of potassium thiocyanate or sodium or potassium iodide (Fig 23) Nearly all of the radioiodine disappears from the completely inhibited toxic gland within two hours whereas its discharge from the normal

blocked gland is relatively slow and the rate of discharge is somewhat similar to the rate of uptake Therefore the rapidity of this loss is an accurate index of the degree of *hyperplasia and toxicity present*, and thus affords the clinician a procedure both qualitatively and quantitatively useful in the diagnosis of hyperthyroidism

(c) *The proportion of the accumulated radioactive iodine* which leaves the thyroid under the influence of a standard dose of thiocyanate under the above conditions is an index of the degree of thyroid inhibition *at the time the procedure is carried out* That is *the portion* which fails to leave the gland has obviously become organically bound prior to the administration of the thiocyanate and is no longer subject to its discharging influence Thus we have a *method of measuring from* time to time the degree of block attained in any patient with thyrotoxicosis By means of it we may more accurately regulate the dosage of antithyroid compound in each individual patient

The technic of this test is essentially as described by Stanley and Astwood (1948) (a) For diagnosis 100 mg of 2 mercaptomidazole are administered orally one half to two hours before giving the radioactive iodine (I^{*}) (b) For checking the effectiveness of treatment the radioactive iodine is given at a selected hour following the last dose of antithyroid compound usually from one to four hours The remainder of the procedure is the same for groups (a) and (b) In all instances, *100 microcuries of I without added carrier are given by mouth* in weakly alkaline solution diluted to about 25 cc with normal saline followed by about 25 cc of water to wash the material from the flask the mouth and the esophagus Serial counts are then made at ten to thirty minute intervals over the isthmus of the thyroid gland with a shielded Geiger Muller counter as described by Stanley and Astwood (1947) When the accumulation of I^{*} reaches a maximum as indicated by successive counts of the same magnitude, potassium thiocyanate *10 Gm freshly dissolved in 25 to 50 cc of water is given by mouth* During the succeeding hour counts are made over the gland at ten minute intervals to determine the rate of discharge of the I^{*} The rate of loss is maximal during the first half hour and usually ceases during the second or third hours Background counts are made over the left anterior chest at appropriate intervals during *the procedure* The condition of the thyroid gland is gauged from the data obtained through inspection of these observations by calculating the amount and *rapidity of iodine uptake by the thyroid* and the rapidity and extent of its extrusion following the administration of thiocyanate

12 **The Urinary Excretion of Radioiodine** (Figs 2 and 23) —If the excretion of labeled iodine is low this is an *indication of Graves disease* Therefore if the diagnosis is in doubt as for instance when the symptoms of the disease are associated with a low or relatively low basal metabolic rate *or* when the basal metabolic rate is elevated as a result of

factors not concerned with thyroid activity the rate of excretion of radioiodine may materially aid in determining the true status of thyroidal activity

A tracer dose of radioiodine representing an average of 100 microcuries of radioactivity is administered orally to an untreated subject suspected of having hyperthyroidism The percentage of excretion of the ingested dose of iodine is calculated from the specific radioactivity of an aliquot of all urine passed in the succeeding 18 hours If a seemingly toxic patient shows no palpable goiter and little or no radioactivity over the gland as measured by a Geiger counter then the entire body may be searched for evidence of aberrant hyperactive thyroid tissue as radioactivity will be increased in any such area

In the 18 hour period above described the percentage of the tracer dose of iodine which is excreted by nontoxic subjects will average about 60 per cent although a range of values from 23 to 98 per cent has been observed by McArthur and her associates (1948) who devised this test Thyrotoxic patients excrete an average of 25 per cent of the ingested dose with a low value of 7 per cent and a high value of 45 per cent The above mentioned workers feel that because of overlapping in the middle range positive proof of hyperthyroidism is not achieved by the test unless the percentage of labeled iodine excreted is 20 per cent or less By the same reasoning no gland should be considered in a state of normal activity unless 10 per cent or more of the iodine is lost in the urine within the 18 hour period following ingestion

13 **The Determination of Urinary Thyrotrophic Hormone** —Both Borell (1945) and Galli Mainini (1947) have described methods of determining the amount and activity of circulating and excreted thyrotrophic hormone The procedure used by Galli Mainini follows The night specimen of urine is acidified with hydrochloric acid and precipitated with two volumes of ethyl alcohol After standing in the cold the precipitate is separated by centrifugation It is then taken up with 10 to 12 c c of water Three cubic centimeters of this solution are given to each of four toads weighing 100 grams or more in three equal daily doses The thyroid is examined for hyperplasia on the fourth day The test is positive in cases with exophthalmos acromegaly and myxedema It may prove to be of value in determining the wisdom of operation or massive roentgen ray therapy in thyrotoxic subjects who show any recognizable degree of exophthalmos and may prove prognostically valuable in those who show evidences of malignant exophthalmos postoperatively

14 **Other Tests** —*Levels for ergothioneine* in the red blood cells are low in patients with thyrotoxicosis (Palmer and Mowbray 1948) Various *renal clearances* show alterations in thyrotoxic patients with and without cardiac failure and may prove both diagnostically and

prognostically valuable in selected cases (Merrill and Cargill 1947). Several *iodine tolerance* tests have been devised (Elmer 1931, Perkin, Brown and Lang 1931, Watson 1936, Perkin, Lahey and Cattell 1936, Perkin and Lahey 1937, and Watson and Barber 1937) and possess definite merit in the individual case. However, with the refinements that have recently taken place in the estimation of blood protein bound iodine, the latter procedure will usually afford all the information necessary. If it fails to do so, then the radioiodine uptake or excretion test (q.v.) is probably more sensitive and better indicated than any modification of the iodine tolerance procedure.

Chapter XXXVII

HYPERTHYROIDISM IV CLINICAL DIAGNOSIS AND COMPLICATIONS

CLINICAL DIAGNOSIS

In its classical forms hyperthyroidism is easily recognized The hyperreactivity of the individual as a whole the distress from heat the warm moist hands the continuous sweating the hypermotility of the heart the rapid pulse and the wide pulse pressure are rarely if ever lacking either in Graves or Plummer's type of the disease If in addition the gland is soft diffusely enlarged with a thrill and bruit present over it and exophthalmos and other characteristic eye signs appear one has little hesitation in making a clinical diagnosis of Graves disease or toxic diffuse hyperplasia of the thyroid When the gland is nodular and the general symptoms mentioned above are observed in greater or lesser degree Plummer's disease is probably present In either instance the diagnosis is usually made before laboratory tests are ordered

The borderline cases in which many features of the classical type may be lacking are frequently confused with a wide variety of conditions from which they may be differentiated with considerable difficulty even after extensive study Noehren (1940) has exhaustively analyzed a thousand cases sent to him for operative procedure One hundred and eighty five of these (almost 20 per cent) were found on careful investigation to have no thyroid disease The experience of this surgeon alone emphasizes the necessity for carefully differentiating the less outspoken cases of thyrotoxicosis from other conditions in order to avoid not only unnecessary but also harmful surgical intervention

There is no pathognomonic manifestation of hyperthyroidism Several features which it holds in common with other conditions may on careful scrutiny afford a key to the right diagnosis

1 The nervousness of hyperthyroidism is continuous whereas in many of the conditions with which it may be confused such erethism is more likely to be paroxysmal There is *continuous* physical and mental hyperactivity In this connection let us emphasize again the fact that it is rare to see exophthalmic types of goiter in which emotional stress of one form or another has not been a precipitating factor

2 The tremor of hyperthyroidism is very fine rarely, if ever, coarse

3 The patient with hyperthyroidism is *continuously* warm, not at first hot and then cold as is the subject suffering from the climacterium

4 A hot moist skin is characteristic it is rarely dry and hot never dry and cold

5 Characteristically the tachycardia of hyperthyroidism fails to disappear after rest or during sleep contrast the behavior of that due to neurocirculatory asthenia or excitement

6 Loss of weight with an excellent appetite should always prompt the clinician to suspect hyperthyroidism however, it must not be forgotten that the most severe cases may have anorexia of high degree

7 The absence of all local signs relating to the status of the thyroid gland such as enlargement thrill bruit or change in consistency, makes a diagnosis of hyperthyroidism unlikely

8 A normal or low basal metabolic rate is rarely obtained in hyperthyroidism The obverse statement that a high basal metabolic rate always indicates hyperthyroidism is far from true Many things may increase the oxygen consumption such as nervousness on the part of the patient at the time of the examination technical errors in preparing the patient or in taking the test and a number of unrelated clinical conditions Noehren (1910) notes that the pulse rate rather consistently parallels the basal metabolic rate the latter going up two points for each additional pulse beat

9 An elevation of the protein bound fraction of blood iodine confirms the diagnosis of hyperthyroidism but the procedure is not as yet adapted for use in the general hospital laboratory

10 Widening of the pulse pressure and hypermotility of the heart help to confirm the diagnosis of hyperthyroidism for the other conditions in which they may occur are relatively easy to distinguish from thyrotoxicosis

11 In a borderline case a therapeutic test with an antithyroid compound is justifiable Both nodular and diffuse forms of toxic goiter can be controlled by thiouracil or a closely related compound whereas many of the conditions which may simulate them are not at all affected

12 In Graves disease the gland has a meaty feel to palpation in Plummer's disease it is nodular in simple goiter it is soft like jelly and in malignancies it is stony hard

13 Nearly 60 per cent of the patients with thyrotoxicosis show a spaded atrophic condition of the nails (Fig 51) that is never present in neurocirculatory asthenia or other neuroses that may be confused with it

DIFFERENTIAL DIAGNOSIS

In those under 10, hyperthyroidism is most frequently confused with neurocirculatory asthenia simple colloid goiter or puberty or adolescence or low grade chronic infection such as tuberculosis syphilis or brucellosis In patients over 10 the condition is most often mistaken for the climacterium Among the conditions which must be distinguished are

1 Glandular Conditions —

a The Climacterium —The emotional disturbances the phobias the nervous erethism the insomnia the hot flushes and the easy tendency to profuse perspiration seen in the climacterium may often suggest toxic goiter especially if the patient happens to have a coincidentally existing simple colloid type of gland As a rule however in the climacterium the basal metabolic rate is normal and the flushes of heat are *paroxysmal* and intermittent Weight is gained rather than lost Values for blood protein bound iodine are within normal limits If further diagnostic help is needed a therapeutic test with estrogenic or androgenic preparations will quickly settle the issue Of course it must be remembered that hyperthyroidism and the climacterium may not infrequently occur simultaneously

b Acromegaly —Cases have been reported in which the overactivity of the thyroid has been a predominating feature in acromegaly (McCullagh and Schneider 1941) although the hypermetabolism of this disease is not always due to an increase in thyroid function (McCullagh Gold and McKendry 1950) As a rule however such manifestations make themselves known only after the acromegaly is already well established

c Increased Adrenocortical Activity and Adrenocortical Tumors — These lesions may sometimes cause a rather striking elevation of the basal metabolic rate Because of the normal relationship existing between the thyroid and the adrenal overactivity of the adrenal cortex may be associated with many manifestations simulating hyperthyroidism The presence of masculinizing features and of a demonstrable adrenal enlargement a moderate polycythemia and some elevation of blood electrolytes may all be helpful in arriving at the primary diagnosis In conjunction with the adrenal conditions and hyperthyroidism it should be emphasized that steroids of the adrenal cortex notably cortisone are capable of raising the basal metabolism in the presence of myxedema and without altering thyroidal function as measured by radioiodine uptake (Beierwaltes Wolfson Jones Knorpp and Siemenski 1950) Thus it appears that the elevation of basal metabolism seen in Cushing's syndrome may be at least in part a direct effect of the adrenal cortex and not mediated via the thyroid

2 The tremor of hyperthyroidism is very fine rarely, if ever, coarse

3 The patient with hyperthyroidism is *continuously* warm not at first hot and then cold, as is the subject suffering from the climacterium

4 A hot moist skin is characteristic it is rarely dry and hot never dry and cold

5 Characteristically the tachycardia of hyperthyroidism fails to disappear after rest or during sleep contrast the behavior of that due to neurocirculatory asthenia or excitement

6 Loss of weight with an excellent appetite should always prompt the clinician to suspect hyperthyroidism however it *must not be forgotten* that the most severe cases may have anorexia of high degree

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mon and striking In such psychoses the determination of the basal metabolic rate has little value as it may vary widely from subject to subject The disappearance of tachycardia during sleep the absence of a goiter the normal values for blood iodine and the tendency for other signs and symptoms to be spasmodically rather than continuously present all indicate a psychosis rather than hyperthyroidism While we must not mistake psychotic subjects for those with thyrotoxicosis it is equally true that we should not overlook the psychotic manifestations which are occasionally due to and complicate the clinical picture of hyperthyroidism They are usually toxic in nature and rarely appear until the thyrotoxicosis is very severe *In such cases conservative management is always advisable as surgery is poorly tolerated*

b Neurocirculatory Asthenia—Neurocirculatory asthenia nervous exhaustion or irritable heart as it is variously called is the most common condition to be confused with hyperthyroidism Tremor palpitation tachycardia and weight loss are the major symptoms common to *both conditions The tremor is difficult to distinguish as it is usually* fine in type in either state However it is accompanied by *warm* moist hands in hyperthyroidism and *cold* clammy hands in neurocirculatory asthenia The palpitation is usually a purely subjective phenomenon in neurocirculatory asthenia with the apical impulse rarely visible and sometimes difficult to feel while it is both a subjective and objective sign of such violence in hyperthyroidism as to cause the entire chest wall to heave with each cardiac systole

Tachycardia usually disappears during rest or sleep in subjects with neurocirculatory asthenia and is relatively uninfluenced by these acts in those with thyrotoxicosis A loss of weight occurs in neurocirculatory asthenia because of anorexia and a low caloric intake It appears in hyperthyroidism in association with a good even excellent appetite and is due to the much heightened caloric requirement of the individual which even his high ingestion of food is incapable of meeting

Rest improves the subject with hyperthyroidism so much so that he is eager to be active although lacking endurance The subject with *neurocirculatory asthenia complains* bitterly of fatigue which is not relieved by rest or sleep and indeed is often aggravated by inactivity

The *dyspnea* and tachypnea of hyperthyroidism are those of an overburdened circulation and have all the distinguishing features of such In neurocirculatory asthenia *the dyspnea may appear* or *be* worse at rest and the rapid breathing be that of an hysterical or climacteric type

Repeated determinations of the basal metabolic rate will yield consistently high values in hyperthyroidism whereas in neurocirculatory asthenia the rate is usually normal and if high in a single test will not be so found on repetition

d Diabetes Mellitus—The weight loss and voracious appetite of diabetes mellitus associated with muscular weakness and a loss of strength may lead one to suspect thyrotoxicosis when diabetes mellitus is actually present The picture is even more confused in view of the fact that glycosuria and hyperglycemia are relatively common in thyrotoxicosis without the development of permanent damage to the islands of Langerhans of the pancreas In diabetes mellitus there is no goiter the basal metabolic rate is usually normal and the blood protein bound iodine is not elevated Difficulty will arise only when both conditions are simultaneously present In this connection it must be remembered that diabetes mellitus does not predispose to thyrotoxicosis but thyrotoxicosis does materially increase the incidence of diabetes mellitus

e Thyrotoxicosis Factitia—It is often impossible to distinguish the clinical picture of self induced hyperthyroidism from that of the spontaneous variety Little difficulty will be experienced in ascertaining the true nature of the condition if a satisfactory history can be obtained However in certain psychiatric subjects this may be impossible (Perkin McFarland and Hurxthal 1941 Hurxthal 1941 Skanse and Riggs 1948) In such instances, tracer doses of radioactive iodine are excreted more rapidly than in the normal patient and the uptake of iodine by the thyroid gland is normal rather than elevated as it is in endogenous hyperthyroidism (Skanse and Riggs 1948)

In connection with thyrotoxicosis factitia it is interesting to call to mind the case of Robbins and Man (1949) whose 31 year old patient ingested 63 grams of desiccated thyroid substance at a single dose but developed no thyrotoxic symptoms despite the fact that her serum precipitable iodine rose to 10 9 mg per 100 c c

f Hyperparathyroidism—One case has been reported in which the classical features of hyperparathyroidism were present and obscured the true diagnosis of hyperthyroidism until the absorption rate by the thyroid of radioiodine was found to be high (Stanley and Lazekas 1949) Under antithyroid medication all manifestations disappeared including recurrent vomiting azotemia fixed urinary specific gravity hypercalcemia and hypercalciuria

2 Nervous and Mental Conditions—

a Psychosis—Major organic psychoses particularly involutional melancholia may simulate hyperthyroidism In such conditions the effects of sympathetic nervous system stimulation are usually in evidence and tachycardia excessive perspiration a fine tremor restlessness and hyperreactivity may appear Some psychotic subjects lose considerable weight and the facial expression often exhibits an anxiousness not unlike that present in hyperthyroidism A wide variety of phobias may occur among which a fear of impending disaster is com

mon and striking In such psychoses the determination of the basal metabolic rate has little value as it may vary widely from subject to subject The disappearance of tachycardia during sleep the absence of a goiter the normal values for blood iodine and the tendency for other signs and symptoms to be spasmodically rather than continuously present all indicate a psychosis rather than hyperthyroidism While we must not mistake *psychotic subjects for those with thyrotoxicosis* it is equally true that we should not overlook the psychotic manifestations which are occasionally due to and complicate the clinical picture of hyperthyroidism They are usually toxic in nature and rarely appear until the thyrotoxicosis is very severe In such cases conservative management is always advisable as surgery is poorly tolerated

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Repeated determinations of the basal metabolic rate will yield con*sistently high values in hyperthyroidism* whereas in neurocirculatory asthenia the rate is usually normal and if high in a single test will not be so found on repetition

c *Encephalitis*—The stare the nervousness, the tachycardia, the loss of weight and the high basal metabolic rate are shared in common by hyperthyroidism and encephalitis A carefully taken history may indicate the correct diagnosis The presence of positive neurological signs points toward an encephalitis When a fine tremor occurs in that condition it is usually submerged in or overshadowed by coarser movements Iodine and antithyroid compounds do not improve encephalitis nor lower the elevated metabolism of that disease whereas they effect a dramatic change in hyperthyroidism

3 Cardiac Disease—Both functional and organic cardiac disturbances have been confused with hyperthyroidism Ten per cent of Nochtens (1910) mistakenly diagnosed cases were due to organic heart disease Hypertensive heart disease rheumatic carditis and aortic regurgitation from any cause are the commoner organic lesions that have led to an erroneous diagnosis

It is often extremely difficult to distinguish the tachycardia the forceful apical pulsations the increased excitability and irritability the tremor and the stare of *hypertensive cardiovascular disease* from that of hyperthyroidism particularly as the basal metabolic rate may be equally elevated in both conditions A high diastolic blood pressure favors a hypertensive etiology while a low one is usually seen in thyrotoxicosis Hurxthal and Parker (1913) emphasize that the snapping pulse waves heard on auscultation of the blood pressure in hyperthyroidism are not present in cases of hypertension The antithyroid compounds may afford a therapeutic test of extreme value in the doubtful cases as the manifestations of hypertension including the elevated metabolism are not affected thereby

A detailed description of the hypertensive diencephalic syndrome has been made recently by van Buchem (1918) He emphasizes the point that thyroid enlargement is sometimes present thus making differentiation from thyrotoxicosis still more difficult

Rheumatic carditis or *syphilitic aortitis* may be confused with hyperthyroidism but difficulty is experienced only when there is some degree of right or left heart failure or both If the cardiac phenomena are due to hyperthyroidism the circulation time is usually shortened or normal If they are caused by primary disease of the heart then the circulation time is prolonged

In thyrotoxicosis the most common disturbances of cardiac rhythm are *auricular paroxysmal tachycardia* and *auricular fibrillation* Occasionally it is difficult to decide whether the arrhythmia is due to hyperthyroidism or to some unrelated cause The sudden appearance and disappearance of paroxysmal tachycardia in a person who appears to be in good health between the attacks points to a nonthyroid origin When auricular fibrillation occurs in hyperthyroidism the condition is usually severe, so that the thyrotoxic signs are sharply defined particu

ly the hyperactivity the moist hot flushed skin and the hyper motility of the chest wall

At times the hyperthyroidism produces cardiac phenomena which suggest a primary lesion of the heart We have seen several cardiac diagnoses made by as many physicians in a single hyperthyroid individual Among these may be mentioned rheumatic carditis with isolated mitral valvulitis rheumatic heart disease with double mitral and aortic lesions syphilitic aortitis with regurgitation and arteriosclerotic cardiovascular disease with hypertension *All lesions have disappeared promptly following adequate therapy with antithyroid compounds* and the same observers have found that no evidence favoring primary cardiac disease remains

4 **Blood Dyscrasias** —*Lymphatic* or *myelogenous leukemia* may be associated with an elevation of the basal metabolism to as high as +70 per cent This increased metabolism is not affected by antithyroid compounds but is sometimes lowered by roentgen radiation in proportion to the decrease produced in the number of circulating white blood cells

Sweating exophthalmos and tachycardia may be present in leukemia In other regards these conditions have little in common with hyperthyroidism

Polycythemia vera and *pernicious anemia* are frequently associated with an increase in basal metabolism but no other features of these diseases should offer any serious difficulty in arriving at a differential diagnosis

5 **Systemic Infection** —Tuberculosis heads the list of the infections which may be confused with hyperthyroidism

a Tuberculosis —Consideration of several features common both to hyperthyroidism and tuberculosis will aid materially in distinguishing one from the other (1) The loss of weight and strength in thyrotoxicosis occurs despite a normal or markedly increased food intake In tuberculosis the appetite is poor and reflex gastrointestinal complaints such as gaseous distention belching constipation acid eructations *and so forth* are common In tuberculosis the patient is continuously fatigued whereas in hyperthyroidism he may start the day full of energy but soon becomes tired (2) The pulse pressure is large in thyrotoxicosis and frequently small in tuberculosis (3) The nervousness of thyrotoxicosis is objective in character in tuberculosis it is subjective In the latter condition the patient has a sensation of inward nervousness shows a languid behavior and often an apathetic attitude whereas in hyperthyroidism he is more liable to be exhilarated at least mentally (4) The elevation of the basal metabolism in tuberculosis is moderate and corresponds to the degree of temperature present (5) The skin is hot moist and flushed in thyrotoxicosis in pulmonary tuberculosis with fever the skin is hot and dry with bouts of

perspiration A malar flush is present but the rest of the face is pale in contrast to the generalized flush of thyrotoxicosis In differentiating pulmonary tuberculosis from hyperthyroidism it must not be forgotten that the two may exist simultaneously The progress of the former is more rapid when hyperthyroidism is present Conservative treatment of the hyperthyroidism materially improves the prognosis Unfortunately the physician frequently ascribes the thyrotoxic symptoms erroneously to the febrile tuberculous state thus increasing the patient's already serious hazards The determination of the protein bound fraction of blood iodine will be helpful in establishing the coexistence of hyperthyroidism It is never elevated in uncomplicated tuberculosis (Klassen, Riley and Curtis 1945)

b Other Infections—Infectious mononucleosis brucellosis cardiovascular syphilis and a variety of low grade septicemias may show some manifestations that simulate those produced by hyperthyroidism The presence of temperature the finding of a specific cause and the absence of goiter and its cardinal symptoms will usually settle the diagnostic question

6 **Malignancy**—The general manifestations of malignant cachexia may simulate thyrotoxicosis However the discovery of metastases and the absence of any pathognomonic combination of the signs of thyroid disease will usually clarify the diagnosis

7 **Diseases Associated With Hyperthyroidism Which Sometimes Make Diagnosis Difficult**—Diseases in which the bony disturbances are prominent and may simulate those seen in hyperthyroidism include osteodystrophia fibrosa (Sternberg and Joseph 1942) fibrous dysplasia of bone (Lichtenstein and Jaffe 1942) Paget's disease (Lyon 1942) and hyperthyroidism (Stanley and Lazekas 1949) Conditions in which the hematopoietic system is involved include pernicious anemia (Christian 1911 Boenheim Schwimmer and McGavick 1945 Means Baker and Richardson 1947 Mulder and Mulder 1947 Selvaag 1948) and thrombocytopenic purpura (Conklin and Shrank 1941) Among the metabolic conditions to be considered in association with hyperthyroidism are diabetes mellitus (John 1928 1940 McDonough et al 1941) myasthenia gravis (Thorn and Tierney 1941 Kowalski et al 1941 1942) familial periodic paralysis (Hildebrand and Kepler 1941) and localized myxedema (Amerbach and Kunce 1941 Zondek 1943) Miscellaneous conditions associated with thyrotoxicosis with more than average frequency include neurocirculatory asthenia (Moschcowitz and Bernstein 1941) periarteritis nodosa (Rich 1945) and peptic ulcer (Wu 1945) hypertension (Selvaag 1948) and achlorhydria (Selvaag 1948)

COMPLICATIONS OF HYPERTHYROIDISM

1 **Cardiac Failure**—(See Hyperthyroidism Course Chapter XXXV) The incidence of cardiac failure in hyperthyroidism is roughly

proportional to age but rarely occurs before 30 Because of this the condition is observed more than twice as frequently in Plummer's disease as it is in exophthalmic goiter and is present in about one third of the former group

When any large series of cases is considered the average duration and intensity of the thyroid overactivity seem to vary directly with the incidence of cardiac failure although this certainly may not hold true for any given case The quite normal heart may tolerate thyrotoxicosis indefinitely However when hyperthyroidism occurs in a person whose heart is already impaired congestive failure may occur (Lerman and Means 1932c) In younger individuals the rheumatic heart is a common underlying disease in older ones hypertension or arteriosclerosis

In any event the increased load placed upon the heart by thyrotoxicosis is sufficient in a considerable group of patients to prevent the heart from meeting the extra demands placed upon it It seems logical to conclude that the forces mentioned by Lerman and Means are important It appears unnecessary to take the viewpoint that a qualitative change in thyroid hormone is essential to the production of thyrocardiac forms of the disease We have repeatedly seen desiccated thyroid substance produce cardiac failure and even death in individuals with previously damaged hearts in dosages which would have little or no influence upon the perfectly normal individual (McGavack and Schwimmer 1941 McGavack Lange and Schwimmer 1943)

In two thirds of the cases the commonest arrhythmia auricular fibrillation produced by an excess of thyroid hormone disappears following treatment of the hyperthyroidism (McGavack Gerl et al 1943 Brothauer 1947) It is characteristic that digitalis controls neither the ventricular rate nor the fibrillation

2 **Diabetes Mellitus** —Carbohydrate metabolism is palpably disturbed in from 7 to 10 per cent of all cases of thyrotoxicosis In approximately 2 per cent the insulinogenic apparatus is permanently damaged so that these patients are diabetic for the remainder of their lives A previously existing diabetes mellitus is usually aggravated by thyrotoxicosis

3 **Disturbances of the Liver** — Pathological changes are commonly observed in the livers of individuals dying of thyrotoxicosis (see Actions of Thyroid Hormone Chapter XIII and Hyperthyroidism Pathology Chapter XXXIV) The fortunately large hepatic reserve with which man is endowed has made it difficult to employ tests capable of demonstrating minor degrees of hepatic damage However slightly more than half of an unselected group of thyrotoxic patients prepared for surgery have shown hepatic insufficiency as measured by the Quick hippuric acid test (Schmidt et al 1941) In about one sixth of this group of sub

jects the degree of impairment of hepatic function was considerable In all instances the dysfunction of the liver was quantitatively related to the duration and intensity of the thyrotoxic state rather than to the type of goiter present Preceding a thyroid crisis or toxic psychosis, hepatic damage is usually demonstrable It has been further observed that the hepatic damage is not irreversible and disappears when the thyrotoxicosis is controlled (Lemma and Nacleno 1915 Schmidt et al 1941)

4 **Psychosis**—The psychosis of hyperthyroidism is toxic in nature and secondary to the hepatic damage For that reason its presence is a poor prognostic sign and calls for rapid rigid control of the thyrotoxic state

5 **Thyroid Crisis**—Because of its fulminant onset lethal course and unsatisfactory management thyroid crisis warrants more than passing consideration Recent reviews of cases of crisis at The University of Michigan (*Buxton 1941*) and the Massachusetts General Hospital (McArthur Rawson, Means and Cope 1917) afford us a critical analysis of case material that in both instances has been used to reconstruct the background against which thyroid storm occurs or is likely to occur Many of the facts and conclusions in the present discussion will be drawn from these two sources without further credit

a Definition—Thyroid crisis or storm is a life endangering augmentation of the symptoms of thyrotoxicosis in which the patient's response is out of proportion to the exciting stimulus whatever its nature (thyroidectomy pneumonia wound sepsis) (McArthur Rawson Means and Cope 1917) From this definition it is clear that crisis is rather an integral part than a complication of thyrotoxicosis It is an exaggeration of mild to moderate reactions which can occur in all hyperthyroid subjects under stress The fever which commonly follows thyroidectomy is a simple example of such a moderate reaction

Manifestations of crisis are particularly prone to appear in the central nervous cardiovascular and hepatorenal systems but there is no uniformity of findings for the final breakdown may occur in any one of these Buxton (1941) aptly amplifies this point It is our impression that thyrotoxicosis is not a fatal disease when correctly treated that thyroid crisis is not a specific entity and that death in this state results from the various complications associated with the augmented metabolism which are often injudiciously and inaccurately treated

b Factors Involved in the Production of Crisis—Two major factors are necessary for the production of crisis in hyperthyroidism loss of reserve on the part of the patient and a precipitating stimulus

(1) *Loss of reserve on the part of the patient* The outstanding alteration of function seen in hyperthyroidism or produced by the

administration of thyroid hormone is an increased metabolism While we have discussed the effects of this metabolic change upon several systems of the body (Hyperthyroidism Clinical Course) a brief recapitulation may serve to bring the true nature and course of crisis better into focus

On the *heart* hyperthyroidism causes a loss of cardiac reserve by a combination of several mechanisms (a) elevated metabolism resulting in accelerated pulse rate heightened blood pressure altered stroke volume and so forth the sum total of which is a rise in cardiac load to as high as fivefold normal (b) increased nutritional requirements for the heart particularly as regards glycogen vitamin B and certain minerals (c) an excessive production of epinephrine like substances and an increase in their concentration within the cardiac musculature (Raab 1941a b Raab 1943 Raab 1941a b) Such substances enhance the metabolic activity of the heart in part through their action upon the cardiac accelerator fibers and in part through their influence upon intermediary carbohydrate metabolites In line with the effect of these sympathomimetic amines upon the production of cardiac lesions in thyrotoxicosis Maddock et al (1936) demonstrated an increase in epinephrine postoperatively in the blood stream of patients who developed crisis

The above are competent causes for the myocardial disturbances seen in crisis—the arrhythmias the anoxic changes in the electrocardiogram the anginal pain the pulmonary edema hypertrophy and dilatation of the heart myocardial degeneration and necrosis cardiac failure and death

Undoubtedly the *central nervous system* suffers most in crisis The manifestations result from an anoxic anoxia and the presence of excessive amounts of sympathomimetic amines Early in thyroid crisis the symptoms are like those of mountain sickness with euphoria talkativeness sudden emotional outbursts (laughing crying singing etc) Later there is a fretfulness and a fixation of ideas Finally delirium maniacal tendencies hyperpyrexia and coma supervene That anoxic anoxia has a major part in these developments is borne out experimentally The oxygen consumption of the brains of hyperthyroid subjects has been found to be as much as four times normal Animals fed thyroid substance withstand anoxia much more poorly than do normal ones Enzyme systems are not lacking in the brain of the hyperthyroid subject and indeed are increased the dehydrogenases more than the oxidases While anoxia undoubtedly plays a causative role in the production of the hyperpyrexia an added factor may be related to the action of epinephrine and kindred sympathomimetic substances which can cause an elevation of temperature may act with enhanced effectiveness in hyperthyroidism and are increased in amount in crisis

The loss of *hepatic* reserve in hyperthyroidism has been discussed fully in the sections on Physiology (Chapter XIII) and Pathology of Hyperthyroidism (Chapter XXXIV) and will not be repeated here. It is well however to emphasize the point that the liver may suffer from the anoxic anoxia in a manner similar to the other organs despite the lowered oxygen tension normally found within it. When oxygen concentration is reduced in hyperthyroid animals there follows extensive necrosis of the hepatic cells about the central vein and an inflammatory cellular reaction occurs in the neighborhood of the portal vessels.

In an exhaustive review Lahey and Nickerson (1945) reached the conclusion that the liver is the organ usually responsible for crisis. Among their reasons for this belief are: (1) The clinical picture of crisis closely simulates exhaustion resulting from hepatic hyperpyrexia. (2) Experimental evidence and the morbid anatomical findings indicate the close association between hyperthyroidism and the liver. (3) Boyce's results with the Quick hippuric acid test of liver function has been offered as proof of liver damage occurring as the result of thyroid disease. (4) The physiological imbalance and pathological changes in the liver due to anoxemia has been established. Anoxia in hyperthyroidism is common knowledge. (5) The interrelationship between hyperadrenalism, hepatic glycogenolysis and the experimental production of toxic thyroid signs by injection of adrenalin has been emphasized.

'The premise of our discussion therefore is that the most important organ exclusive of the thyroid itself concerned in the production of thyroid crisis is the liver.'

The *particular clinical picture* to be observed in any given case of crisis will vary more or less directly with the intensity of the disturbances taking place in the brain, heart or liver and their effect upon one another and the rest of the body.

(11) *The precipitating stimuli which may bring about crisis.* Causes of crisis in the hyperthyroid individual who is already laboring under disturbances in physiology like those just detailed fall into very diverse categories.

Preoperative crisis has been most commonly precipitated by a delay in bringing the toxic patient to the hospital, an intercurrent infection, a poorly planned program of preoperative diagnostic and therapeutic procedures, improper or inadequate sedation and surgical procedures such as biopsy not directed to the relief or control of the toxicity. An acute toxic psychosis in the course of hyperthyroidism is an ominous sign and should be an absolute contraindication for early surgery.

Among the causes of *crisis postoperatively* are

(a) Oversedation particularly the routine use of *opiates* at stated *regular* intervals without regard to the clinical status In so far as possible sedatives with a bulbar action should be avoided as they tend to increase the anoxia or to produce it if not already present

(b) Undue manipulation of the gland during operation Sometimes this cannot be avoided but the consequent increase in tissue thyroxin is often sufficient to initiate the changes that lead to crisis Thyroidectomy itself was the commonest cause of crisis in the cases of McArthur and her associates (1917) Most of the cases which they have summarized were treated prior to the discovery of potent reliable antithyroid compounds Today there is no excuse for storm due directly to the removal of the thyroid It is now possible to control fully the toxicity of hyperthyroidism by the use of antithyroid compounds or radioactive iodine (in those subjects that are sensitive to thiouracil and its derivatives) so that no excessive amounts of thyroid hormone are present either in the tissues or in the thyroid at the time of operation **A fully controlled patient cannot develop crisis** He may of course develop anoxia as a result of mechanical disturbances to his air passages secondary to the operative or anesthetic procedures These will cause no trouble if dealt with *promptly* in an efficient manner

(c) Postoperative hemorrhage and secondary suture

(d) Respiratory infection particularly bronchopneumonia

(e) Cardiac failure with secondarily associated respiratory disturbances such as pulmonary edema

Medical storms have been most commonly associated with pneumonia malnutrition cardiac failure overdigitalization and iodine withdrawal

With present methods of control the number of patients who develop crisis in any one of these ways should be negligible For instance the administration of iodine should not be stopped in the highly toxic patient at least until an antithyroid compound has been used sufficiently long to exert some salutary effect This will usually take two to three weeks provided the dosages are adequate Absolute bed rest is necessary for any patient showing the slightest manifestation of cardiac failure until such time as the hyperthyroidism is under control Pneumonias should be treated with antibiotics The dose of digitalis should be decreased at the slightest sign of glucosidal toxicity or when it is apparent that the antithyroid compound is effecting a reduction in the thyrotoxicosis

c *Clinical Picture*.—Crisis in connection with surgery may occur at any age whereas medical storm is most frequently encountered from the age of 40 onward The incidence of crisis in the male as compared with the female is greater than can be accounted for on the basis of the sex distribution of hyperthyroidism this tends to confirm

the impression that thyrotoxicosis is more severe in men Storms occur with about equal frequency in diffuse and nodular types of goiter The higher the basal metabolism the greater the loss of weight, and the more persistent the tachycardia the more likely is crisis to appear *From this statement should arise an absolute rule of procedure viz* that no operation shall be performed until the basal metabolism is normal and at least 75 per cent of the lost weight has been regained During operation marked increases of blood pressure and pulse rate in a previously highly toxic patient should warn the physician that postoperative crisis is to be feared

In crisis there is an accentuation of all the symptoms of hyperthyroidism Hyperpyrexia, severe tachycardia motor restlessness with irritability nausea vomiting occasionally diarrhea dehydration sometimes jaundice delirium collapse and coma comprise the manifestations of the classical case At times extreme prostration hypotonia apathy and moderate fever are encountered The lack of extreme fever (106 F and above) should not lull one into a false sense of security regarding the apathetic type of patient he demands care just as promptly and just as completely as the more dramatic hyperreactive subject

d Pathology—The postmortem findings in thyroid crisis may be remarkably few McArthur et al (1917) found pulmonary and cardiac complications frequently and were impressed by the paucity of pathological changes in the liver ' Foss Hunt and McMillan (1939) observed central necrosis and fatty degeneration in the livers of 90 per cent of their autopsied cases There is no pathognomonic anatomical feature of crisis but alterations of a nonspecific nature may occur in any organ particularly in the brain heart and liver

e Treatment of Crisis—In no condition is it more true that an ounce of prevention is worth a pound of cure Present methods of dealing with the toxicity of goiter as soon as diagnosed have already diminished the incidence of crisis well nigh to the vanishing point Crisis in connection with operation can be avoided if operation is performed *after* toxicity is controlled 75 per cent or more of the weight lost is regained and the pulse rate has returned to normal Where emergency surgery must be performed as in Puppel's patient with acute appendicitis (1917) thyroid crisis may be unavoidable

The active treatment of thyroid crisis will vary somewhat from patient to patient and will differ in some respects in the medical and surgical groups In presenting several recommendations it is understood therefore that all of them will not be applicable in every case or type of case but that at one time or another they may be useful (1) combat tissue anoxia by removing all mechanical obstruction to the air passages and by administering oxygen (2) diminish the production of thyroid hormone and its discharge from the thyroid by giving

large doses of iodine (2 gm of sodium iodide daily intravenously or 30 to 45 minims of Lugol's solution daily by mouth) standard treatment with a thouracil derivative (q v) and small doses of a sedative with a minimum of bulbar effects (3) correct and maintain mineral and fluid balances (4) protect the liver by administering simple sugars and vitamins (particularly vitamin B complex) (5) supply additional adrenocortical steroid hormones in the form of watery extracts of the adrenal these will aid in the maintenance of fluid balance and in improving hepatic function and (6) control secondary or precipitating infections with antibiotics particularly penicillin

6 **Ophthalmopathic Form of Graves' Disease**—This subject will be discussed under Ophthalmopathic Graves Disease (Chapter XXXIX) (q v) It is a late always serious and fortunately rare complication of hyperthyroidism most frequently appearing after surgical removal of a mildly toxic gland

7 **Postoperative Complications**—The postoperative complications of hyperthyroidism include hemorrhage nerve injury with disturbances in respiration and speech tracheal collapse pulmonary collapse bronchitis bronchopneumonia pulmonary embolism disturbances in cardiac rhythm psychoneurosis acute psychosis crisis hypoparathyroidism and hypothyroidism Fortunately as preoperative and postoperative care has improved most of these conditions have become less and less common Some of them have already been discussed and others belong logically within the province of the postoperative surgical management (q v) The remainder will be considered here

The occurrence of *psychological invalidism* following thyroidectomy (Ruesch et al 1947) is often treated too lightly Indeed if we used more care in our diagnostic evaluation many such cases would not be operated upon at all as quite frequently the thyroid disease is secondary to some other problem which may be endocrine psychic neurotic or even organic in nature

The advent of *acute psychosis* in the hyperthyroid subject is always an ominous sign invariably influencing the prognosis adversely When the condition is due to the thyrotoxicosis per se prompt attention to the glandular overactivity is usually successful in effecting a favorable outcome When a primary psychotic state exists the outlook is always grave and the patient may succumb to the overdrive of the thyroid before any fundamental change can be brought about in the mental aberration

Hypoparathyroidism following thyroidectomy may be insignificant and transient or outspoken and permanent In either case it is wise to recognize it early as the patient will thus avoid many of its unpleasant effects Occasionally the condition is mistaken for recurrent hyperthyroidism because of the irritability tremors and mildly elevated

basal metabolic rate In order to avoid such a mistake as well as to recognize the latent larval or subtetanic forms it is well to establish a base line of determinations during our initial physical examination for subsequent comparison with alterations that may appear later as a result of a postoperative hypoparathyroidism These should include (1) a careful record of any or all paresthesias (2) evaluation of the Chvostek reflex and (3) results of the Trousseau reaction The influence of hyperventilation and of nervous tension upon the appearance and severity of any one or all of these manifestations should be noted Changes of an abnormal type following thyroidectomy must be considered as likely evidence favoring the presence of hypoparathyroidism Should such occur specific tests can then be made if necessary for final confirmation of the diagnosis

Some of the unusual manifestations which may be associated with the chronic hypoparathyroidism that follows thyroidectomy include dysphagia incapacitating asthenia lenticular cataracts epileptiform convulsions and blurring of vision with bilateral papilledema (Levy 1917) The presence of such bizarre findings emphasizes the necessity for repeatedly examining postoperatively those patients who are not doing well or who complain vaguely of paresthesias or nervousness

Treatment of the latent case of hypoparathyroidism rarely demands heroic therapy Three to six grams of calcium gluconate or lactate daily by mouth and from 100 000 to 400 000 U S P units of vitamin D are usually sufficient to control the condition In the transient forms of tetany this regime may be gradually eliminated by slowly decreasing the dose of each medicine If on the other hand such therapy does not result in the maintenance of normal blood levels for calcium then dihydrotachysterol should be added Use that dose which is necessary to maintain a normal blood calcium and which falls just short of producing a positive Sulkowitch test in the urine In the majority of subjects this will be somewhere between 3 and 20 minims daily The amount of dihydrotachysterol should be held to the minimum compatible with complete clinical control for it is an expensive drug and an overdose can seriously deplete the reserve stores of calcium within the osseous system of the body The high cost of parathormone and the rapid production of antihormone following its administration have long since justified its abandonment as a therapeutic measure in hypoparathyroidism

Hypothyroidism may follow thyroidectomy despite the most careful surgical technic Its diagnosis has already been discussed at length (q v) and will seldom be missed if a careful physical examination is performed six weeks after operation Treatment is the same as for any other form of hypothyroidism

Chapter XXXVIII

HYPERTHYROIDISM V TREATMENT

Rational therapy for hyperthyroidism must be aimed at the correction of the neuroendocrine disturbances which produced it Any factor involved in the synthesis of thyroid hormone may be at fault The primary alteration may be concerned with abnormal cerebral activity the hypothalamic stimulation of the anterior pituitary an increased activity of the anterior pituitary the production of excessive amounts of thyroid stimulating hormone by the pituitary and alterations in the thyroid gland leading to the elaboration and discharge of toxic quantities of thyroxin

Despite recognition of these and other processes necessary for the development and utilization of the metabolic hormone of the thyroid the predisposing causes of hyperthyroidism are not entirely clear In exophthalmic goiter however cerebral disturbances seem to play a fundamental role where as a lack or relative lack of iodine is a prominent precipitating feature in the active episodes of every form of thyrotoxicosis

From a practical standpoint the fundamental object of treatment is to diminish the output of thyroid hormone In this connection we may speak of *corrective* and *adjunct* therapy Under the former term we refer to any treatment which will decrease the amount of thyroid hormone formed Under the heading of adjunct therapy we refer to all measures which will (a) conserve the expenditure of energy (b) replace stores of substances depleted by the hypermetabolism and (c) restore to normal such functions as have been deranged by the activity of excessive amounts of thyroid hormone within the tissues of the body

CORRECTIVE THERAPY

Under the section on physiology we have discussed at some length the relationship between the nerve centers the anterior pituitary and the thyroid gland- all coordinating in a balanced activity for the production of thyroid hormone in sufficient amounts to maintain bodily processes in health In thyrotoxicosis one or more of these factors is disturbed in such a way that excessive amounts of thyroid hormone are produced Therefore corrective therapy must be designed to block

such overproduction of thyroglobulin The measures helpful in accomplishing this may be looked upon as acting at a specific point in the thyroid hypothalamico hypophyseal system to break a vicious cycle Important among them are

1 **Psychotherapy**—We have yet to see a case of exophthalmic goiter in which an emotional stress of considerable magnitude was absent Such a disturbance is capable of increasing the rhythmic impluses from the hypothalamus which serve to regulate the rate at which thyrotrophic hormone is produced by the anterior pituitary gland Conversely a correction of the psychic disorder will normalize the hypothalamic impulses and thus tend to restore the thyroid pituitary balance Details of the application of psychotherapy are scarcely within the scope of the present discussion Usually however its principles can be adapted to the individual problem by the family physician He of all people is most intimately acquainted with the patient and her household Such treatment requires patience and may take a considerable period of time to become effective Inasmuch as complicating features may arise at any time during the course of thyrotoxicosis it is hardly fair to use this method of therapy alone any more than it is wise to neglect it entirely as is often done

The ideal objective of psychological therapy is the removal of the causes for worry *This will take time and may not ever be possible* of accomplishment The apprehension of the thyrotoxic subject is born of his irritability excitability restlessness and hyperkinesis His *hyperreactivity makes him unusually susceptible to any environmental* influence and to the slightest suggestion of those around him An attitude of frankness reassurance encouragement and optimism will do much to quiet the jangled nerves and relieve the mental tension Frank talks about the disease reassurance by actually helping the patient to make necessary arrangements for surgery or other special therapy encouragement in carrying out a simple but effective schedule of physical activity and relaxation optimism regarding the final outcome—these are the cornerstones of a successful approach to the nervous and mental elements of the disease Formal psychotherapy seems ill advised at least until such time as toxicity is controlled and the purely mental nature of the underlying condition proved

2 **Rest**—Rest occupies a place in both corrective and adjunct treatment as both mental and physical rest are required Freedom from emotional stress relieves the higher brain centers diminishes impulses from the hypothalamus and thereby ends the overstimulation of the pituitary *The elimination of psychic or mental disorder* is frequently difficult to accomplish but should be the aim of every well planned therapeutic regime

Bodily energy and tissue activity are conserved by insistence upon additional periods of physical rest A vacation with change in environ

ment may aid in attaining both the mental and the physical objectives However if that is not possible it may be necessary to deal with the emotional problems gradually and to relieve the physical stress immediately by short periods of rest in relation to the hours of work each day

The degree of control necessary to exercise over physical activity will vary directly with the severity of the hyperthyroidism the age of the patient and his or her previous habits Fatigue should be avoided as its effects may be cumulative It is equally important to avoid boredom So much effort has often been spent in enforcing literally the physician's order for a specific number of hours of quiet and absolute rest that the patient finds himself more tired at the end than at the beginning thereof It is preferable that the physical activity be selected according to the tastes of the patient and in the more severe cases that frequent short periods of rest are interposed

3 **Iodine**—While iodine serves as one of the two essential raw materials in the production of thyroid hormone its position in thyroid physiology and its use in the treatment of hyperthyroidism are based on much more far reaching considerations most of which have already been discussed under the section on Physiology (Chapters VII IX XI and XII) In connection with the management of thyrotoxicosis it may be said to act in one of three ways depending upon the dosage and the particular conditions to be met in the individual case

In small doses (corresponding to 1 minim or less of Lugol's solution daily) iodine acts in hyperthyroidism mainly to supply the relative deficiency of iodine resulting from its excessive excretion (as much as 9 times normal—Laroche 1916) When thus supplied iodine lessens the expenditure of energy necessary for the production of a given quantity of thyroxin With a reduction in the work of the thyroid cell a normal or more nearly normal pattern of thyroid activity ensues and involution of the gland is favored The over all clinical result is relief of the hyperthyroidism (Thompson et al 1930 1932 Houssay and Deulofeu 1943)

Secondarily iodine may favorably influence thyrotoxicosis through interference with the enzymic processes responsible for the formation of thyroid hormone It is axiomatic that any substance necessary to the completion of an enzymic reaction may reverse or inhibit that reaction if present in a greater than optimal quantity Apparently doses of iodine from 12 mg upward (corresponding to 1 5 minims or more of Lugol's solution) are capable of such reversal or inhibition and thus decrease the hyperthyroidism by diminishing the amount of thyroid hormone produced Simultaneously the excess of iodine favors the storage of hormone rather than its extrusion into the blood stream thus further reducing the amount of thyroid secretion available for furthering metabolic activity throughout the body However if

the high levels of iodine administration are long continued this whole mechanism of repression breaks down and the thyroid again manufactures excessive amounts of its specific secretion

The third way in which iodine may suppress the formation of thyroid hormone is through its action upon the pituitary and upon preformed thyrotrophic hormone The capacity of the pituitary for concentrating iodine is second to that of the thyroid providing we exclude the rapid concentration for excretion by the kidney This high concentration appears to decrease the capacity of the pituitary for the production of thyroid stimulating hormone (TSH) In addition large doses of inorganic iodide are capable of inactivating preformed TSH by some this is believed to be a more prominent action than that exerted upon the pituitary directly The actual amounts of iodine which will act favorably in the individual case will vary considerably One of the important factors in such variation will be the status of the autonomic nervous system Sympathicotonia will aggravate the physiological and clinical disturbances already present in hyperthyroidism In such cases iodine excretion is increased circulating TSH is further depressed and thyroid hyperplasia is augmented Under such conditions the optimal dose of iodine may be higher than in those patients where sympathetic overactivity is minimal or does not exist at all

In general it is upon the larger doses of iodine that we depend for the preoperative care of the patient As above mentioned such therapy at first controls the toxic manifestations but may later become totally ineffective It is important therefore to plan surgery at a time when an optimum reaction has been obtained Usually this will occur following ten to twenty days of treatment with doses ranging from 5 to 15 minims of Lugol's solution three times daily

When used in conjunction with the administration of an antithyroid compound in preparation for surgery Lugol's solution should be employed as soon as the basal metabolism has dropped to +20 or below The combined treatment is continued until the basal metabolism is +15 or below and the soft mushy gland produced by thiouracil has become full and firm under the influence of the added iodine which results in an increased storage of colloid The time necessary for this to take place may vary from one to three weeks *Both the thiouracil preparation and the iodine are continued until the day of operation* The danger of release from the suppressive action of the thiouracil which begins immediately after it is stopped with consequent difficulties in postoperative management far outweighs any fancied or real danger of agranulocytosis in connection with any one of the five antithyroid compounds to be mentioned in our ensuing discussion *If proper control is attained* prior to surgery then *postoperative crisis cannot occur* for the hyperthyroid state does not exist

In the medical care of hyperthyroidism with the antithyroid compounds of the thiourea type iodine also has a place Here it is desirable to use doses of iodine more nearly within the physiological range 0 5 to 2 minims of Lugol s solution daily will be sufficient and should be started as soon as the basal metabolic rate has fallen to +20 per cent or below Such doses appear to be sufficient to correct slowly the hyperplasia and hypertrophy induced by a thouracil derivative They encourage the storage of colloid at the same time In other words iodine thus used aids in the involution of the formerly toxic follicles Such treatment should be continued for from two to four *months after all medication with the thouracil preparation is discontinued*

Iodism from the use of iodine in hyperthyroidism has been rarely recorded Newman and Ross (1947) were able to find eight instances *in the literature to which they added one of their own* Most of these reactions were mild or moderate in degree characterized by fever rash coryza and enlarged lymph nodes In three instances the patients were seriously toxic but in no instance did fatality result Should an intolerance to iodine appear its administration should be discontinued and never tried again

Inasmuch as dosage is relevant to the type of over all effect to be obtained by the use of iodine in hyperthyroidism the approximate amounts of iodine contained in unit doses of several *commonly used* preparations are given in Table XIX

TABLE XIX

IODINE CONTENT OF COMMONLY EMPLOYED PHARMACEUTICAL PREPARATIONS

PREPARATION	DOSE		AMOUNT OF IODINE PER DOSE	
	MIN	C C	MG	GRAINS
Sodium iodide sat (100 per cent) sol	1 0	0 1	62	0 8
Potassium iodide sat (100 per cent) sol	1 0	0 1	47	0 7
Potassium iodide	5 0 gr	0 3 (m	248	3 0
Lugol s solution	1 0	0 15	78	0 1
Lugol s solution	30 0	2 0	234	4 0
Lugol s solution	45 0	3 0	351	6 0
Hydriodic acid syrup	1 0 dr	5 0	70	1 0
Iodine tinct U S P	1 0	0 15	12	0 1

1 Thiouracil and Closely Related Compounds—The discovery of the antithyroid compounds of the thiouracil group and their application to the diagnosis and treatment of hyperthyroidism represent the most outstanding forward stride in the management of thyroid disease since the isolation of the thyroid hormone late in the last century. These substances in proper doses suppress the overproduction of thyroid hormone in thyrotoxicosis as completely and effectively as thyroid hormone relieves the manifestations of myxedema. They have failed to control hyperthyroidism only in those subjects who developed a toxic or hypersensitive reaction to their administration. In many instances they have been discontinued without any tendency for recurrence of the thyrotoxic state. These effects are accomplished by an interference with the enzymic processes that lead to the production of thyroid hormone by the thyroid gland. In the intact animal this action is associated with the production of a thyroid gland which is highly hyperplastic and at least potentially overfunctioning; a fact to keep in mind when discontinuing treatment with a thiouracil derivative.

Among the antithyroid compounds which have been tried thus far in human beings 1-methyl-2-mercaptoimidazole, 2-mercaptoimidazole, propylthiouracil, methylthiouracil, and thiouracil have been shown to be useful in the order named (Fig. 17 and Table XX). The first two mentioned have been under investigation only a short time. To date they are not available for general use, but their action is thus far unusually promising, so that an attempt will be made to include here instructions for their use. Of the widely employed and readily available preparations, propylthiouracil and methylthiouracil have been the most satisfactory, as they are almost twice as effective, weight for weight, as thiouracil. The former is about one-fourth as toxic as thiouracil, while methylthiouracil is about one-half to two-thirds as toxic. Of the five compounds under discussion, 2-mercaptoimidazole preparations *probably act more rapidly than the others* to achieve control of the thyrotoxic state, with thiouracil, methylthiouracil, and propylthiouracil following in the order named (Fig. 17). Thiouracil has now been withdrawn from the market because of the relatively high incidence of agranulocytosis (2.5 per cent), with death occurring in 0.5 per cent of those to whom it was administered. While similar reactions were equally common with methylthiouracil in the large doses originally used, they have been relatively rare in the smaller, *still effective* doses now employed. We know of but two cases in which severe neutropenia (2.0 and 1.0 per cent polymorphonuclear cells, respectively, with total white counts of 1200 and 1950 cells per cubic millimeter, respectively) has been *reported in patients taking propylthiouracil* (Parks, 1948; Bartels, 1948).

Earlier reports which showed methylthiouracil to be 1.2 to 0.6 per cent as toxic as thiouracil employed much larger dosages than are necessary for effective treatment. With the dosages *recommended* in Table XX the above statement should be true.

TABLE XX

DOSAGE CHART FOR THIOURACIL COMPOUNDS IN HYPERTHYROIDISM

PERIOD OF TREATMENT (DAYS)	DOSE (GM./DAY)				
	PROPYL-THIOURACIL	METHYL-THIOURACIL	2 MERCAPTO IMIDAZOLE	1 METHYL-2 MERCAPTO IMIDAZOLE	THIOURACIL
0–7	0.400	0.300	0.100	0.015	0.600
7–14	0.400	0.400	0.100	0.015	0.600
14–Control (21–36)	0.300	0.400	0.100	0.015	0.400
Maintenance	0.050–0.150	0.050–0.200	0.010–0.030	0.002–0.006	0.100–0.300

Methylthiouracil in the doses recommended controls hyperthyroidism with the same certainty as thiouracil although requiring a slightly longer time to do so. Propylthiouracil is the least reliable of the five drugs under consideration and may take as much as 10 to 11 weeks at the dosage levels recommended (Table XX) to bring about complete relief of toxicity. There have indeed been some cases in our experience which it was not possible to control fully with this drug alone. In some such instances the hyperthyroidism can be abolished by exceeding the doses recommended in Table XX but care must be taken not to employ such amounts for any prolonged period of time.

As a group these compounds afford us the treatment of choice in managing (1) all patients with hyperthyroidism who are being prepared for surgery, (2) all children and adolescents who have a Graves or exophthalmic type of goiter, (3) aged persons with hyperthyroidism associated with a diffuse hyperplasia of the gland or multinodular toxic adenomata, (4) hyperthyroid patients in cardiac failure, (5) hyperthyroidism appearing during pregnancy, and (6) recurrent hyperthyroidism particularly if previous surgical procedure was followed by nerve injury, an increase in or development of exophthalmos, or other problems making further surgery highly undesirable.

These antithyroid compounds offer us an elective method for dealing with all adult patients with Graves disease and those with small multinodular toxic goiters. Except in conjunction with preoperative care their use is contraindicated in all cases of chronic thyroiditis, uninodular toxic goiters, substernal or intrathoracic toxic goiters, and large multinodular toxic goiters. Their continued use is precluded in all subjects who develop agranulocytosis or generalized urticarial febrile types of reaction.

Thiouracil and Closely Related Compounds—The discovery of the antithyroid compounds of the thiouracil group and their application to the diagnosis and treatment of hyperthyroidism represent the most outstanding forward stride in the management of thyroid disease since the isolation of the thyroid hormone late in the last century. These substances in proper doses suppress the overproduction of thyroid hormone in thyrotoxicosis as completely and effectively as thyroid hormone relieves the manifestations of myxedema. They have failed to control hyperthyroidism only in those subjects who developed a toxic or hypersensitive reaction to their administration. In many instances they have been discontinued without any tendency for recurrence of the thyrotoxic state. These effects are accomplished by an interference with the enzymic processes that lead to the production of thyroid hormone by the thyroid gland. In the intact animal this action is associated with the production of a thyroid gland which is highly hyperplastic and at least potentially overfunctioning, a fact to keep in mind when discontinuing treatment with a thiouracil derivative.

Among the antithyroid compounds which have been tried thus far in human beings, 1 methyl 2 mercaptoimidazole, 2 mercaptoimidazole, propylthiouracil, methylthiouracil, and thiouracil have been shown to be useful in the order named (Fig. 17 and Table XX). The first two mentioned have been under investigation only a short time. To date they are not available for general use, but their action is thus far unusually promising so that an attempt will be made to include here instructions for their use. Of the widely employed and readily available preparations, propylthiouracil and methylthiouracil have been the most satisfactory, as they are almost twice as effective, weight for weight, as thiouracil. The former is about one fourth as toxic as thiouracil, while methylthiouracil is about one half to two thirds as toxic. Of the five compounds under discussion, 2 mercaptoimidazole preparations probably act more rapidly than the others to achieve control of the thyrotoxic state, with thiouracil, methylthiouracil, and propylthiouracil following in the order named (Fig. 17). Thiouracil has now been withdrawn from the market because of the relatively high incidence of agranulocytosis (2.5 per cent), with death occurring in 0.5 per cent of those to whom it was administered. While similar reactions were equally common with methylthiouracil in the large doses originally used, they have been relatively rare in the smaller, still effective doses now employed. We know of but two cases in which severe neutropenia (2.0 and 1.0 per cent polymorphonuclear cells respectively, with total white counts of 1,200 and 1,950 cells per cubic millimeter, respectively) has been reported in patients taking propylthiouracil (Parks, 1948; Bartels, 1948).

Earlier reports which favored methylthiouracil at 1 to 0.5 per cent rather than thiouracil employed much larger doses than are necessary for effective action. With the doses recommended in Table XX the above statements hold true.

the advent of hypothyroidism As a rule the earliest sign of the latter in the course of treatment with antithyroid compounds is an increase in the size of the thyroid gland This may be shortly followed by frank myxedema if the drug is not stopped No case of permanent myxedema has been observed by us in treating more than 500 patients with antithyroid compounds However the enlargement of the gland may be irreversible and a nodular goiter may replace a diffusely hyperplastic one if the basal metabolism is maintained for long periods of time below +5

When the basal metabolism reaches +20 or below therapy with Lugol's solution is begun as per instructions above (see iodine treatment of hyperthyroidism in this chapter) It is our impression that 1 minim daily is satisfactory 3 minims daily are certainly less helpful and 1 minim every second day may be too little for optimal effects We have no accurate objective data as yet to delimit the dosage more clearly but are certain that the indiscriminate use of iodine without some attention to dose may be not only ineffective but even harmful

The time required to effect control of hyperthyroidism with thiouracil or one of its closely allied antithyroid compounds (Table XX) and the dose necessary to maintain such control vary not only with the com

TABLE XXI

BEHAVIOR OF THE CLINICAL MANIFESTATIONS OF HYPERTHYROIDISM TREATED WITH ANTITHYROID COMPOUNDS

RUBRIC	USUAL TIME FOR CHANGE TOWARD NORMAL (DAYS)	
	INITIAL	COMPLETE
Sense of well being	3–9	Control
Tremor*	14–35	———
Weight	10–14	———
Blood pressure and pulse pressure	14–28	14–28
Pulse rate and quality	Very variable	28–Variable
Size of thyroid	Variable	Rarely occurs
Exophthalmos	Variable	Rarely occurs
Basal metabolic rate	10–28	Control
Total cholesterol†	10–28	Control
Protein bound iodine of blood	10–28	Control
Creatinuria	10–28	Control

As ob ved der a ne s sweating i t skin rr tabil ty x phth in si of th thyr id or th r symptom i al o f value in app a sing th o all ond ti n of the p ti nt †A tu tly the ab lute valu is n t s gnifi a t alth ugh it is u ot oft n l w o l w no l p l t t ain nt and i m rimal at the time n t d Th ta a rea nably t ady in re e th figure a ont ol i rea hed The eaft r this re ert lowly to n rmal with ut gard f the ub equent tatus of the pati nt

In Table XX the dosage regimes are given for the five compounds under discussion. While thiouracil has been wisely withdrawn from the market and is therefore no longer available to the clinician it was the first of these drugs to be widely used and is included in the table for purposes of comparison.

We have found it unnecessary to hospitalize patients for any portion of their treatment with antithyroid compounds. In the majority on the contrary improvement is achieved more easily at home amidst familiar surroundings than it is in the atmosphere which continuously emphasizes sickness and often lacks a personal touch and concern. There are of course some instances in which emotional problems or tension within the home have precipitated the hyperthyroid state. In some of these it may be important to remove the patient temporarily from the irritating or aggravating factor. Hospitalization may offer a solution often however a well planned vacation will be even more restorative. Decisions regarding the best course in any given case must be tempered with a clear understanding on the part of the physician of the patient's willingness and ability to cooperate her financial status and the influence of added economic stress upon her entire emotional and mental make up. In general we advise against hospitalization and in the patients who are being prepared for surgery arrange admission into the hospital for from 36 to 48 hours prior to the time set for operation. All necessary checkup examinations can be completed in one day. Since the patient reaches the operating room in a completely nontoxic condition none of the elaborate preparation formerly attendant upon an operation for hyperthyroidism is necessary. The patient is made aware of all plans as they unfold and is prepared for her thyroid operation as she would be for any other surgical event.

When methylthiouracil is used for controlling the thyroid condition the patient should be seen by the physician at weekly intervals until control is established and the initial dose of drug is reduced. With propylthiouracil and the mercapto imidazoles the interval between visits may at first be two weeks. With all of these drugs visits more often than once monthly are unnecessary after maintenance levels of dosage are reached. If treatment has to be carried on for more than six months at low levels of dosage visits may be spaced at still more infrequent intervals. Before every visit the patient should have a determination of her basal metabolic rate and a complete blood count. In conjunction with every second visit an estimation of the protein bound blood iodine or of the serum cholesterol should be made to serve as a further laboratory check against the basal metabolic rate which often fails to reflect the true status of the patient when repeatedly performed. The most desirable range of values for the basal metabolism in controlled cases varies from +5 to +15 per cent. Higher values may be associated with some residuum of the thyrotoxic state while lower figures often presage

If the clinical condition has remained satisfactory during these three months then a decrement in the daily dose of the drug equivalent to one dosage unit is made at each monthly visit until only one such unit is being used every other day The dosage units for propyl thiouracil methylthiouracil 2 mercaptoimidazole and 1-methyl 2 mercaptoimidazole are 25 25 10 and 2 mg respectively After one such unit is employed every other day for a month without any evidences of returning toxicity administration of the drug is discontinued If at any time during the reduction regime there is evidence of a recrudescence of the hyperthyroidism the last controlling dose is resumed and maintained for three months before a decrease is again attempted

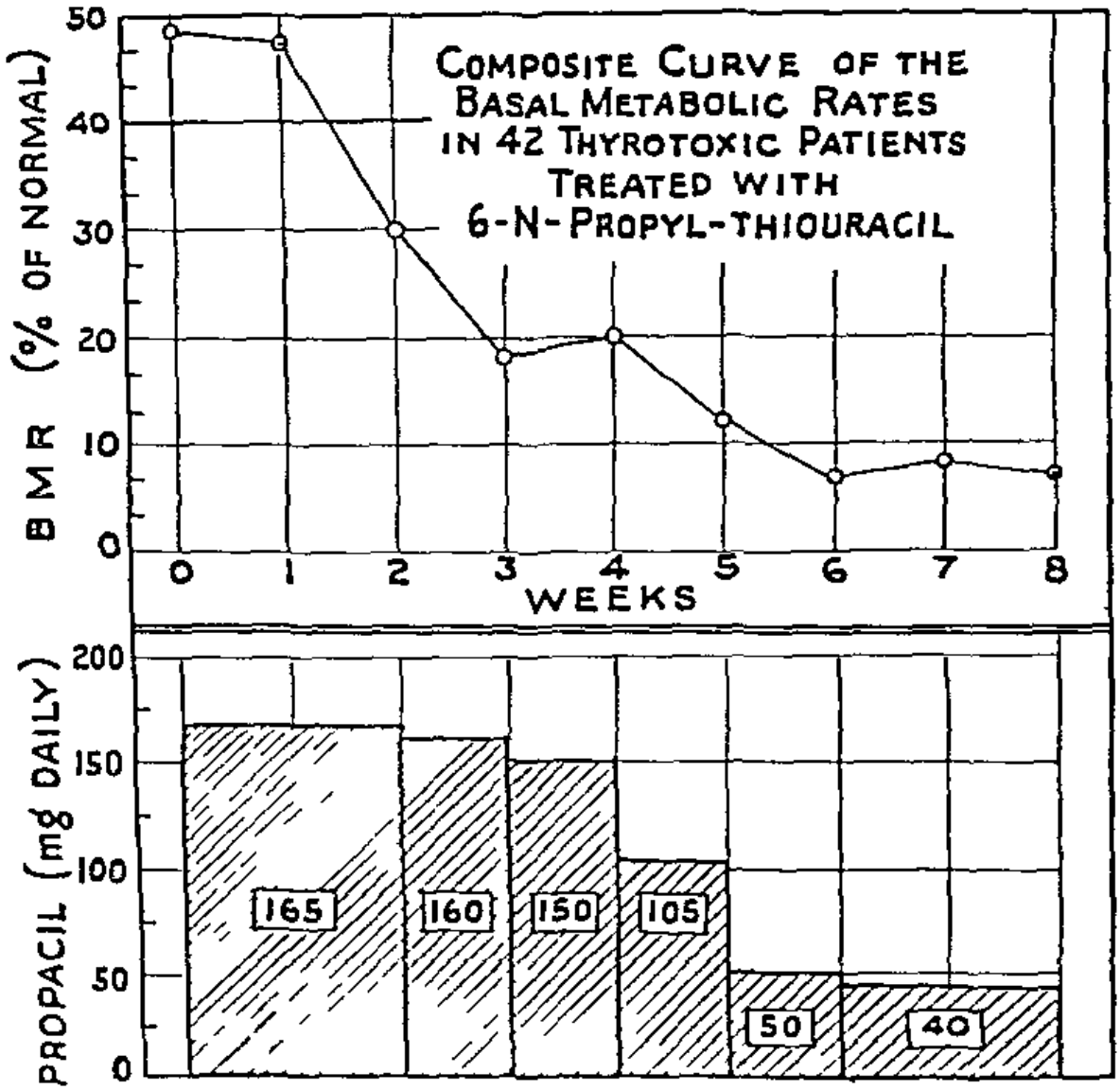


Fig 1—Response to propylthiouracil of the basal metabolic rate of four patients with hyperthyroidism Each point on the curve between 5 and 6 weeks represents the metabolic rate of one patient with hyperthyroidism At this time the maintenance dose (300 to 400 mg daily) of the drug was employed (After McGavack Cerletty Vogel and Schutz 1943)

pound used and the *mount employed but also in an unpredictable* fashion from patient to patient In Table XXI we have tabulated the manifestations about which data may be profitably recorded during each follow up visit The behavior of the basal metabolism in connection with treatment is typified in Figs 70 and 71 These afford a satisfactory clinical picture for determining the status of the patient as treatment proceeds After complete control of the toxic state is attained the patient is continued on a maintenance dose of the selected drug for at least three months before any effort is made to reduce the *mount or to* omit it entirely Of course if during this time signs of hypothyroidism appear or evidences of toxicity recur the administration of the drug is adjusted accordingly

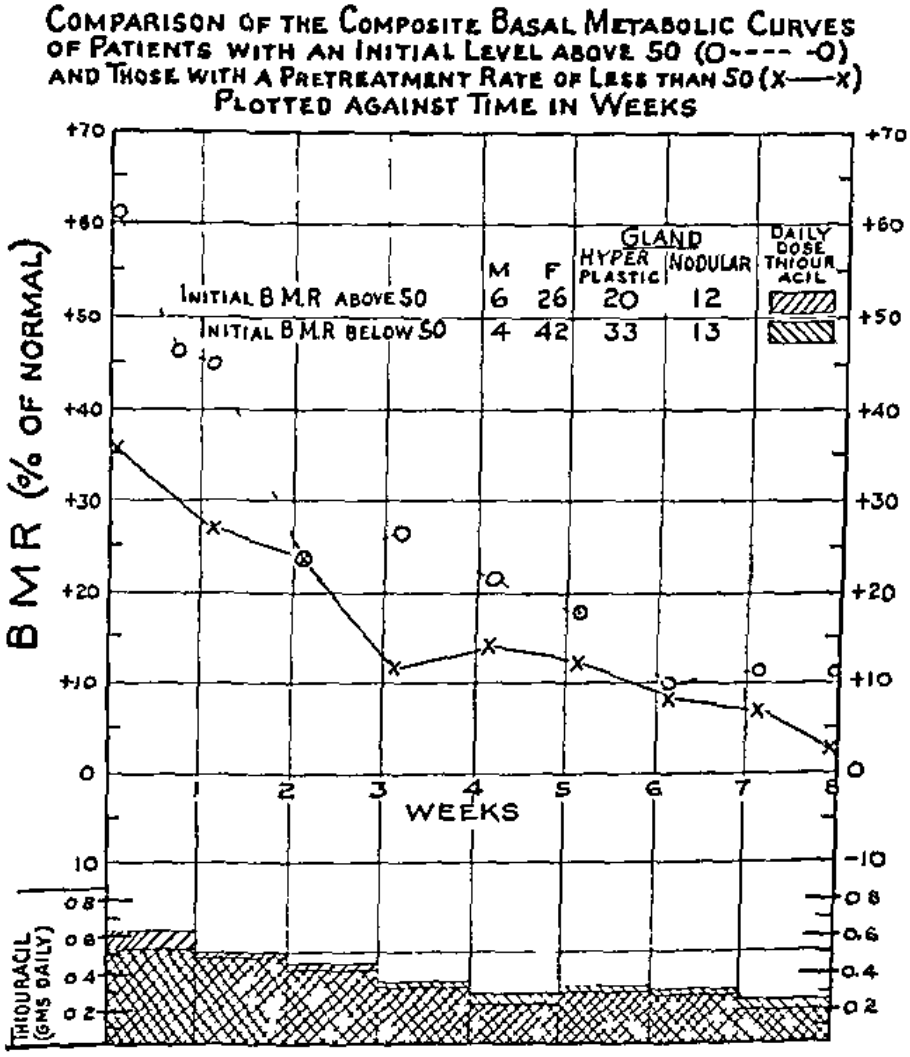


Fig 0—Re ion t th o r ll of the b l n t bolic r te of 8 thy t xic ubj ct The two cur es rep r ent th averag d d ta re pectiv ly f r tho e subj cts wh se *initi l b l r* tabolism wa greater th n + 0 (32 patients) a d th e wh l tr at ent act b lic r t was less than + 0 p r cent (46 ojects) *It is e ide t th t th initial val e for the l* n t bolic rate bears no math matical relati n hip *whatsoev r* to the time nec s ry to bri g the l s l me tabolism to normal

If the clinical condition has remained satisfactory during these three months then a decrement in the daily dose of the drug, equivalent to one dosage unit is made at each monthly visit until only one such unit is being used every other day. The dosage units for propyl thiouracil, methylthiouracil, 2 mercaptoimidazole and 1 methyl 2 mercaptoimidazole are 25, 25, 10 and 2 mg. respectively. After one such unit is employed every other day for a month without any evidences of returning toxicity, administration of the drug is discontinued. If at any time during the reduction regime there is evidence of a recrudescence of the hyperthyroidism, the last controlling dose is resumed and maintained for three months before a decrease is again attempted.

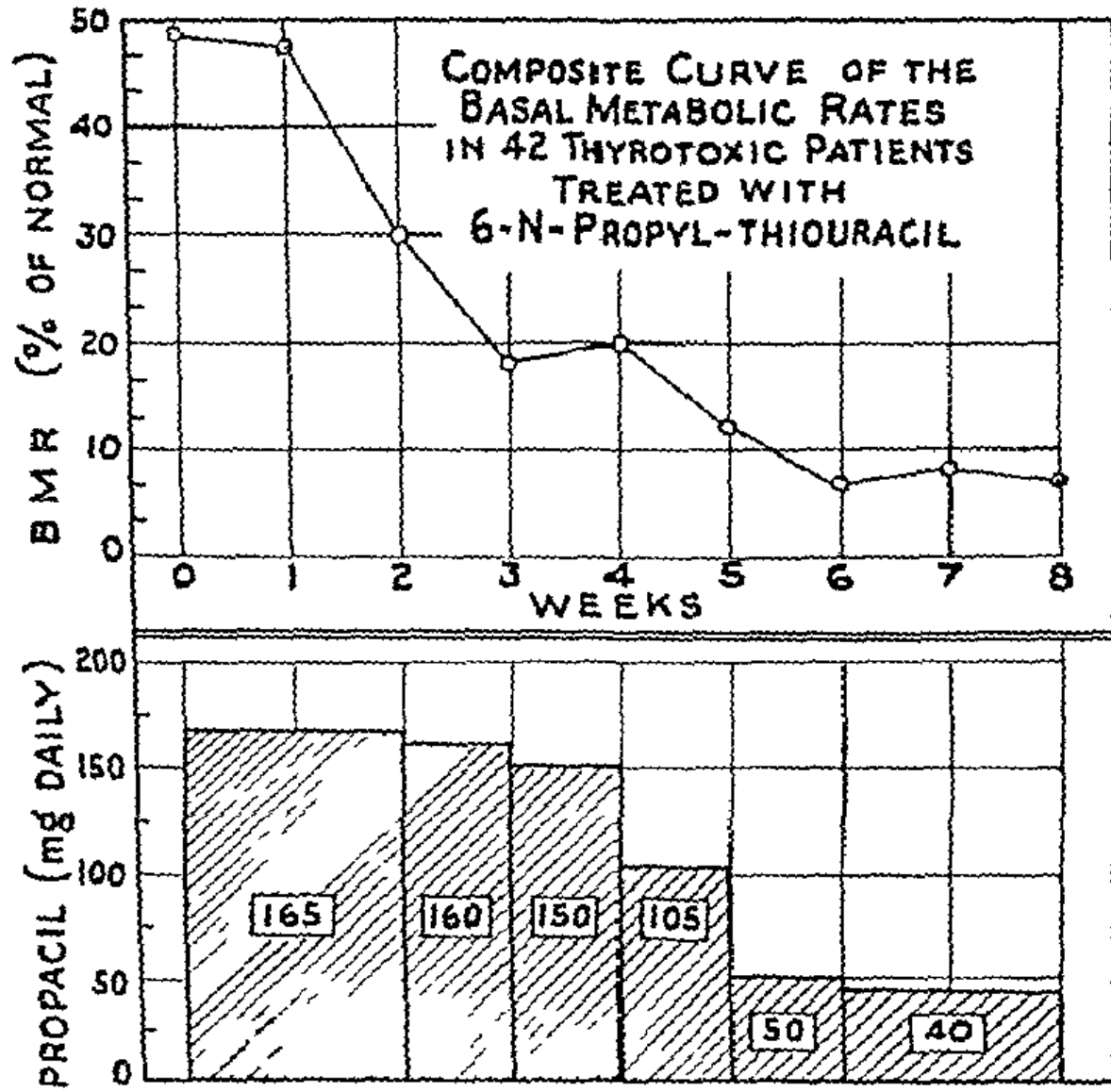


Fig. 1.—Hypothetical illustration of the manner in which the daily dosage of propyl thiouracil may be reduced in the course of treatment of a thyrotoxic subject. On the basis of observations made on 42 patients, it is estimated that the majority of persons with hyperthyroidism of moderate severity can be controlled with daily doses of 150 to 200 mg. of propyl thiouracil. As a result of this reduction regime, the daily dosage is decreased from large (300 to 400 mg. daily) to small amounts. (After McGavack, Goetsch, Vogel and Shuter, 1947.)

If hyperthyroidism reappears within 12 weeks after such a course of treatment has been completed the condition is looked upon as a relapse It is ascribed to the discontinuance of therapy before a normal balance has been re established between the mental activity the nervous system the thyroid and the other glands of internal secretion In such instances the therapeutic regime should be re established

If hyperthyroidism returns more than twelve weeks after cessation of therapy this must be looked upon as a 'recurrence' initiated by factors identical with those which caused the first attack or entirely different stimuli of similar magnitude and character What treatment shall then be used becomes a matter for decision in each individual case We may try the antithyroid compound again, which other things being equal is our own preference In other subjects a permanent suppression of thyroid activity may be preferable either through the administration of radioactive iodine or the subtotal surgical ablation of the gland If the condition has recurred twice following each of two adequately and properly administered courses of therapy with a thiourea derivative we advise surgery as the most practical solution for the problem

The following quotation (McGavack 1949b) deals with the toxic effects of the drugs

Agranulocytosis and urticarial febrile reactions constitute the only two toxic responses to thiouracil and its derivatives which necessitate a complete cessation of antithyroid compound therapy Hives and fever have never threatened life but recur routinely on repetition of the medication and therefore preclude its further use The seriousness of agranulocytosis is indicated by the fact that it has ended fatally in nearly one third of the patients developing it It occurs in from two to three per cent of the patients taking thiouracil slightly less often in those using methylthiouracil and has been described but once in thousands of patients who have received propylthiouracil

The following rules have been useful in avoiding it

1 Never exceed the dosage schedule mentioned in [Table XV]

2 Check the patient's status at periodic intervals as indicated above paying strict attention to the phenomena mentioned in [Table XVI]

3 Instruct patients to stop the drug if not feeling well and to communicate with you *immediately* This dictum applies all the more forcibly if there is fever sore mouth or sore throat or a combination of any or all of the three

4 If any contingency mentioned in (3) has occurred recheck the blood count at such a time If on such an occasion or at the time of a regular visit there is evidence of leukopenia or granulocytopenia proceed as follows

i Repeat counts daily or twice daily until the white and differential counts have returned to normal

ii Discontinue therapy only if one of these three conditions is fulfilled in your study of each of two leucocyte counts taken six to nine hours apart or if the day to day count shows progressive changes for the worse

a The total count is 3 000 per cu mm or less although the differential count is normal (polymorphonuclear cells 50 per cent or more)

b The polymorphonuclear cells represent 20 per cent or less of the total number of leucocytes although the white count is normal (5 000 per cu mm or more)

c The total count is 4 000 per cu mm or less and the polymorphonuclear percentage is 35 or less

Should complete agranulocytosis occur in spite of attention to above details the patient should be hospitalized as soon as the condition is recognized or appears imminent Treatment includes (1) *the forcing fluids to wash out the* drug particularly from the bone marrow where it appears in highest concentration and (2) the administration of aqueous penicillin 50 000 to 100 000 units every three hours for the prevention of infection or equivalent amounts of a *long acting preparation of the drug These procedures must be continued until* granulocytes reappear in the blood stream that is for a period of from eight to thirteen days In our hands restitution to normal has apparently not been hastened by transfusion or by any of the drugs such as pyridoxine pentnucleotide *crude liver concentrates* and splenic leucocytic extracts commonly recommended to increase the numbers of polymorphonuclear elements in the blood stream or bone marrow

If no idiosyncrasy appears the long continued use of antithyroid compounds is well tolerated and often justified (Poate 1950)

5 **Surgery** —As is the case with treatment by antithyroid compounds our aim in surgically treating hyperthyroidism is to prevent the elaboration and detrimental activity of excessive quantities of thyroid hormone To accomplish this a portion of the thyroid factory is removed The indications for operative intervention have been given *above under the discussion of antithyroid compounds (this chapter)* One of the thiouracil derivatives is always used in conjunction with iodine for preparing the patient for surgery Since complete control of the toxicity can be effected by this method in all patients except those who show a hypersensitive or toxic reaction to the drug no elaborate preoperative regimes are needed nor is crisis to be feared either pre or postoperatively

During the preoperative preparatory period the patient should be followed at home just as she would be were a medical regime to be continued indefinitely except for the fact that the doses of iodine are larger It may again deserve emphasis that both Lugol s solution and the antithyroid compound are continued until the day of operation On admission to the hospital 36 to 18 hours prior to surgical procedure laboratory data obtained should include tests of hepatic function pro *thrombin time* basal metabolic rate complete blood count blood cholesterol and cholesterol esters circulation time bleeding time and blood protein bound iodine Details of pre and postoperative care and of surgical technics are noted in Section IV Suffice it to say here that in conjunction with thiouracil therapy the iodine should be used a sufficiently long time not only to allow for the storage of colloid but also to permit a reduction in glandular vascularity Hallahan and Perloff (1950) *advise the giving of Lugol s solution* for a period of eighteen days or more if the tendency to hemorrhage is to be avoided

6 **Roentgen Radiation** —Good results have been reported following *the use of roentgen radiation of the thyroid gland* in about one third of the patients with exophthalmic goiter In those with toxic nodular

If hyperthyroidism reappears within 12 weeks after such a course of treatment has been completed the condition is looked upon as a relapse It is ascribed to the discontinuance of therapy before a normal balance has been re established between the mental activity the nervous system the thyroid and the other glands of internal secretion In such instances the therapeutic regime should be re established

If hyperthyroidism returns more than twelve weeks after cessation of therapy this must be looked upon as a 'recurrence' initiated by factors identical with those which caused the first attack or entirely different stimuli of similar magnitude and character What treatment shall then be used becomes a matter for decision in each individual case We may try the antithyroid compound again which other things being equal is our own preference In other subjects a permanent suppression of thyroid activity may be preferable either through the administration of radioactive iodine or the subtotal surgical ablation of the gland If the condition has recurred twice following each of two adequately and properly administered courses of therapy with a thiouracil derivative we advise surgery as the most practical solution for the problem

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The following rules have been useful in avoiding it

1 Never exceed the dosage schedule mentioned in [Table XX]

2 Check the patient's status at periodic intervals as indicated above paying strict attention to the phenomena mentioned in [Table XXI]

3 Instruct patients to stop the drug if not feeling well and to communicate with you *immediately* This dictum applies all the more forcibly if there is fever sore mouth or sore throat or a combination of any or all of the three

4 If any contingency mentioned in (3) has occurred recheck the blood count at such a time If on such an occasion or at the time of a regular visit there is evidence of leukopenia or granulocytopenia proceed as follows

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6 **Roentgen Radiation** —Good results have been reported following the use of roentgen radiation of the thyroid gland in about one third of the patients with exophthalmic goiter In those with toxic nodular

goiter the results have been rather disappointing Such therapy has as its object the destruction through radioactivity of sufficient glandular tissue to reduce the output of thyroid hormone Before the advent of potent chemotherapeutic agents roentgen radiation represented one of the few ways to check overactivity of the thyroid gland in patients who *for one or more reasons were not considered good operative risks* Disadvantages are that (1) the treatment is prolonged (2) a change in thyroid status is slow in appearing and (3) the end results are somewhat uncertain

It seems quite likely at the present time that this form of therapy will soon be completely outmoded Such a conclusion seems all the more forceful in view of the acute mediastinocardiac reactions which have followed irradiation of the thyroid gland In Rose and Wolferth's (1911) cases the pattern of the electrocardiogram was most suggestive of acute pericarditis with underlying myocardial involvement' The condition was described as 'an acute sterile inflammatory reaction of the mediastinal pleura or the mediastinal contents Because of the adhesions which form following such a type of reaction it has been suggested that roentgen radiation should be used cautiously if at all

7 **Radioactive Iodine**—Despite the fact that eight years have elapsed since the first radioactive isotopes of iodine were used in the treatment of human hyperthyroidism (Hertz and Roberts 1942 Hamilton and Lawrence 1942) developments in this field are still so rapid and kaleidoscopic that a statement made today may be inadequate to express the known facts tomorrow

All therapy in human beings has been carried out with I^{130} or I^{131} with half lives of 12.6 hours and 8 days respectively Actually the I^{130} used has been a mixture containing approximately 90 per cent of I^{130} and 10 per cent of I^{131} With the more recent availability of I^{131} in nearly pure form and with its more utilitarian half life of eight days it is now the isotope of choice for the treatment of hyperthyroidism Therefore all further comments in this section will apply to it alone

The established facts upon which treatment with radioiodine is based include

1 The increased avidity of the hyperthyroid gland for iodine as shown by its collection of as much as 80 per cent of a tracer dose of radioiodine within a few hours after oral administration

2 The relatively rapid excretion by the kidney of the majority of the radioiodine not taken up by the thyroid gland

3 The almost complete destruction of the thyroid in dogs and rabbits by administering I^{131} in doses that showed no damaging effect upon any other organ or tissue of the body

4 Variations in the above actions by the administration of iodine thyrotrophic hormone thiourea and similarly acting compounds

The difficulties to be encountered in the successful application of isotopic therapy to the patient with hyperthyroidism justify considerable care in the selection of subjects for which it shall be used Inasmuch as the therapeutic activity depends upon the beta radiation which penetrates tissue for little more than 2.0 mm the major field of usefulness is at present confined to diffusely hyperplastic glands that for one of the following reasons cannot be more readily and satisfactorily treated in some other way (1) failure to respond to apparently adequate doses of an antithyroid compound or repeated relapses after such responses (2) sensitivity to antithyroid compounds (3) serious surgical hazard due to age cardiac condition bleeding dyscrasia and so forth (4) recurrence of toxicity after repeated surgical procedure particularly where disturbance of one vocal cord exists or hypoparathyroid tetany has occurred For other than investigative purposes the above criteria limit the field of application of radioiodine to a very small percentage of our patients with thyrotoxicosis

In hyperthyroidism contraindications to therapy with radioiodine include pregnancy beyond two and one half months renal disease and certain nodular goiters Inasmuch as the fetal thyroid is capable of absorbing and concentrating iodine as early as the fourteenth week (Chapman Corner Robinson and Evans 1948) it seems unwise to give an isotope with a half life of eight days much beyond the tenth week of gestation

It has been felt that renal disease represents a condition in which therapeutic doses of radioiodine might do considerable harm However there is little or no positive evidence that this is the case Furthermore one group of observers has recently reported no increase in radioiodine in the kidneys of patients with severe acute glomerular nephritis (Williams Jaffe Towery Rogers and Lennon 1949) In distinguishing which toxic nodular goiters should and which should not be treated with radioiodine it becomes necessary to classify such lesions in relation to their behavior toward iodine Dobyns and his associates (Dobyns and Lennon 1948 Dobyns Skanse and Maloof 1949) have shown that while the degree of function of an adenoma is usually related to the degree of cellular differentiation this is not always the case Some hyperplastic adenomas with cellular hypertrophy are hyperfunctioning but there are also other hyperplastic nodules which are not functioning Furthermore nodules capable of picking up and concentrating large doses of iodine are hyperfunctioning may exist with or without evidence of hyperthyroidism In view of these findings we may distinguish at least three types of nodular goiter in hyperthyroidism (a) Hyperplasia of nodular and parenodular tissue with overfunction of both (b) Hyperfunction of the parenodular tissue and no activity within the nodule (c) Hyperfunction within the nodule only often with secondary suppression of function in the remainder of the gland It is in the second

group that radioiodine is contraindicated, as it will fail to reach and therefore fail to destroy the nonfunctioning thyroid nodule. It is furthermore from this group of subjects that a majority of thyroid malignancies arise so that once such a lesion is demonstrated surgical removal is important. One group of workers (Williams, Jaffe, Towery, Rogers and Tagnon, 1949) while not favoring the administration of radioiodine immediately after a long course of thiouracil or a kindred preparation believes severe exacerbations of the thyrotoxic state have been avoided by the use of propylthiouracil for a few weeks before the radioiodine, discontinuing its use approximately four days before the latter is administered.

The patient should be prepared for treatment with radioiodine by withholding all iodine and thiouracil like therapy for at least four weeks. A tracer dose of from 50 to 100 microcuries of I^{131} is then administered to determine the percentage uptake by the thyroid for the first 24 hour period. At the end of this time the therapeutic dose is given carrier free. The actual dose employed will depend upon (a) the fraction concentrated in the thyroid (calculated by direct measurement over the gland and from the rate of excretion of the radioactive material), (b) the weight and nature of the thyroid gland (calculated by palpation and comparison with known standards—errors as high as 200 per cent may occur), (c) the disintegration schema of the isotope (this seems fairly well established for I^{131} [Hertz, Roberts, Means and Evans, 1939; Pipe, 1939; Downing, Deutsch and Roberts, 1942; Evans, 1948] but may be more complicated than was earlier supposed [Skanse, 1948]) and (d) the time necessary for decay of radioactivity to zero. From these data the actual dose to be used in any given case can be calculated with a fair degree of accuracy in millicuries or in roentgen equivalents (r e) (Fig. 21). A satisfactory dose probably lies between 100 and 150 microcuries per estimated gram of thyroid tissue, although all of the above factors must be taken into account in determining the amount given in any individual case, for it is the amount of radioiodine returned in the gland that really counts.

Direct conversion of millicuries to roentgen units is impossible as the former unit is a measure of atomic disintegration and the latter a gauge of energy dissipation. Nevertheless it is possible to make a calculation of roentgen equivalents from the data above mentioned according to the simple formula of Hertz and Roberts (1946) which closely approximates the results to be derived by that of Marinelli, Quimby and Hine (1948) (Chapter XVII).

$$RE = \frac{117\,000 \times (\text{dose of } I^{131} \text{ in mc}) \times (\text{fractional uptake in thyroid})}{(\text{estimated weight of the thyroid in Gm})}$$

For example, if a dose of 10 millicuries were given to a patient whose fractional uptake was 50 per cent and whose thyroid was estimated to

weigh 30 grams the calculated dose in roentgen equivalent units would be 7 800 thus

$$RE = \frac{117\,000 \times 10 \times 0.50}{30} = 7\,800 \text{ r e}$$

Other factors enter into final evaluation of roentgen radiation and I radiation—for example the speed with which the radiation occurs the rate of discharge of iodine from the thyroid and the evenness of distribution of the radioactivity The last mentioned factor is not always readily accounted for as the several portions of a purely hyperplastic gland may show considerable variation in the amount of radioactive material present as demonstrated both radioautographically (Leblond Pertuiset Puppel and Curtis 1946 Williams Jaffe Towery Rogers and Tagnon 1949a b) and chemically (Salter Johnston and Gemmel 1948)

The rate of discharge of the radioactive iodine from the thyroid is a *highly important factor in estimating the total effective radiation* given Because of this Quimby (1948) and Werner Quimby and Schmidt (1949) having modified the basic formula they employed (see Chapter XVII) for estimating the roentgen equivalents (r e) of radiation in any given case

$$\text{r e} = \frac{\text{mc administered} \times \% \text{ uptake} \times \text{effective half life} \times 160}{\text{weight of gland (Gm)}}$$

In this formula the term equivalent roentgen or roentgen equivalent physical is used to include both beta and gamma ray dosage since the roentgen correctly applies only to x rays and gamma rays The per cent uptake is determined at the end of 24 hours care being taken that the aperture of the counter and its distance from the neck *are so adjusted that radiation from the entire gland is measured* Effective half life as used in the formula above differs from the physical half life by the amount of radioactive iodine that is expected from the thyroid in the form of hormone Such loss obviously diminishes the total radiation obtained and must be calculated for each individual patient by making weekly measurements of the content of radioiodine remaining in the thyroid The factor 160 is the calculated radiation in equivalent roentgens when one microcurie of I remains in 1 Gm of tissue for total decay *The largest factor of error in the use of this* formula is the difficulty encountered in estimating the weight of the thyroid Indeed it does not differ in this respect from any of the formulas previously proposed One of the more careful groups of observers (Soley Miller and Foreman 1948) admits an error of from 42 per cent below to 31 per cent above the actual weight Despite this wide range of error the formula just given is probably the simplest and most easily applicable guide now available in daily routine for the calculation of total radiation delivered to the thyroid

In the main results with I have been gratifying in the control of Graves disease provided the dosage levels were kept between the figures above noted—100 and 150 microcuries per estimated gram of thyroid tissue although Johnson et al (1949) have used 500 microcuries per gram without observing any case of permanent myxedema Improvement may begin toward the end of the second week but remission is usually not established until the end of the second or middle of the third month (Werner Quimby and Schmidt 1948 Williams Jaffe Towery Rogers and Fagnon 1949) At the present time it appears possible to obtain therapeutic success in 90 per cent or more of the patients with Graves disease to whom I is given although it must be remembered that the use of this isotope is still an experimental procedure in neither the final effects nor all of the complicating features are yet known Some of the advantages of radioiodine over other forms of treatment are (1) the simplicity of the procedure (2) lack of interference with the patient's routine of living, (3) absence of the skin reactions seen following roentgen ray therapy (4) a mortality of zero and (5) the relative infrequency of toxic manifestations The disadvantages include (1) the necessity for trained personnel and expensive equipment (2) special precautions for handling radioactive material (3) the possible influence of radioiodine upon the urinary tract and (4) difficulty in ascertaining the evenness with which the effect has been exerted *throughout* the thyroid gland

Complications observed as a result of the use of I in the management of thyrotoxicosis include

(a) Acute thyroiditis In a high percentage of cases some tenderness of the gland appears within three to four days after the radioactive material is administered This usually subsides in ten days but has been known to persist for several months

(b) X ray sickness The nausea vomiting malaise and fever seen following roentgen ray therapy may occasionally appear in conjunction with the use of I In using from 200 to 250 microcuries per estimated gram of thyroid tissue Haines and his associates (1948) observed this reaction in one of 10 patients

(c) Thyroid crisis The Mayo Clinic group believe that this can occur (Haines 1948) if too little radioactive isotope is employed Contrariwise in experiments with rats Feller Chaikoff Taurog and Jones (1949) have shown that it is the largest doses of I^{a} which produce the greatest elevation of values for protein bound iodine in the serum and hence might be expected to cause exacerbation of the thyrotoxic state All investigators have reported a temporary increase in the thyrotoxicosis in some of their patients

(d) Exophthalmos The tendency for malignant exophthalmos to occur is greatest after surgery and least marked following roentgen

ray therapy while its incidence in connection with the use of I^{131} occupies an intermediate position

(e) Myxedema The incidence of this complication has varied with different groups of observers throughout the country and has been transient in many instances Its incidence increases with very large doses of the radioactive isotope is rarely seen when the thyroid uptake does not exceed 100 microcuries per estimated gram of tissue but has been observed when as little as 35 microcuries per estimated gram of tissue were employed (Werner Quimby and Schmidt 1949)

(f) Cancer The possibility that cancer may follow the beta radiation with I^{131} cannot be denied although no cases have thus far been reported in which such an association has been considered likely Because this possibility cannot yet be completely discounted the majority of investigators prefer to employ I^{131} only in the patients of older age groups

3 Hormonal Therapy—Poise and counterpoise are so commonly met in the physiological balance that is maintained among the organs of internal secretion that one might expect to utilize some hormonal product successfully in each and every type of hyper or hypofunction of an individual gland In the case of the thyroid some of its relationships with other secretory structures seem well established (Chapter XIV) In the main however the secretions from them have produced little change in the fundamental picture of thyrotoxicosis although admittedly they are good ancillary therapy under certain circumstances

(a) Estrogens Estrogens have been employed in cases of hyperthyroidism occurring at the time of the climacterium Much of their value has been their specific effect upon the concomitantly appearing ovarian deficiency rather than upon the thyrotoxic state However some suppression of thyroid function seems to occur if the dosages are large—60 000 to 300 000 international units weekly approximately equivalent to 3 to 10 mg of an estradiol preparation or 6 to 30 mg of estrone Even under such circumstances the end results have been somewhat uncertain

Several workers have found estrogenic therapy helpful in the pre and postoperative management of the exophthalmic form of toxic goiter (Storck and Holcombe 1942 Storck and Sabatier 1942 Dixon 1945 Berger 1946) They and additional workers (Shute and Shute 1942) found favorable responses in the basal metabolic rate the pulse rate and the systolic blood pressure readings in subjects who were refractory to other preoperative measures Berger (1946) continues the estrogen postoperatively in conjunction with thyroid hormone in the belief that alterations in the pituitary gland are thus minimized and the incidence of crisis thereby lowered While favorable results from estrogenic therapy in thyrotoxicosis are in accord with some of the

In the main results with I^{131} have been gratifying in the control of Graves' disease provided the dosage levels were kept between the figures above noted—100 and 150 microcuries per estimated gram of thyroid tissue although Johnson et al (1949) have used 500 microcuries per gram without observing any case of permanent myxedema Improvement may begin toward the end of the second week but remission is usually not established until the end of the second or middle of the third month (Werner Quimby and Schmidt 1948 a b Williams Jaffe Lowery Rogers and Lignon 1949) At the present time it appears possible to obtain therapeutic success in 90 per cent or more of the patients with Graves disease to whom I^{131} is given although it must be remembered that the use of this isotope is still an experimental procedure as neither the final effects nor all of the complicating features are yet known Some of the advantages of radioiodine over other forms of treatment are (1) the simplicity of the procedure (2) lack of interference with the patient's routine of living (3) absence of the skin reactions seen following roentgen ray therapy (4) a mortality of zero and (5) the relative infrequency of toxic manifestations The disadvantages include (1) the necessity for trained personnel and expensive equipment (2) special precautions for handling a radioactive material (3) the possible influence of radioiodine upon the urinary tract and (4) difficulty in ascertaining the evenness with which the effect has been exerted *throughout* the thyroid gland

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(c) Thyroid crisis The Mayo Clinic group believe that this can occur (Hines 1948) if too little radioactive isotope is employed Contrariwise in experiments with rats Feller Chaikoff Taurog and Jones (1949) have shown that it is the largest doses of I^{131} which produce the greatest elevation of values for protein bound iodine in the serum and hence might be expected to cause exacerbation of the thyrotoxic state All investigators have reported a temporary increase in the thyrotoxicosis in some of their patients

(d) Exophthalmos The tendency for malignant exophthalmos to occur is greatest after surgery and least marked following roentgen

9 **Other Antithyrotoxic Agents"** — *Paraxanthine* (1 7 dimethylxanthine) normally present in the blood and tissues of mammals has been claimed to prevent the action of thyroxin (Carter et al 1943) However in extensive experimental and limited clinical trial Williams (1945) failed to find such an antagonistic influence upon (a) the metamorphosis of tadpoles induced by thyroxin (b) the calorigenic action of thyroglobulin on surviving liver tissue slices and (c) the course of thyrotoxicosis in a single patient

In animals several agents have been shown to exert some inhibiting effect upon the action of thyroxin they have not been tested for such action in man *Pantothenic acid* present in nearly all cells given to rats in daily doses of 100 to 200 mg decreases the action of large amounts of thyroxin (Abelin 1945b 1946) *Beta alanine* and *d valine* also exhibited an effect similar to pantothenic acid presumably as precursors of that substance (Abelin 1946)

Woolley (1946) has prepared several *ethers of N acetylduodotyrosine* that are capable of counteracting the pharmacological action of thyroxin in tadpoles Such a group of compounds is believed to act by producing signs of deficiency of the hormone to which its members are structurally related This probably occurs through their capacity to enter into similar reactions and compete for the same accessory metabolites without being able to fulfill the biological functions of the substances they supplant

An extracted liver residue has been found which materially increases the survival time of rats fed massive doses of desiccated thyroid substance thyroxin or an iodinated casein Furthermore the inhibiting effect of these thyroactive preparations upon growth was completely blocked by the liver fraction (Frshoff 1947 Ershoff and Marx 1948 Ershoff and McWilliams 1948) Other workers have observed similar responses in the chick by supplementing the diet with fish solubles or by injecting Reticulogen Lilly (Robblee et al 1948) These substances may later be worthy of trial in human beings

Maintenance of a high *dietary cholesterol* significantly prolonged the survival time of rats fed toxic doses of hormone (Marx Meserve and Duel 1948) but when fed to rabbits in conjunction with propylthiouracil there was no retardation in the appearance of vascular changes (Horbel and Hirel 1948)

ADJUNCT THERAPY

1 **Sedation** — Restlessness and insomnia go hand in hand as among the most troublesome symptoms which must be combated throughout the duration of the thyrotoxic state They are intensified preoperatively Here a sympathetic understanding attitude on the part of nurse and doctor will be extremely helpful and may obviate the necessity for *sedative medication* Repeated reassurance about the condition and its

known relationships between the ovary and thyroid probably mediated by way of the pituitary (Vander 1915) *their usefulness in everyday* practice is open to considerable question Antithyroid compounds are certain in action reasonable in price Estrogens are unreliable in action—except for the relief of symptoms specifically climacteric in nature—and are relatively expensive

(b) Testosterone The employment of testosterone or one of its preparations in the treatment of hyperthyroidism is based upon its ability to influence nitrogen balance favorably The retained nitrogen is used for the formation of tissue protein Simultaneously there is a decrease in the creatine excretion in those patients who have sustained great loss of weight and severe muscular wasting (Kinsell et al 1941 Rettenstein 1941) While this influence favorably affects muscular mass and vigor it simultaneously diverts some of the energy producing materials to the job of building new tissue Its value may therefore depend to some extent upon the ability of the patient to take large quantities of energy producing foods with an overall caloric intake equal to or slightly in excess of energy requirements This is not an easy order in some of the more severely toxic subjects who may require from 6 000 to 7 000 calories daily It may be better to wait until the metabolic rate has been lowered—at least in some measure—before starting the use of testosterone Upon such circumstances it will be of great value in the emaciated subject who lacks appetite muscular strength and interest in regaining his or her vitality

(c) Adrenal cortex The adrenal cortex plays a major role in the regulation of sugar metabolism having much to do with its formation from other foodstuffs the interconversion from one form to another its storage as glycogen its mobilization under conditions of normality and stress, and its utilization by the tissues In thyrotoxicosis the tremendously increased demand for energy taxes this function of the adrenal to the utmost The glucocorticoids or steroids from the adrenal cortex with an hydroxyl or ketone grouping at carbon atom 11 seem to be chiefly concerned with this function Unfortunately there is no one of these readily available for the use of the clinician at the bedside although pregnenolone and cortisone may soon be within reach of the clinician in his everyday practice Watery extracts of the adrenal are expensive but do contain effective quantities of these materials In a limited experience we have found the watery extract useful in the more severely toxic subjects who have developed moreover profound asthenia and marked muscular wasting A secondary insufficiency of the adrenal seems to exist in some of these patients From 5 to 20 c c of any standardized preparation are necessary daily In many instances the cost is prohibitive but occasionally its use is extremely important if only for a few days until one of the thiouracils can become effective

3 Vitamins —Liberal amounts of vitamins A B and C should be used in thyrotoxic patients for reasons already discussed (*Chapter XV*) These are easily administered as a mixture in a dosage equivalent to three or four times the minimum daily requirements of each Many commercial preparations contain all of these as well as liberal amounts of vitamins D and E which can certainly do no harm

A definite antithyroid effect for vitamin A has been proved in amphibia and in man (Drill 1943 Simkins 1947) The favorable action may be ascribed to a suppression of thyroglobulin function through a combination of thyroxin and carotene with consequent inactivation of the former (Euler and Heussman 1932 Fleischmann and Kann 1936) Other theories quoted by Simkins (*1947*) include protection of the liver against the action of thyroxin thus conserving glycogen opposing effects of vitamin A and thyroxin on lipid metabolism depression of the pituitary thyroid axis influence upon the action of iodine by absorption from body tissues secondarily acting upon the thyroid to affect the storage of colloid and lower the utilization of oxygen by that structure It is suggested by still more recent work that vitamin A relieves the sympathicotonic phenomena of thyrotoxicosis by decreasing the sensitivity of the tissues to epinephrine and sympathin (de Visscher 1946)

The doses of vitamin A used in hyperthyroidism should range from 200 000 to 400 000 units daily

4 Calcium —The excretion of calcium by both the urinary tract and the bowel may be increased as much as 200 per cent in hyperthyroidism Often severe osteoporosis and occasionally spontaneous fractures result (Gross 1941) Even in the face of continued thyrotoxicosis the negative calcium balance thus established can be made positive by adding sufficient calcium to the diet (Gross 1941 Puppel 1941 Puppel et al 1942 1943 1945) Puppel and his associates (1941 1942 1943) advise the patient to take about 600 c c of milk daily and supplement this with calcium tablets and vitamin D Dicalcium phosphate with viosterol 5 wafers daily has been the most satisfactory of a number of calcium compounds we have employed If these instructions are followed the daily need of the average thyrotoxic subject (2 0 Gms) is amply covered Puppel and his associates (1945) believe that definite improvement in general symptomatology particularly in the tremors sweating irritability and hyperkinesis can be brought about by this therapy alone Moreover they have observed an increase in weight a gain in strength a decrease in both pulse pressure and pulse rate and a drop in basal metabolic rate without other treatment They further suggest that the regime mentioned lowers the incidence of thyroid crisis The muscular joint and bone symptoms are always relieved and the osteoporosis is completely dissipated It seems advisable to continue the high calcium intake for several weeks after the

treatment are important. Occupational therapy or some pursuit of interest to the patient will help the hours to pass pleasantly as well as profitably. Before the advent of thiouracil and allied compounds cool sponge baths (80 to 90 F.) morning and evening and an icebag over the heart were thought to decrease palpitation *and nervousness* and often favored sleep. Until the antithyroid compound can develop a maximal effect phenobarbital may be useful; usually 15 mg. (¼ gr.) three times daily will be sufficient. An added dose of 60 or 90 mg. at bedtime may control insomnia. In connection with earlier studies with thiouracil we purposely withheld any sedation; it is remarkable how rapidly the necessity for quieting drugs disappeared. Patients experienced a sense of well *being within three to five days and were usually sleeping comfortably by the eighth to tenth day.*

2. **Diet.**—The care formerly devoted to diet especially preoperatively is no longer necessary since antithyroid tools like propylthiouracil and radioiodine have become available. Nevertheless there is still a very small group of cases in which it may be impossible to use either of these. In such instances several fundamental facts regarding food should be kept in mind.

A severely thyrotoxic patient expends from 6 000 to 7 000 calories of energy daily. At bed rest he is doing as much work as a person at continuous moderate activity would accomplish. In addition he is working inefficiently and for a given task will use approximately 10 per cent more energy than a normal person (Briggs, McClintock and Baldridge, 1935).

If he is to be kept abreast of his fuel requirements it is obvious that his intake must be very high. Nitrogen balance can usually be maintained even in the face of the increased work by the use of 1.0 gram of protein per kilogram of body weight. Readily assimilable carbohydrates *may be forced as they afford* easily available energy and protect the glycogenic activity of the liver. A large amount of fat must be used cautiously as there is often hypermotility *of the intestines* as a result of the thyrotoxic state. Under such circumstances an excess of fats can readily lead to diarrhea and therefore to further wastage rather than conservation of energy.

In brief the diet should be well balanced. Milk, milk products, fruits and fruit juices, *eggs, liver and so forth* are given as desired and tolerated. Calorie value can be added without altering taste by the use of milk sugar in all portions of milk and fruit juices. *It may* also be added to morning cereals. Unless the patient is unable to tolerate one of the antithyroid compounds no effort is made to force or to curb the appetite; this usually adjusts itself readily as the toxic state is brought under control.

3 **Vitamins**—Liberal amounts of vitamins A, B and C should be used in thyrotoxic patients for reasons already discussed (Chapter XV). These are easily administered as a mixture in a dosage equivalent to three or four times the minimum daily requirements of each. Many commercial preparations contain all of these as well as liberal amounts of vitamins D and E which can certainly do no harm.

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The doses of vitamin A used in hyperthyroidism should range from 200 000 to 100 000 units daily.

4 **Calcium**—The excretion of calcium by both the urinary tract and the bowel may be increased as much as 200 per cent in hyperthyroidism. Often severe osteoporosis and occasionally spontaneous fractures result (Gross 1941). Even in the face of continued thyrotoxicosis the negative calcium balance thus established can be made positive by adding sufficient calcium to the diet (Gross 1941, Puppel 1941, Puppel et al. 1942, 1943, 1945). Puppel and his associates (1941, 1942, 1943) advise the patient to take about 600 c.c. of milk daily and supplement this with calcium tablets and vitamin D. Dicalcium phosphate with viosterol 5 wafers daily has been the most satisfactory of a number of calcium compounds we have employed. If these instructions are followed the daily need of the average thyrotoxic subject (2.0 Gms.) is amply covered. Puppel and his associates (1945) believe that definite improvement in general symptomatology, particularly in the tremors, sweating, irritability and hyperkinesis, can be brought about by this therapy alone. Moreover they have observed an increase in weight, a gain in strength, a decrease in both pulse pressure and pulse rate, and a drop in basal metabolic rate without other treatment. They further suggest that the regime mentioned lowers the incidence of thyroid crisis. The muscular, joint, and bone symptoms are always relieved, and the osteoporosis is completely dissipated. It seems advisable to continue the high calcium intake for several weeks after the

all cases of Graves disease In England it is seen probably at least two or three times a year, at most general or ophthalmic hospitals (Mulvany 1944) Cattell (1934) found that 11 per cent of the patients showed clinically significant disturbances in the eye following thyroidectomy Soley (1944b) was able to study 37 such patients in a nine year period but his was an admittedly selective material stemming from a peculiar interest in clinically malignant cases of exophthalmos

The age incidence of patients with ophthalmopathic Graves disease did not differ from that of other forms of the condition in Soley's group (1944b) In Mulvany's series of patients the average age among 22 men and 6 women was 51 and 47 years, respectively (1944) Mulvany leaves the impression that the thyrotrophic (ophthalmopathic) form of Graves disease is associated with the climacterium while the thyrotoxic (classical) form occurs somewhat earlier Duval (1946) and Robertson (1945) believe that the average age is between 40 and 50 years while Brain and Turnbull (1938) found 26 of 30 patients to be more than 40 years old

Ophthalmopathic Graves disease is thought by some to be more common in women or equally frequent in the two sexes (Means Hertz and Williams 1944 Soley 1944a b Schall and Reagon 1945) while other observers believe it is from one and one half to five times more often seen in men (Brain and Turnbull 1938 Mulvany 1944 Robertson 1945 Duval 1946) In any event the relative frequency is much greater in men as compared with the incidence of the classical forms of thyrotoxicosis a fact usually attributed to the influence of testicular function upon exophthalmos (Marine 1938 1940 Mulvany 1944 Dobyns, 1946a)

Pathology There appears to be general agreement regarding the pathological changes seen in malignant exophthalmos (Naffziger 1933 Marine 1938 Pulson 1939 Pochin 1939 1945 Soley 1944a b Means 1944 Mulvany 1944 Rundle and Pochin 1944 Rundle and Wilson 1944 Minn 1946 Dobyns 1946b c d 1950 Rundle 1947) Mulvany (1944) and Dobyns (1946b c d) delineate five major elements in these alterations (1) the presence of edema (2) generalized round cell infiltration (3) fat mobilization and redistribution (4) a peculiar type of muscular degeneration not marked by nuclear reduplication and (5) a heavy increase in perimuscular and interstitial fibrosis While the degree to which each of these five factors is present varies considerably with the duration and severity of the clinical condition their combined action invariably results in an enlargement of the extrinsic muscles of the eye as well as widespread changes in other organs The normal circumference of an average muscular bundle (8 to 10 mm) may be extended to 60 to 70 mm causing the muscles to resemble young cigars (Mulvany 1944) Brain and Turnbull (1938) and Brain (1945) measured the average diameter of the muscle fibers and found the normal to be 116 microns whereas in ophthalmopathic goiter it was

308 microns It is this increase in volume of the retrobulbar tissues which actually *forces the eye to move forward* To this all the other distressing local symptoms and dramatic signs are secondary The edematous swollen muscles become markedly inefficient and eventually are replaced by dense strands of fibrous tissue so that the eyeball may become completely *anchored* within the orbit

Dobyns (1946b d 1950) has extensively studied the tissue changes which occur in guinea pigs following the administration of sufficient amounts of thyrotrophic hormone to produce exophthalmos of high degree While it is difficult and perhaps incorrect to assume that *all* the alterations have or will occur in human beings who have a relative or absolute increase in thyrotrophic hormone and a simultaneous decrease in thyroid hormone nevertheless some mention of these changes should be enlightening The reaction is extremely widespread and involves the fat depots skeletal and cardiac musculature liver kidneys and structures of the reticuloendothelial system

A cellular reaction occurs early which predominantly consists of polymorphonuclear leukocytes and macrophages loaded with fat droplets This is later followed by a lymphocytic reaction and the development of fibroblasts and connective tissue These changes develop concomitantly with exophthalmos There is a generalized depletion of the fat content of fat depots which is replaced by a translucent gelatinous material with some increase in collagenous fibers

Both skeletal and cardiac musculature lose their cross striations in an irregular or spotty fashion They are found to contain numerous tiny fat droplets which have the same spotty distribution and tend to line up in a pattern representing the cross striations of the fibers

Large amounts of fat collect in the liver and are presumed to be delivered there from the depleted fat depots At first these appear in the form of tiny droplets adjacent to the blood sinusoids and later may occupy the entire cell Simultaneously with these changes the levels for plasma fat and acetone bodies are increased

The renal epithelium particularly that of the convoluted tubules and the large phagocytic cells of the reticuloendothelial system in the lungs spleen and lymph nodes also become loaded with lipoid materials

All these changes take place under the influence of thyrotrophic hormone irrespective of the presence or absence of the thyroid or the gonads

In human beings *much of the work of Dobyns has been substantiated* at least in so far as the changes in the orbit are concerned in patients dying of exophthalmic goiter (Rundle and Pochin 1944)

In view of Layne (1949) observation that adrenotrophic and growth factor of the pituitary as at present isolated show a fat mobilizing effect it may be that some of the high g s attributed to thyrotrophic hormone are actually due to a separate and distinct principle which cannot be isolated from other hormones by present methods

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Rawson and his collaborators (1942, 1946) have enlarged upon this concept They have shown that thyroid stimulating hormone is normally *inactivated* but *not destroyed* by thyroid hormone and the cells of the thyroid gland is it can be fully reactivated when treated with mild reducing agents under proper conditions In other words the thyroid stimulating hormone is oxidized and thus inactivated in the course of exerting its action upon the enzymic processes within the *the thyroid cell In thyrotoxicosis* thus *capacity for inactivation* is markedly increased in the average case However in those patients who show an ophthalmopathic form of the disease the thyroid is incapable of oxidizing all of the thyroid stimulating hormone so that some remains in an active form to affect other portions of the body Indeed much may be excreted unchanged as the urine of such subjects has a high thyroid stimulating activity a condition not found in association *with normal or other types of nontoxic glands* Rawson et al (1942) postulated that this excess of activated thyroid stimulating hormone increased the disturbances within the eyeball which give *rise to malignant exophthalmos In such instances it is clear that* thyroidectomy should further aggravate the condition an hypothesis frequently confirmed clinically Fig 72 represents the mechanism of these changes semischematically

In Galli Mannini's concept (1942) a balance is usually established between the extraocular muscle pull and the intraorbital outward pressure which together maintain the eyeball in its normal position That is the pull of the muscles backward just equals the tension or pressure within the orbital tissues One of the first effects of thyrotoxicosis is muscular weakness which obviously decreases the pull of the extraocular muscles while the tissue tension may remain the same or even increase as will be explained below This will result in a slight forward movement of the eyeball giving rise to the widened palpebral fissure the slight stare and the lid lag clinically exhibited in some cases of thyrotoxicosis This forward *movement of the eyeball* at least temporarily re establishes the equilibrium However here a second mechanism becomes important Thyroid stimulating *hormone exerts a water retaining action upon the tissues while thyroid* hormone has an opposite or diuretic action Therefore with every increment in thyroid stimulating hormone further edema of the orbital *tissues occurs thus increasing the intraorbital tension and exophthalmos* (Dobyns 1945 Naffziger 1948a b) As the condition continues edema occurs not only in the stretched and overstrained muscles and *other retrobulbar tissues but also in the eyelids and bulbar conjunctiva* giving rise to most of the severer manifestations of the malignant form of exophthalmos Naffziger (1948a b) stresses the importance of interrupting this vicious cycle before the disease has progressed too far as even with supraorbital decompression the most severe cases may

It is clear therefore that *malignant exophthalmos* is probably only one manifestation of a much more widespread disease which is due to a relative or absolute excess of activated thyrotrophic hormone For instance, the myasthenia observed in the animals treated by Dobyns (1916d) could be correlated with the fatty infiltration of the muscular fibers These are an integral part of the profound alterations occurring in the metabolism of fat throughout the body with which there is an associated widespread connective tissue reaction The manifestations of all forms of exophthalmic goiter need further evaluation in relation to these effects of thyrotrophic hormone

Morbid Physiology and Etiology—Observations of Marine (1938) and of Marine and Rosen (1933) led to the conclusion that thyroid insufficiency (relative or absolute) and anterior pituitary hyperactivity appeared to be two of the essential factors underlying the development of the exophthalmos of Graves disease However, in drawing this conclusion Marine was disturbed by the fact that exophthalmos had apparently not been described in myxedema or in cretinism in both of which thyroid insufficiency and pituitary overactivity may be present Recently malignant exophthalmos has been described accompanying spontaneous myxedema (Guyton 1917) and may occur more frequently than formerly recognized Soley's data (1912) on the degree of exophthalmos following thyroidectomy also show a positive relationship between marked exophthalmos and the myxedematous state

Since malignant exophthalmos is as common in men as in women despite the increased incidence of thyrotoxicosis in the latter and since exophthalmos can be caused in male animals more readily than in female it has been suggested (Marine 1938 Mulvany 1911) that an increase in male gonadal activity is also a necessary factor for the production of this form of exophthalmos Experimentally Marine (1938) supported this point by showing that the parenteral administration of synthetic androgens promoted the development of the exophthalmos in his rabbits and that conversely gonadectomy abolished an existing exophthalmos A high serum phosphorus and a low serum calcium furthered the appearance and maintenance of the exophthalmic state

Mulvany (1911) and other workers (Blum and Turnbull 1938 Dobyns 1915 1916a d Mann 1916 Rundle 1917) believe that both types of exophthalmos have their origin in an excess of thyroid stimulating hormone in the pituitary the difference being merely one of degree with a greater amount of thyrotrophic hormone acting upon the eye in the malignant type than in the so called thyrotoxic type This contention is supported by the fact that in some cases thyroidectomy is followed by a malignant form of the disease in which it is clear that excessive amounts of thyroid stimulating hormone are present to act upon the eye (Engle 1939 Crandall 1911)

not be relieved by the additional space which the operative procedure affords It has been estimated that the disease causes an increase of 30 to 40 per cent in the total bulk of the intraorbital tissues Of this it is believed that a little over two thirds is due to the deposition of fat mainly in the fibrofatty tissues of the orbit (Pochin, 1939 1945 Rundle and Pochin 1944 Rundle 1945 1947 Mann 1946) Dobyns (1946b) found that large deposits of collagenous material also occur in the orbit, chiefly in conjunction with the fatty structures

The ophthalmopathy is still further aggravated if certain sterones particularly testosterone are present (Mulvany 1944) Testosterone markedly increases the edema which is associated with the presence of excessive amounts of thyrotrophic hormone Moreover this drug produces muscular hypertrophy which still further augments the bulk of material contained within the orbit It seems therefore that the major mechanism concerned in the development of thyrotrophic or malignant exophthalmos is straightforward and simple consisting of an increase in retrobulbar pressure as a result of which the eye is pushed out of the orbit (Mulvany 1944) Hyperthyroidism per se plays no part in the mechanism on the contrary the whole process is furthered by thyroidectomy

Some years ago much that was said about exophthalmos depended upon the observer's impression of the appearance of the eyes so that the combination of wide palpebral slits stare and lid retraction was often mistakenly recorded as proptosis

In thyrotoxicosis high sympathetic tone is usually present and causes retraction of the upper lid which gives rise to the widened palpebral fissure and the staring eye described by Dalrymple (1849) Proptosis *may* accompany this change but has been shown in man not to be due to sympathetic stimulation (Mutch 1936 Pochin 1939 Rundle 1947 Naffziger 1948a b) It results from an increase in the orbital contents as already described which is a result of the action of pituitary thyrotrophic hormone

When all the evidence is considered it seems fair to conclude that ophthalmopathic Graves disease has its origin in the unopposed action of reduced (or active) thyrotrophic hormone of the pituitary that produces widespread histological changes of many tissues and organs in which water retention fat mobilization and replacement by collagenous and fibrous tissue are the outstanding features While a diminished liter for thyroid and gonadal hormones in the body tends to increase the severity of the process lowered function of the indicated glands is not necessary for its occurrence The eye suffers most as a result of this disease because swelling within its bony casement the accompanying thyrotoxic myopathy and a tendency for retraction of the upper lid abnormally increase the degree of exposure of the anterior portion of the orbit thus subjecting it to abnormal types and degrees of stress

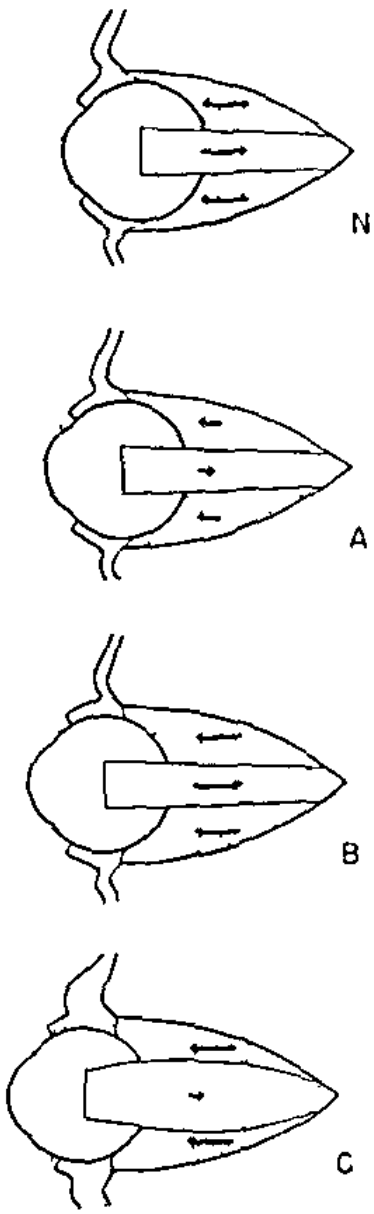


Fig 2—C lli Mainini oncept of the m cha ism which m y b in olved in th produc tion of the exophthaln os of Cra e dis a e The llds the eyeball one n uscle an l the intra orbital tissue are rei r sent d Th arrow ndi ate the dl e tl n of pre u an l t r sl l The dot repre ent the ar ount of fluid in the t ues In Schema N is shown the lluati n m l alth The pull of the muscle is of th ar le m gnitu le as the tissu l res ur nd bal nc s it o th t the position of the glol e l that found in normal person indicated in the e sch m ta by the interrupted line Schema \ how the fir t st p in the de elopment of exophth lmo The n us le has weakened exert le s tens on ndi ated by the shortened arrow The ti su pr sure th re fore forces the eyeball fo w rd As this happ n ti ue p ur fall a d fluid pa se fro n the capillaries to tis ue to occ py the sp ce u ntil a new quilil ri m is re ched with the mu el s stretch d and the eyel all protrudl ig—Sch a B In S h ma C Is show l tl e situ tion l l ro gre i e exophthalr os in which a w aken d n l d gener te muscl cannot withst nd the ti ue pressure and in its turn becomes eden atou as do th llds ar d su rounding ti ues (After Galli Mainini 1942)

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Clinical Evolution—The ocular manifestations of malignant exophthalmos can be conveniently grouped into three stages (Mulvany 1944) (1) the *incipient* stage in which proptosis takes place as a result of the gradual enlargement of the eye muscles with only a slight rise in intraorbital pressure (2) the 'progressive stage' in which an increase in intraorbital tension is followed by congestion and edema and (3) the 'malignant stage' in which corneal ulceration occurs usually followed by loss of the eye unless radical surgical procedures are carried out These stages vary considerably in duration and in the mildest cases the condition may stop spontaneously commonly in the first and frequently in the second stage If the condition is not checked in the second stage it almost invariably progresses to the third stage sooner or later

Lacrimation is perhaps the commonest single symptom and is usually a troublesome feature from the beginning It is probably more dependent upon a disturbance of the secretory activity of the lacrimal gland itself than upon exposure of the eyeball Photophobia commonly accompanies lacrimation Pain may vary from a feeling of uneasiness behind the eyeball to a severe intense form of ophthalmic neuralgia necessitating the use of morphine or other strong sedatives Double vision and difficulty in converging while not early symptoms may sometimes be those for which the patient seeks relief In view of the long course taken by the oblique muscles the diplopia may at first be noticed only on looking upward obliquely later any and all of the extraocular muscles may be involved

Of the physical signs the proptosis is the earliest and most constant Rarely it is unilateral (Rundle 1947) occasionally it is more marked on one side than on the other The exophthalmos is always greater in degree than that seen in the so called benign or thyrotoxic form of exophthalmos Mulvany (1944) has summarized in seven points the way in which he believes this proptosis differs from that seen in the thyrotoxic form of the disease a The presence of subjective phenomena as outlined above b The unequal development of the proptosis which is not infrequent c The absence of lid spasm permitting free eversion of the lids d The degree of proptosis which owing to the absence of lid spasm is more real than apparent in contradistinction to the thyrotoxic variety which owing to the width of the palpebral fissure is often more apparent than real e The sensation of hard resistance in estimating the retrobulbar tension f The presence of congestive features g The rarity of dislocation of the globes in front of the lids' Most authorities agree with the viewpoint quoted except in regard to the proptosis which is nearly always bilaterally comparable Upper lid retraction occurs early in malignant exophthalmos and is probably due to deposits of fat (Pochin 1939 1945 Rundle and Pochin 1944) or to a mechanical disturbance brought about by

the pathological changes occurring in the orbit Disturbances in muscular coordination increase with the increasing severity of the alterations in retrobulbar structures and are not directly due to any lesion or lesions of the nerves

The local vascular changes are first observed in the fine network of venules in the ocular conjunctiva These are associated with a bagginess and edema of the eyelids apparently due to venous palpebral obstruction There are congestion and swelling of the optic disks often accompanied by retinal hemorrhages This is probably secondary to venous engorgement caused by the direct pressure of the swollen muscles upon the optic vein The resulting papilledema is rarely followed by optic atrophy and complete blindness More commonly the loss of sight is due to corneal ulceration

Whether or not we look upon the thyrotoxic or benign form of exophthalmos and the thyrotrophic or malignant form as clinically separate entities as does Mulvany (1944) or on the other hand recognize the same factors at work under different conditions in both as do Means and his associates (Means 1944 Means Hertz and Williams 1941) is more a matter of academic rather than practical interest In the first place the viewpoints of these superficially divergent opinions are on closer scrutiny amazingly similar and in the second place from the clinician's standpoint the benign (thyrotoxic) and malignant (thyrotrophic) types of the disease are sharply differentiated The most profitable approach is perhaps by way of comparison of the two conditions A number of authorities have called attention to distinguishing features (Brain and Turnbull 1938 Brain 1945 Martin and Pennell 1941 Mulvany 1944 Means 1944 Marine 1938 Paulson 1939 Hall 1944 Schall and Reagon 1945) Mulvany (1944) has set the majority of this material down in detailed form which serves as the basis for the tabulation in Table XXII

Diagnosis – In order to avoid errors in appraising exophthalmos it is necessary to make actual measurements of the proptosis present which is in turn a rather accurate index of the extent of increase in orbital contents Such measurements may be made in a variety of ways but are probably best determined by use of the Hertel exophthalmometer (1905) employing the deepest concavity of the external orbital margin as a fixed point By this method measurements in normal subjects have ranged from 11 to 20 mm with an average reading around 16 mm (Brain and Turnbull 1938 Soley 1942 1944 Dobyns 1945 Rundle 1947 Naffziger 1948a b)

There is general agreement that there is an increase in the prominence of the eyes at least for several weeks after the surgical treatment of hyperthyroidism (Soley 1944a b Dobyns 1945 Rundle 1947 Naffziger 1948a b Lederer 1948) which is not observed following other surgical procedures (Dobyns 1945) In the great majority of subjects

Clinical Evolution —The ocular manifestations of malignant exophthalmos can be conveniently *grouped into three stages* (Mulvany, 1941) (1) the incipient stage in which proptosis takes place as a result of the gradual enlargement of the eye muscles with only a slight rise in intraorbital *pressure* (*2*) *the* congressive stage, in which an increase in intraorbital tension is followed by congestion and edema and (3) *the* malignant stage in which corneal ulceration occurs, usually followed by loss of the eye unless radical surgical *procedures* are carried out These stages vary considerably in duration and in the mildest cases the condition may stop spontaneously commonly in the first and frequently in the second stage If the condition is not checked in the second stage, it almost invariably progresses to the third stage sooner or later

Lacrimation is perhaps the commonest single symptom and is usually a troublesome feature from the beginning It is probably more dependent upon a disturbance of the secretory activity of the lacrimal gland itself than upon exposure of the eyeball Photophobia commonly *accompanies* lacrimation Pain may vary from a feeling of uneasiness behind the eyeball to a severe intense form of ophthalmic neuralgia necessitating the use of morphine or other strong sedatives Double vision and difficulty in converging while not early symptoms may sometimes be those for which the patient seeks relief In view of the long course taken by the oblique muscles the diplopia may at first be noticed only on looking upward obliquely Later any and all of the extraocular muscles may be involved

Of the physical signs the proptosis is the earliest and most constant Rarely it is unilateral (Rundle 1917) occasionally it is more marked on one side than on the other The exophthalmos is always greater in degree than that seen in the so called benign or thyrotoxic form of exophthalmos Mulvany (1941) has summarized in seven points the way in which he believes this proptosis differs from that seen in the thyrotoxic form of the disease "a The presence of subjective phenomena as outlined above b The unequal development of the proptosis which is not infrequent c The absence of lid spasm permitting free eversion of the lids d The degree of proptosis which owing to the absence of lid spasm, is more real than apparent in contradistinction to the thyrotoxic variety which owing to the width of the palpebral fissure is often more apparent than real e The sensation of hard resistance in estimating the retrobulbar tension f The presence of congestive features g The rarity of dislocation of the globes in front of the lids Most authorities agree with the viewpoint quoted except in regard to the proptosis which is nearly always bilaterally comparable Upper lid retraction occurs early in malignant exophthalmos and is probably due to deposits of fat (Pochin 1939 1943 Rundle and Pochin 1941) or to a mechanical disturbance brought about by

TABLE XXII—*Continued*

	BENIGN	MALIGNANT
Clinical Features		
7	Age Early part of life	7 Middle and late middle life
8	Female to male 9 1	8 1 1
9	Hyperthyroid symptoms Moderate or marked	9 Slight or absent may even be hypothyroid
10	Local symptoms	10
	(a) Exophthalmos Average of 2 5 mm	(a) Average 7 mm
	(b) Subjective symptoms Absent	(b) Frequent and early consisting of pain lacrimation photophobia double vision and difficulty in focusing
	(c) Lid spasm Present	(c) Absent
	(d) Congestive features Absent	(d) Early and constant at first slight edema of ocular conjunctiva with appearance of fine network of venules Later edema and chemosis of the lids possibly due to compression of palpebral venous arcades the pressure of the lids upon the cornea and deposition of fat
	(e) Ulceration Almost never	(e) Corneal necrosis almost inevitable in severe cases
	(f) Palsies of individual muscles occasionally occur	(f) Mechanical hindrance to movement of the eye is seen early Total immobility is not uncommon
11	Basal metabolic rate High	11 Normal slightly increased or low
12	Urinary excretion of iodine Increased	12 Markedly increased
13	TSH in the urine in an inactivated form	13 A portion of the urinary TSH is always active
14	Blood iodine Increased	14 Normal
The Effect of Treatment		
15	Proptosis Improved or not changed by thyroidectomy	15 Aggravated by thyroidectomy
16	Unchanged or worse from thyroid medication	16 Usually improved

TABLE XXII

A COMPARISON OF SOME OF THE FEATURES OF THYROTOXIC (BENIGN) AND THYROTROPHIC (MALIGNANT) FORMS OF EXOPHTHALMOS

BENIGN	MALIGNANT
Endocrine morbid physiology	
1 TSH present in excess but fully inactivated by the highly toxic thyroid gland	1 TSH present in excess but only partially inactivated by a moderately toxic or even nontoxic thyroid gland
2 TSH plays a minor role in producing slight orbital edema	2 Markedly excessive amounts of TSH not inactivated by the thyroid gland act upon the orbit to increase postorbital retention of fluid and thereby increase tension and pressure within the musculature and other contents of the orbit
3 The myasthenia of thyrotoxicosis and the sympathicotonia associated with hyperthyroidism result in a weakened pull of the extraocular muscles which against a slightly increased retrobulbar pressure permits proptosis	3 Myasthenia is mild and sympathicotonia is absent
4 Other hormonal factors such as the status of the adrenal are of secondary importance	4 Certain steroids particularly testosterone aggravate the condition probably in relation to their ability to cause water retention and muscular hypertrophy
5 Produced by weakened voluntary extraocular muscles operating in the presence of normal or very slightly increased postbulbar tension	5 Results from increased retrobulbar pressure occasioned by enlargement of extraocular muscles and final weakening of same
Pathology	
6 Predominantly a neuromuscular degeneration with general wasting of muscle fibers and granulation of the nerve fibers The overall size of the muscles is normal Edema general fibrosis and round cell infiltration are absent The lacrimal gland is normal Nutrition of the eyeball is little if at all impaired	6 Primarily a muscle and fatty tissue disorder with edema diffuse and extensive fibrosis and abundant round cell infiltration There is marked muscular enlargement the circumference becoming 8 to 10 times that of the normal The lacrimal gland is constantly affected the nutrition of the eyeball is damaged with congestion chemosis and ulceration Papilledema and retinal hemorrhages are common

1 *Thyroid Hormone*—The purpose of using thyroid hormone is threefold it depresses the secretory activity of the pituitary inhibits the action of preformed thyrotrophin and has a diuretic action Robertson (1945) pushes such medication when necessary to the point of producing a basal metabolic rate around +30 per cent He adds mercurial diuretics to the regime on days when the eyelids are edematous and painful Such a combined therapy has well controlled the exophthalmos in his cases and obviated any necessity for surgical intervention

Paschkis and Cantarow (1947) believe thyroid hormone to be the medication of choice in euthyroid or hypothyroid subjects with severe exophthalmos Sloan (1947) and Beierwaltes (1948) have found that the combination of desiccated thyroid substance and Lugol s solution prevented or checked the progression of malignant exophthalmos While some workers are opposed to the use of thyroid hormone if the basal metabolism is already elevated others feel that such patients tolerate it well (Rienhoff 1941)

When desiccated thyroid substance is to be given moderately large to large doses are usually recommended as high as 10 grains have been given daily In our hands patients with any degree of toxicity have not tolerated this treatment too well while in the absence of toxic symptoms from the thyroid it has been the most helpful agent

2 *Iodine*—The regulatory influence of blood levels for iodine upon the activity of the pituitary preformed thyrotrophin and the enzymic processes by which the thyroid forms its specific secretion have already been detailed (Chapters VII XI and XII) As a result of these effects iodine should be of considerable value in the treatment of malignant exophthalmos used either alone or in conjunction with the administration of thyroid hormone Where any toxicosis exists Means and his associates (1941) advised the combined use of iodine and thyroid extract on the basis that iodine can cancel out much of the toxic effect of the thyroid material but leaves its diuretic action unopposed It is our present impression that the combination suggested by them affords some relief although there is no room for overenthusiasm about any medical regime so far devised

When Lugol s solution is employed the doses should range from 2 to 10 minims three times daily

3 *Mercurial Diuretics*—Mercurial diuretics seem to be of temporary help in partially relieving the edema about the eyes (Zondek and Tycho 1945 Robertson 1945) They represent a far cry from truly physiological therapy in this type of condition but when employed in conjunction with other more fundamentally directed treatment such as thyroid hormone or iodine they may be of value in tiding the patient over periods of emergency

this increased protrusion of the eyes does not exceed 3.0 mm. and averages 1.5 mm. Indeed, in about 5 per cent of all patients with hyperthyroidism and exophthalmos the latter recedes slightly following a subtotal thyroidectomy (Soley, 1941a, b).

If the exophthalmos increases 3.0 mm. or more following surgery, as a general rule this is accompanied by some of the manifestations of a thyrotrophic or ophthalmopathic form of the disease. Whether surgery has been performed or not, a similar state usually exists when the proptosis, measured as described above, exceeds 22 to 25 mm. (Braun and Turnbull, 1938). It is only by the measurement of the proptosis that we can demonstrate its degree or, indeed, in some instances its existence.

A further clinical point in diagnosis is the importance of examining for proptosis with the eyelids closed. Often the apparent prominence noted with the eyes open disappears completely (Rundle, 1947). Unilateral lid retraction is not infrequent in otherwise uncomplicated thyrotoxicosis, but unilateral proptosis is extremely rare.

An instrument for orbitonometric determinations has recently been devised which may be helpful in early distinguishing the benign from the malignant forms of exophthalmos (Means and Stanbury, 1950).

Differential Diagnosis of Exophthalmos.—Proptosis more marked on one side than on the other, as measured by the exophthalmometer, is extremely rare in either the benign or malignant types of Graves disease (Rundle and Wilson, 1945; Naffziger, 1948a, b). As a general rule, a unilateral exophthalmos of severe degree represents a local condition which can usually be surgically removed. Among such conditions may be included local septic processes with or without osteomyelitis, hyperostoses, brain and orbital tumors, the Hand-Schuller-Christian syndrome, cavernous sinus thrombosis, aneurysm, arteriovenous fistulas, and infection of the lacrimal glands.

Treatment.—The whole plan of treatment for ophthalmopathic Graves disease should be aimed at the relief of orbital swelling and not at the thyrotoxicosis which, if present at all, is usually mild. In other words, measures favoring water depletion are indicated and those promoting water retention are contraindicated. For example, among the hormones, thyroid stimulating hormone of the pituitary and estrogens are distinctly contraindicated on the grounds alone that both favor the retention of water. By the same token, any procedure which will decrease the output of thyrotrophic and gonadotrophic hormones of the pituitary should be encouraged.

In the incipient and early, in the regressive stages, conservative therapy should certainly be given careful trial. Among the measures which may be employed, somewhat in the order of their reported usefulness, are

should conservative measures fail to bring relief during the second stage surgery should be promptly instituted

The indications for operative procedure and its technique are discussed under the postoperative complications of hyperthyroidism (Chapter XLVI)

4 *Radioactivity*—Too much should not be expected of irradiation of the pituitary although there is theoretical justification for its use and in some cases it seems to have afforded relief (Means Hertz and Williams 1941 Mulvany 1941) Personally we are opposed to its use on the grounds that the action is nonspecific in an area where a large number of specific balanced activities are controlled If the patient is thyrotoxic and beginning symptoms suggest a malignant exophthalmos roentgen radiation of the thyroid appears to be preferable to surgery because its effect is exerted much more slowly and permits more time for readjustment of the local ophthalmic condition

5 *Estrogens*—While estrogens tend to cause water retention they are also capable of depressing the gonadotrophic and thyrotrophic output of the pituitary gland Experimentally they have been found to prevent exophthalmos in castrated animals injected with pituitary extracts however the results in such experiments were uncertain and not uniform If estrogens are employed clinically the dosages should be large They are probably best suited to application in climacteric women

6 *Thiouracil Derivatives*—Beierwaltes (1948) found an increase in the exophthalmos of several patients treated with thiouracil derivatives for more than one half year Inasmuch as mild cases of malignant exophthalmos may be more or less self limiting it seems wise to control thyrotoxicity with one of the antithyroid compounds for the tendency to critical changes in the exophthalmos is much less marked under such conditions than it is following surgery (Aranow et al 1946 Sloan 1947)

7 *Surgery*—Above are the measures which should be used in the milder cases of malignant exophthalmos where the integrity of the eye is not believed to be in danger In such cases surgery should be studiously avoided for it must be recognized always as a palliative procedure even though frequently *responsible for saving both life and the eye*

At the first sign that an irreversible loss of some portion or function of the eye is imminent there should be no further delay in the institution of decompression surgery In other words if conservative measures fail to halt the process in the second or ingravescent stage after reasonable clinical trial then resort should be had without delay to some form of operation relieving the high pressure in the postbulbar region The procedure of Naffziger and Jones (1932) which creates a potential space by removing the orbital roof or some modification thereof should be employed Sewall's modification (1936) first employed by Kistner in 1939 creates an actual space rather than a potential space by removing the floor of the frontal sinuses and ethmoids

While surgery is not necessary in the first stage it is too late in the third stage Emphasis must therefore be placed upon the point that

ground should suggest amyloid however the waxen appearance seen on sectioning most organs containing amyloid may be entirely absent In some instances no follicular structure can be detected When present the follicle contains very little colloid

The infiltration of amyloid into the thyroid begins in the interacinar spaces and compresses the follicular structures Eventually many of the follicles are reduced to clefthke spaces lined by a cuboidal or low columnar epithelium which shows desquamative and degenerative changes In some instances the follicles are cystic and contain only desquamated epithelial cells Such follicles usually rest directly in contact with the amyloid of the adjacent stroma In some of these amyloid may be seen in the basement membrane with an associated thickening of that structure Occasionally isolated multinucleated giant cells are present The intima of many of the arterioles is likewise infiltrated with amyloid Fatty tissue frequently appears in conjunction with the deposition of amyloid in the thyroid

Clinical Picture —Amyloid infiltration of the thyroid is nearly always secondary to a chronic bacterial or neoplastic process elsewhere Therefore the clinical picture to be observed depends upon the severity of the primary condition and the degree of amyloidosis present in other organs such as the liver kidney spleen and adrenal glands Even though the thyroid is more or less completely replaced by amyloid hypofunction of the gland has never been described Indeed Walker (1942) found an elevated basal metabolic rate in one of his two patients

More than half of the patients have an enlarged firm thyroid which in some instances is nodular and may simulate carcinoma In approximately 15 per cent pressure symptoms are troublesome

In our own experience amyloid infiltration of the thyroid has been an asymptomatic condition incidentally discovered at autopsy except in one instance In this patient an enlarged very hard irregularly nodular goiter suggesting malignancy developed in the course of an advanced pulmonary tuberculosis In view of the latter no attempt was made to treat the thyroid condition the true nature of which was proved at postmortem examination

Treatment —In about one in ten of the reported cases of amyloidosis of the thyroid operation has been performed for a mistaken diagnosis of carcinoma No local treatment is indicated The condition subsides only if the primary cause can be successfully managed

II HODGKIN'S DISEASE

Hodgkin's disease may appear wherever reticuloendothelial cells exist The infrequency with which it attacks the thyroid may be due to the relatively small number of such cells in the stroma of that organ

Chapter XL

MISCELLANEOUS DISEASES OF THE THYROID

I AMYLOID DISEASE

Incidence and Etiology—Amyloidosis of the thyroid is a very rare condition Walker was able to find 56 cases reported in the literature and added two of his own in 1912 A number of cases may have been overlooked through failure to examine the thyroid carefully postmortem as amyloid infiltration has been recently reported in 13 of 22 cases of generalized amyloidosis (Dahlin 1949) in which the gland was thoroughly examined Furthermore, there are at least two instances on record in which amyloid, although carefully searched for, was not found in any other part of the body (Oberling 1927 Schilder 1909) In a small percentage of cases perhaps between 5 and 10 per cent the amyloid infiltration of the thyroid is associated with a generalized primary type of amyloidosis Zemp (1917) made an extensive but not exhaustive survey of the literature and in 1917 was able to find 44 cases of primary systemic amyloidosis and added one of his own A goiter of amyloid origin occurred in 8 of these 45 cases and more recently Riser and Davis (1947) have added a ninth

All the remaining cases of amyloidosis of the thyroid are secondary in type In about 65 per cent the disease to which they are secondary is pulmonary tuberculosis Long standing pyogenic infections of the bronchial tree with bronchitis and/or bronchiectasis are precursors of the condition in 10 to 15 per cent of the cases and a similar number have been reported in which neoplastic processes were primary Syphilis has been seen in a single instance but tuberculosis was also present in the same individual (von Eiselsberg 1904)

Pathology—A suppurative process in the lung generally tuberculous in character is the usual primary lesion Generalized amyloid infiltration particularly in the liver kidneys spleen and/or adrenal glands usually occurs *prior to or in association with the thyroid* involvement

In 60 per cent of the cases the thyroid is enlarged However it may be normal in size as in Dahlin's cases (1949) or even small one gland weighing 10 grams has been described The cut surface of the thyroid is coarsely lobulated and very firm The yellow homogeneous hack

III SCLEROLYMPHOLIPOMATOSIS

There has recently been described the case of an 11 year old girl from the left side of whose neck a small relatively soft tumor the size of an olive was removed together with a considerable amount of surrounding tissue (Sumner 1945) On gross examination it appeared not at all like a thyroid gland and on cut section presented a smooth pale yellow appearance resembling fatty tissue On microscopic examination some elements of normal thyroid tissue could be distinguished and at least one very small possibly functioning adenoma was noted However the major portion of the gland and the single nodule for the removal of which surgery was performed were transformed into adipose tissue embedded in connective tissue the whole being infiltrated with considerable lymphoid tissue elements The presence of the condition at both the normal metabolic activity and the unusual nature of the lesions are responsible for the use of the descriptive name sclerolymphohlipomatosis A not too dissimilar condition without nodule formation has also been described in association with thyrotoxicosis (Barnes 1949)

IV SARCOIDOSIS

As far as we can determine there have been five references to sarcoidosis involving the thyroid gland (Spencer and Warren 1938 Oldberg 1943 Gramstrom et al 1946 Freiman 1948 Dickie and Middleton 1949) In all of these the thyroid alterations have represented merely a part of a more widespread process recognized only histologically In no instance have the thyroid lesions been directly responsible for any change in thyroid function although hyperthyroidism was proved to exist coincidentally in two cases (Oldberg 1943 Dickie and Middleton 1949)

Incidence—Hodgkin's disease affecting the thyroid has been seen at nearly all ages and occurs as frequently *in one sex as in the other*

Pathology—The typical structure of a Hodgkin's granuloma is present and may completely replace all functioning thyroid tissue

Clinical Picture—The symptoms are those due to pressure of the rapidly enlarging thyroid mass They appear early and include a dry hacking cough dysphagia dyspnea and alterations in voice While both lobes of the thyroid may be involved the mass *on one side* is usually larger than that on the other and it is to that side that the earlier and more prominent swelling of the cervical lymph nodes occurs Eventually the anterior chain of nodes may be matted together as a single mass which however, remains freely movable in relation to surrounding structures and presents a sharply defined nontender border The peribronchial lymph nodes usually cast enlarged radiographic shadows

Diagnosis and Differential Diagnosis—The diagnosis of Hodgkin's disease of the thyroid is usually confirmed by biopsy of a cervical lymph *node However enlargement of the spleen and a mild secondary anemia* with eosinophilia should lead the clinician to suspect the condition before biopsy is performed Confusion may arise with

a Carcinoma of the Thyroid—The outline of the gland is less distinct its consistency more firm its surface more nodular and the accompanying cervical lymph nodes less discrete in carcinoma of the thyroid than in Hodgkin's disease of the same structure Moreover there is greater tendency for fixation both of the thyroid and of the lymph nodes to adjacent tissues in malignancy than there is in Hodgkin's granuloma

b Riedel's Struma and Hashimoto's Disease—The thyroid enlargement in these conditions shows a smooth surface with very ill defined borders Cervical adenopathy is rarely if ever present

Prognosis—The prognosis of *Hodgkin's disease of the thyroid is* the same as for Hodgkin's disease in other locations Pressure symptoms may be responsible for death at an earlier date than when the disease occurs in other locations although these may usually be relieved by roentgen ray therapy

Treatment—Roentgen irradiation of the thyroid and all areas of adenopathy is the treatment of choice While there is still question regarding the prolongation of life by such a procedure there is no *doubt* about the added comfort experienced by the patient for the swellings disappear with very small doses As little as 100 roentgen units may cause *an amazing change* The thyroid tumefaction is often replaced by fibrotic tissue under such therapy (Vanden Berg and German 1939)

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SECTION IV

Surgical Considerations

James M Winfield
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Chapter XLI

HISTORY OF THE TECHNIC OF THYROIDECTOMY

Early Surgical Notes — The details of attempts to remove goiters in the years before the discovery of anesthesia the development of the hemostatic forceps and the enumeration of the concepts of antiseptic and aseptic surgery are almost too ghastly and horrible to believe The operation was fraught with such danger that it was performed only in cases presenting severe suffocative symptoms The mortality was unbelievably high (Coller 1937)

In some of the early Hippocratic writings reference appears to have been made to goiter but no clear cut differentiation was made between it and other tumefactions of the neck The Greeks of the Hippocratic era did recognize the curative properties of substances found centuries later to contain iodine and did use sea water and seaweed products therapeutically Celsus described bronchocele and recommended operation through a midline incision and evacuation of fluid contents or if the tumor was solid exteriorization and treatment with liniments But he says it is easier to remove it with the scalpel Although Galen realized that tumors pressed upon the trachea and was cognizant of the danger of injury to the recurrent nerve he does not refer to goiter in his writings Halsted (1920) quoting Mandt cites Albucasis (Abdul Casem Khalaf Ben Abbas) as undertaking a genuine extirpation of a goitre in the second half of the tenth century

In 1850 goiter operations were prohibited by the French Academy of Medicine In 70 goiter extirpations to that time the mortality had been 41 per cent Gunther (Halsted 1920) carefully reviewed and corrected the treatises by Mandt and Hedenus compiling a chronological list of 41 operations performed up to 1861 He points out that early accounts (much those of Celsus and Albucasis) refer to extirpated lymph glands rather than to goiter Gunther credits Johann Henrich Brutin of Zurich with the first successful extirpation in 1634 The operations prior to 1861 were chiefly enucleations of circumscribed nodules ligation of one or two thyroid arteries or resections of portions of the gland

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in the remaining 225 cases was 0.8 per cent. In 1898, 600 new cases were reported by Kocher with but a single fatality, a mortality of 0.18 per cent. With each succeeding year additional operative reports came from this famous clinic covering a total of about 5,000 cases at the time of Kocher's death in 1917.

Halsted (1920) lists Kocher's significant contributions as follows:

(1) Discovery of the fact that total extirpation of the thyroid gland is followed by body changes to which he gave the name cachexia thyreopriva or strumipriva.

(2) The studies with his lifelong friend Enghuns of malignant tumors of the thyroid gland.

(3) The perfecting of the operation of thyroidectomy.

(4) The stimulus which he gave to the operative treatment of Graves disease and to the study of the milder forms of hyperthyroidism.

(5) The recognition of ungrafted forms of Graves disease.

(6) The demonstration of the value of the ligature of the arteries as a preliminary step to lobectomy in the highly toxic cases.

(7) The danger of the indiscriminate administration of iodine to patients with goiter.

Of Kocher's further achievements Coller (1939) has commented:

1. He did much to simplify the antiseptic method and develop the aseptic technique.

2. His studies in the anatomy of the more or less constant vascular arrangement of the gland are noteworthy.

3. One of the first to make critical follow-up studies on his cases.

4. He emphasized the value of iodine as a preventive measure.

5. His careful operative technique prevented to a large degree injury to the recurrent laryngeal nerve, so common an occurrence in Billroth's Clinic.

6. In order to avoid cachexia strumipriva Kocher strongly advocated lobectomy, reserving removal of both lobes for malignancy or the very unusual case in which removal of one lobe did not suffice to free the trachea.

7. Kocher considered tetany to be the acute form of cachexia strumipriva.

8. Kocher popularized the transverse collar incision which bears his name although it was first described by Boeckel in 1885.

Kocher and Reverdin.—At nearly the same time Kocher and Reverdin published papers on their results following total thyroidectomy. Kocher named the resulting thyroid insufficiency cachexia strumipriva and Reverdin operative myxedema. Credit for recognition of the syndrome and its origin in total thyroidectomy created considerable controversy.

Reverdin's claim to priority was based on his short communication to the Medical Society of Geneva on Sept. 13, 1882. At this time he mentioned only the edema of the hands and face without albuminuria and in one case the cretinoid appearance. He did not mention and presumably did not surmise that the thyroid insufficiency was the etiological factor concerned in the production of the myxedema as he continued to perform total extirpation of the gland. In the May 15, 1883 issue of the *Revue Medicale de la Suisse Romande* Reverdin wrote that total extirpation offered many advantages and that partial thyroidectomy was not a method of choice but a method of necessity. Four weeks later (June 15, 1883) in the same medical journal he reversed his stand and stated that partial thyroidectomy should be given the preference and total thyroidectomy should be reserved for selected cases. Crotti (1938) infers that Reverdin was considerably influenced by Kocher's masterly description of myxedema in April 1883. When Kocher became convinced that myxedema was the result of total thyroidectomy, he never practiced it again except in the management of malignant lesions.

To the 41 cases tabulated by Gunther Halsted adds 65 operated upon prior to 1861 bringing the total to 106 authentic operations for goiter

If we are to believe the description of Gross (quoted by Halsted 1920) written in 1866 thyroid surgery had advanced little if at all from the time of the earliest operations If a surgeon should be so adventurous or foolhardy as to undertake the enterprise I shall not envy him or his feelings while engaged *in the performance of it or after he has accomplished it* should he be so fortunate as to do this Every step he takes will be environed with difficulty every stroke of his knife will be followed by a torrent of blood and lucky will it be for him if his victim lives long enough for him to finish his horrid butchery Should the patient survive the immediate effects of the operation if this it may be called death will be almost certain to overtake him from secondary hemorrhage or from inflammation of the cervical vessels esophagus and respiratory organs No honest and sensible surgeon it seems to me would ever engage in it It is a far cry from this dramatic description of butchery" to the well planned readily executed relatively safe operation of the present day

Late Nineteenth Century Advances—In this age of modern surgery we take much for granted and frequently overlook the epoch making events of the latter half of the nineteenth century which made possible the evolution of our present day technic for thyroidectomy In particular three events should be borne in mind (1) the introduction of general anesthesia by Morton and Long in 1846, (2) the work of Pasteur and Lister leading up to the introduction of antisepsis *in 1867 later supplemented by the aseptic method of steam sterilization de* veloped by Von Bergman in 1886 and (3) the development of the hemostatic forcep by Pean and Kocherle in 1874

The names of Billroth Kocher and von Mikulicz head the list of great continental surgeons who rapidly advanced the technic of thyroid surgery during the second half of the last century

Billroth—The significance of Billroth's contributions is reflected in the contributions from his assistants notably Wolfler von Mikulicz von Eiselsberg von Haberer and Schloffer While at Zurich 1861 to 1867 Billroth performed operations on the thyroid gland in 20 patients 8 of whom died 7 from sepsis In the preantiseptic era 1867 to 1876 at Vienna in addition 16 of his patients were operated upon with 5 deaths During the antiseptic period 1877 to 1881 he operated upon in additional 48 patients with 4 deaths a mortality of 8 3 per cent In this latter group reported by Wolfler unilateral injury of the recurrent laryngeal nerve occurred 11 times bilateral 2 times Billroth's operative material afforded Wolfler an opportunity to study the thyroid and to publish his extensive monographs which included the first description of postoperative tetany It provided the impetus for the experimental work on transplants of the thyroid and parathyroid by von Eiselsberg and also stimulated von Haberer's interest in the thymus According to Halsted (1920) In the *early Eighties Billroth had operated upon more cases of goiter than any one* in the world had emphasized the danger of wounding the recurrent laryngeal nerve in performing the operation of lobectomy and had furnished many sad examples of tetany consequent upon total extirpation of the gland

Kocher's contribution Kocher (Halsted 1920) more than any other single surgeon perfected the technic of thyroidectomy and his numerous communications are well known Up to 1883 he had performed 11 extirpations of goiter with thirteen deaths a mortality of *12 8* per cent Out of *31* patients with *total* excision 18 returned for examination 16 of whom had symptoms of cachexia strumipriva Symptoms of tetany were observed in only one of the 18 cases *In 1889 he reported a new* series of 250 cases with a mortality of 2 4 per cent Excluding 20 malignant goiters and five cases of Basedow's disease the mortality

Chapter XLII

INDICATIONS FOR SURGERY

In discussing goiter Halsted (1920) said "Medical men have every right if they choose to try non surgical measures in the early stages of the disease But if failing not only to arrest the disease but also to cure their patients quickly they do not advise operation in the safe and curable stage they should be held to as strict an accountability as when they fail to call for surgical treatment until a patient with acute appendicitis for example has developed a general diffuse peritonitis"

Let us recall the words of that great master surgeon Kocher when he said speaking to the internists "Gentlemen do not fail to send us your patients early We will send them back to you and in so doing you will find in our work better results and more pleasure"

We may consider the indications for surgical resection under specific types of goiter

Nontoxic Diffuse Goiter (Colloid Goiter)

Colloid goiter is one of the most frequently encountered types of goiter most often seen in conjunction with puberty and pregnancy The enlargement is usually smooth symmetrical and of slight to moderate degree Rarely does it require removal for cosmetic reasons Pressure symptoms are uncommon The basal metabolic rate may be normal or depressed On occasion colloid goiter may be associated with mild symptoms of myxedema An untreated case in which hypothyroid symptoms exist and which persists through pregnancy may lead to the development of cretinoid offspring

In goiter belts prophylactic treatment with iodine (Chapter XXVIII) will prevent the formation of colloid goiter but with few exceptions will fail to cause a regression in size when the lesion is fully established Both enlargement and bruit may subside rapidly when thyroid hormone is employed As the enlargement regresses nodular areas may be palpated so that in either the medically treated or wholly untreated goiter of this type a nontoxic or toxic nodular goiter may eventually develop (Chapter XXXII)

Surgical resection of the colloid goiter is seldom indicated Since the condition actually represents a work hypertrophy on the part of the thyroid its removal is actually contraindicated in the absence of pressure symptoms and secondary adenomata

Von Mikulicz and Partial Thyroidectomy—In 1886 Johann von Mikulicz devised his technic for bilateral partial resection which was designed to prevent tetany cachexia strumipriva and recurrent nerve paralysis Resection differed from enucleation in that the isthmus was dissected from the trachea and a portion of the gland left attached in the tracheo esophageal groove By this method protection of the nerves and parathyroids was achieved and by leaving thyroid tissue cachexia strumipriva was avoided This is the prototype of our modern operation

American Pioneers—In this country there were few important contributions to the therapy of thyroid disease prior to the turn of the century At that time under the leadership of Halsted Mayo and Crile interest in thyroid disease was stimulated Halsted refined the technic of Kocher and von Mikulicz advocated local anesthesia and recorded a number of observations concerning the blood supply of the parathyroid glands and the effects of transplantation of the parathyroids C H Mayo popularized preliminary ligation of thyroid vessels in an effort to make thyroidectomy a safe treatment for hyperthyroid disease He was principally responsible for starting the period of multiple stage operations Crile preached the doctrine of avoiding surgical shock and introduced anoci association

Improved Therapy for Preoperative Management.—It was not until after the reintroduction of iodine by Plummer (1923) that the toxic patient could be adequately prepared for surgery There remained a group who did not respond to the preoperative preparation were poor surgical risks or had early postoperative recurrence of toxic symptoms and signs Pemberton anticipated this when he stated There is obviously the need for some other therapeutic measure which will either abate the intensity of hyperthyroidism or will fortify the patient better to endure the postoperative reaction This need has been fulfilled by two groups of agents (1) radioactive iodine compounds first employed therapeutically by Hertz and Roberts (1941) and Hamilton and Soley (1940) and (2) the antithyroid drugs of the thiocarbonamide type introduced into clinical medicine by Astwood (1943)

centage will rise In addition although the usual laboratory criteria of toxicity are absent the patient may present mild systemic manifestations

We are in complete accord with Cole et al (1945) who state that the gradation between nontoxic and toxic nodular goiter is so narrow that it is extremely difficult to set up criteria which can be used to identify borderline cases specifically as toxic or nontoxic Arbitrarily the patient is considered nontoxic if the basal metabolic rate is less than a +15 and has no significant constitutional symptoms The development of a toxic state may be so insidious that the mild constitutional symptoms frequently seen (20 to 30 per cent) are premonitory signs of toxicity appearing in spite of a normal basal metabolic rate

Malignancy may occur in a clinically benign nodular goiter Crile (1949) has stated that the danger is not that a discrete adenoma may become malignant but rather that it is already malignant and that Until better statistics are available it is suggested that the indications for removal of the nodular goiter be based on clinical judgment rather than on statistical surveys He bases this opinion on the fact that the surgeon is dealing with a selected group of patients who have been screened by (1) the patient (2) the family physician or internist and (3) finally by the surgeon His review includes 537 nodular goiters of all types and discloses an incidence of malignancy of 5 6 per cent In 263 patients with nodular goiter and associated hyperthyroidism no instances of malignancy were found In 271 nodular goiters without associated hyperthyroidism 10 9 per cent were malignant of 176 multinodular goiters 6 were malignant (3 4 per cent) *of 98 solitary nodular goiters 21 were malignant* (21 5 per cent) In this series the accuracy of preoperative diagnosis was above 90 per cent This will be equaled by few if any other surgeons Although we agree that it is not possible with our present limited knowledge to make an accurate statistical report upon the true incidence of carcinoma of the thyroid in nodular goiter it is far better to remove a carcinoma while we are still unable to diagnose it clinically

In relation to prognosis Ward's data (1911) are enlightening In the group of malignancies diagnosed preoperatively 20 per cent survived five years in the group diagnosed at operation 10 per cent survived five years in the group diagnosed by the pathologist 80 per cent survived five years

Some conception of the relative frequency of malignancy in different types of goiter may be gleaned from the reports of Cole and his associates (1915 1919) Fifty four cases of carcinoma of the thyroid were encountered in an 11½ year period There were 517 cases of toxic diffuse goiter with *a single malignancy an incidence of 0 2 per cent* In 378 cases of toxic nodular goiter there were four malignancies or 1 0 per cent carcinoma In the nontoxic nodular group the incidence

Nontoxic Nodular Goiter

In contradistinction to the nontoxic diffuse goiter just described surgical intervention in the nontoxic nodular goiter is most often indicated

There may be a preceding history of a nontoxic diffuse goiter which is followed by a nodular or asymmetrical enlargement (Chapter XXXII) The prophylactic use of iodine in goitrous regions is valuable as a preventive and should also be given to these patients during pregnancy Once a nodular goiter is established iodine will not cause its regression and at times prolonged use may incite hyperactivity even leading to the development of a toxic nodular goiter The clinical symptoms and signs of nontoxic nodular goiter may be mild or in a neglected case may be extremely severe Any one or a number of indications for surgical intervention may exist

The disfiguring goiter may require removal for cosmetic reasons alone It is this type of goiter as it may enlarge to tremendous proportions that is most often responsible for pressure symptoms sometimes of alarming severity Most often the enlargement follows the line of least resistance bulging forward into the neck and even descending in front of the clavicle and sternum At times it does not follow the direction of least resistance, as a lobe or nodule may descend behind the sternum and clavicle giving rise to the retroclavicular or substernal goiter The goiter that changes position lying behind the sternum and clavicles on one occasion and then on another bulging forward over the clavicles has been termed plunging goiter When a goiter descends it usually maintains its cervical attachment by a thin neck of thyroid tissue but this may be reduced to a tenuous band of fibrous tissue It may lose all connection with the gland because of atrophy of the pedicle and thus form an isolated intrathoracic goiter

The pressure symptoms include difficulty with breathing and deglutition At first there may be infrequent attacks of coughing and slight dyspnea often first noted when lying down at night The latter may progress to severe shortness of breath with choking attacks and respiratory stridor Continued pressure with partial encirclement of the trachea may lead to saber trachea in addition to displacement Although the malignant forms of goiter are more apt to cause paresis or paralysis of the recurrent nerves this may occur also with the nontoxic nodular goiter Interference with swallowing is not frequent and is usually not severe Pain is rare

It has been suggested previously that continued use of iodine may lead to the development of toxicity and this is undoubtedly a real danger Furthermore the patient with the toxic nodular goiter will often give a history of some years standing of an asymptomatic lump in the neck (nontoxic goiter) Exactly what percentage will develop toxicity it is difficult to prognosticate In the older patient the per

centage will rise In addition although the usual laboratory criteria of toxicity are absent the patient may present mild systemic manifestations

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of carcinoma was 17.15 per cent. In 112 nontoxic multinodular goiters 11 carcinomas were encountered, an incidence of 9.8 per cent. In the *143 nontoxic solitary nodular goiters 35 or 24.4 per cent were malignant*. The incidence in which the correct diagnosis has been made preoperatively has varied widely: 21 per cent (Cole 1915), 40 per cent (Pemberton 1939), 73 per cent (McSwain 1918), 75 per cent (Cole 1919), 90 per cent (Crile 1919).

Carcinoma represents a not unknown form of nodular goiter in childhood, so that even in this age group a thyroid nodule is not *safe*. Kennedy (1940) found 12 carcinomas of the thyroid in 62 children with nodular goiter, an incidence of 19.3 per cent, indicating the serious aspects of nontoxic nodular goiter in children.

Crile (1919) has emphasized the following features of nodular goiter that should be viewed with suspicion: (a) in children, (b) when enlarging or giving symptoms of discomfort or pressure, (c) when firm and hard, and (d) when discrete and different in consistency from the remainder of the thyroid.

In conclusion, it should be stated that the incidence of carcinoma occurring in nontoxic nodular goiter is so high, and it is so difficult to be certain that we are dealing with a benign and not a malignant lesion, that surgical removal becomes the treatment of choice.

Toxic Diffuse Goiter (Exophthalmic Goiter)

Crotti (1938) states: "Graves disease is one in which both the physician and the surgeon must have something to say. The physician prepares the way for the surgeon and, when the work is done, gives it its finishing touch. Great things are not done by the individual alone but by cooperative work. There is no other field in Medicine where the team work principle can be applied to better advantage."

A number of observers during the past twenty years have noted an apparent decrease *in the number of toxic goiters, and this may be due* in part to the increased intake of iodine in endemic goitrous belts. More recently the number of thyroidectomies has rather sharply decreased and is explained by the large number of patients undergoing treatment with thiourea compounds and radioactive iodine.

The etiology and clinical course of exophthalmic goiter have already been discussed (Chapter XXXIV) in some detail. According to Plummer (1923) the disease runs a cyclic course, each cycle being approximately 18 months in length. In the first half of the cycle there is a decline in health, and in the second half a spontaneous improvement. Each cycle produces a lower level of health, and it requires about 10 cycles to cause permanent impairment, particularly of the cardiovascular apparatus.

At this point there is no need to repeat what has already been said in earlier chapters (XXXIV through XXXVIII), but emphasis may be

justly placed upon the examination of the neck eyes and vocal cords A diffuse symmetrical and firm enlargement of the thyroid gland will be palpable in approximately 85 per cent of all patients Some of the remainder may have a gland of normal size In the patient with heavy neck muscles the goiter may not be large enough to be detected by inspection or palpation When the tumefaction lies retroclavicularly or retrosternally it may become palpable if we have the patient strain or cough Small nodules may be impossible to palpate and in such cases we are unable to distinguish clinically between the diffuse toxic and the toxic nodular goiter In the highly toxic exophthalmic goiter there may be a palpable thrill expansile pulsation and an audible bruit over the gland

The ocular signs of exophthalmic goiter are the least constant of its features A staring expression may precede the development of exophthalmos The degree of exophthalmos is best estimated with the eyelids closed or by actual measurement with the exophthalmometer The abnormal widening of the palpebral fissure is responsible for the staring expression and is sometimes referred to as Dalrymple's sign Prolongation of the interval between involuntary winkings is known as Stellwag's sign Lagging of the upper lid as the eye is lowered or von Graefe's sign may be present Other less common and more difficult to elicit signs such as the Moebius sign or failure of convergent strabismus without diplopia Clifford's sign or difficulty in everting the upper eyelid and the Joffroy sign or absence of wrinkling of the forehead when looking up are of slight diagnostic value Any evidences of malignant exophthalmos (Chapter XXXIV) should prompt the surgeon to proceed with caution

Whenever operation is contemplated the condition of the vocal cords should be checked preoperatively at such a time any disturbance in their movements always indicates a complication with involvement of the recurrent laryngeal nerve

In the absence of the cardinal symptoms and signs of Graves disease (goiter exophthalmos tachycardia and tremors) the diagnosis may not be apparent and the condition may simulate the atypical clinical picture of some other disease Atypical monosymptomatic or obscure expressions of masked hyperthyroidism have been recognized since Marie in 1883 noted the occurrence of Basedow's disease with tachycardia and tremor but without exophthalmos or struma Attenuated forms of the disease were termed formes frustes by Charcot in 1885 Kocher termed them atypical Basedow's disease Fahey has emphasized the thyrocardiac and apathetic forms of hyperthyroidism Hyperthyroidism may masquerade as heart disease with cardiac failure hypertension angina pectoris auricular fibrillation diabetes mellitus myasthenia gravis progressive muscular dystrophy tuberculosis malignancy or some form of gastrointestinal disease (Breidenbach 1942)

The treatment of hyperthyroidism may be well divided chronologically into four eras (1) the surgical era of Kocher, Mikulicz Halsted, Crile and Mayo when the basic surgical principles were formulated In fact little refinement in surgical technic has been added (2) the iodine era which began with the rediscovery of iodine by Plummer (1923) which resulted in a shortened preoperative period and drastically reduced operative mortality by preoperative control of thyrotoxicosis in many cases (3) the epoch making discovery of the antithyroid drugs by Astwood (1943) the Mackenzies (1942) and Richter and Chisby (1942) working independently, and shortly thereafter clinical application of these compounds to hyperthyroidism and (4) the recognition of the value of radioactive iodine in the treatment of hyperthyroidism by Hertz and Roberts (1942) and by Hamilton and Lawrence (1942) Although antedating the work on the antithyroid compounds radioiodine has not been extensively employed as a therapeutic agent in exophthalmic goiter In order to treat intelligently the patient with the Graves type of hyperthyroidism our problem is the selection of the proper therapeutic agent or combination of agents Surgery has been made safe by the preparatory administration of iodine or one of the thiourea compounds and needless to say no patient should be considered a candidate for surgery until there has been adequate preparation With few exceptions iodine should be given only as a part of the immediately preoperative regime as the maximum benefit will usually be obtained within fourteen days and continued use may lead to an iodine fast state with an exacerbation of symptoms

Results with the antithyroid compounds vary in spite of rapid progress in the development of new compounds of lessened toxicity and increased potency Mildly toxic patients those with small glands and those treated over long periods of time are most apt to have a permanent remission (50 per cent Cole 1948 85 per cent Astwood 1946) Rapid relapse will result from inadequate short courses of antithyroid compounds

Cole (1948) has emphasized three advantages of therapy with thiouracil or propylthiouracil stating that it will (1) control hyperthyroidism in 95 to 100 per cent of patients if given sufficiently long time in adequate dosage (2) produce lasting remission in more than 30 per cent of the patients (3) greatly reduce the mortality rate in the thyrotoxic patient

At the present time it is often difficult if not impossible to separate the patients best treated by surgical resection of the gland after adequate preoperative preparation from those best treated by thiourea derivatives

Preference for surgical intervention in Graves disease exists in the following classes

1 Failure to obtain permanent remission after a fair trial with thiourea compounds

2 In those patients in whom there is a toxic reaction to drugs of the thiocarbonamide type

3 Patients presenting a goiter of sufficient size to warrant thyroidectomy for cosmetic purposes (rare)

4 Those patients who present pressure symptoms (rare)

5 Patients in whom the time element is of importance

6 Those patients who do not cooperate sufficiently to permit adequate observation and supervision of treatment

7 That small group of patients in whom we cannot rule out nodularity or the possibility of malignancy

8 Pregnancy of more than three months from termination and after preparation with iodine There are however those who prefer to carry the patients through pregnancy with the aid of the antithyroid compounds with the idea in mind of elective surgery later (Chapter VIII)

A fair and adequately prolonged medical regimen and treatment of exophthalmic goiter with antithyroid compounds is preferred before resorting to surgery in the following instances

1 When the disease is of mild or moderate severity has been present a short period of time and is associated with a small gland

2 In the very young aged or debilitated

3 In the patient in whom there is a coexisting serious constitutional condition such as heart disease diabetes or tuberculosis

4 Persistent or recurrent hyperthyroidism or previous nerve injury

Our experience in the treatment of toxic diffuse goiter with radioactive iodine I^{131} has been too recent to arrive at any conclusion on the basis of personal observation However there are those who believe it may well replace the antithyroid compounds as well as surgical procedure in the therapy of this condition

Toxic Nodular Goiter (Plummer's Disease)

Inasmuch as our management of toxic nodular goiter involves surgical procedure in a majority of cases while our therapy of Graves disease is commonly evolved without such therapy the major distinguishing features of the two conditions may be profitably recounted even at the risk of repeating ourselves (see Chapter XXXIV)

Once a toxic nodular goiter is present the condition usually runs a progressive course unless adequate treatment is instituted Rarely does it burn itself out and rarely do spontaneous remissions occur The patient with a toxic nodular goiter is considerably older than the patient with primary thyrotoxicosis the average difference being ten to fifteen years (35 to 55 years of age) The onset of clinical symptoms and signs

is more apt to be insidious and these may be of a milder nature than in the patient with Graves disease Thyroid crises do not develop as frequently in the nodular as in the diffuse hyperplastic goiter Just when a nontoxic nodular goiter passes into the toxic nodular form may be difficult if not impossible to state but often a nontoxic nodular goiter has been present for ten to fifteen years

The typical patient with toxic nodular goiter may present all the symptoms and signs of primary thyrotoxicosis as previously mentioned She however less frequently presents the eye signs so often seen with Graves disease

The symptoms and signs referable to the cardiovascular system are more frequent in toxic nodular goiter than in Graves disease In fact auricular fibrillation and cardiac decompensation may dominate the clinical picture of the former and lead to an erroneous diagnosis of a primary cardiac condition

Palpation of the thyroid gland will usually reveal an asymmetrical and nodular enlargement in toxic nodular goiter Not too infrequently the nodules will be so small and diffusely scattered throughout the gland that it will be difficult to differentiate it from the diffuse hyperplastic goiter of Graves disease and rarely it may be distinguishable only on microscopic examination A thrill may be palpable and a bruit may be *heard*

Pressure symptoms are present in toxic nodular goiter more often than in Graves disease and less often than in nontoxic nodular goiter The occurrence of malignancy in toxic nodular goiter is uncommon less than 1 per cent

The basal metabolic rate is not usually elevated to the same degree as in Graves' disease

After adequate preoperative preparation preferably with an anti thyroid compound surgical resection (subtotal thyroidectomy) is indicated in toxic nodular goiters

Malignant Tumors of the Thyroid Gland

If we are to improve the prognosis and raise the number of five year survivals of patients with cancer of the thyroid gland the malignant tumor must be attacked at an early stage It is at this stage that it is not possible on clinical examination to differentiate it from the benign nodular goiter Two points bear repetition (1) In over 90 per cent of the cases carcinoma of the thyroid arises in connection with a pre existing adenoma (2) Ward (1944) has emphasized that the five year survival rate in cancer of the thyroid is 80 per cent when the diagnosis is established only by microscopic examination of the excised tumor 40 per cent when diagnosed by the surgeon at the time of operation and 20 per cent when correctly diagnosed preoperatively Cole (1945) has reported carcinoma in 21 per cent of solitary nontoxic nodular

goiters in which a diagnosis of malignancy preoperatively was reached in only 21 per cent It should be evident that accurate preoperative diagnosis while highly desirable is not as important as suspecting malignancy and advising early excision

Cancer of the thyroid is not a hopeless disease and in instituting surgical therapy we must not wait for signs of fixation lymph node involvement or distant metastases any more than we would wait for the appearance of the late signs of a carcinoma of the breast Any asymmetrical enlargement of the thyroid should be viewed with suspicion The size of the adenoma is not related to the presence or absence of a malignancy Once a pre existing nodule assumes a consistency different from that of the remainder of the gland shows fixation to surrounding structures enlarges suddenly or produces any local symptoms malignancy is likely Late and unmistakable signs of thyroid carcinoma are fixation to the overlying muscles and fascia and to the deep structures of the neck lymph node invasion and involvement of the recurrent laryngeal nerves with voice changes Kennedy (1940) found 12 carcinomas among 62 children with nontoxic nodular goiter an incidence of 19 3 per cent which emphasizes the point that cancer is no respecter of age

In nearly every case lateral aberrant thyroid cancer represents a metastatic lesion from the homologous lobe of the thyroid gland (King and Pemberton 1940 Crile 1947 Warren and Feldman 1949) Regardless of the origin of these tumors they grow very slowly They should all be removed and at the time of operation the homologous lobe of the thyroid gland should be excised even though it is grossly normal in appearance

A pathological classification of malignant tumors of the thyroid has already been discussed (Chapter XXXIII) However as a background for our surgical indications the clinicopathological classification of Horn et al (1947) affords a satisfactory point of departure for everyday work

Group I Cases without clinical evidence of malignant tumors of the thyroid gland in which the neoplasms are discovered only after microscopic examination of the tissues removed

Group II Cases without clinical evidence of malignant tumors of the thyroid gland in which suspicion of carcinoma is aroused on the basis of the age of the patient and a recent rapid enlargement of a goiter of long standing in which a well localized wholly intracapsular lesion is discovered at operation the true nature of which is confirmed on microscopic examination

Group III Cases with clinical or pathological evidences of malignant tumors of the thyroid gland which have invaded or extended out-

side of the capsules of the thyroid gland but which show neither clinical nor roentgenological evidence of metastases

Group IV Cases with clinical or pathological evidences of malignant tumors of the thyroid gland as well as clinical or roentgenological evidences of metastases

When these groups of Horn et al are brought into relationship with the pathological classification then criteria can be developed which are useful both from a diagnostic and a prognostic point of view

In Group I in which the lesion is encapsulated, easily removed with its capsule intact and exhibiting invasion of blood vessels as the only sign of malignancy radical neck dissection is not indicated (Meissner 1948)

In Group II where the capsule is not penetrated and there is no evidence of lymphatic permeation but a recognizable malignant lesion is identified at the time of operation hemithyroidectomy and homolgous radical neck dissection are indicated The patient is given postoperative radiation

In Group III every attempt should be made to perform as radical a removal as possible even in those patients with large fixed masses together with radical neck dissection Postoperative radiation is given

In Group IV the patients will usually not be considered surgical However in some of these resection and tracheotomy will be performed in order to relieve the obstructive phenomena and prepare the way for other therapeutic measures Such removal of all or a major portion of the primary tumor will create a field more readily accessible to roentgen radiation and will prove to be a measure of great value in increasing the capacity of distant metastases to pick up and concentrate radioactive iodine

Chapter XLIII

PREOPERATIVE PREPARATION

Since the advent of the antithyroid compounds the entire preoperative preparation of the patient exhibiting hyperthyroidism has been revised The internist will prepare 90 per cent or more of these patients in such a manner that they will come to operation completely free of toxic symptoms and signs As a result of adequate preparation with antithyroid compounds many of the previous hazards that attended resection in thyrotoxicosis have been eliminated The major advantages include safety during the operative procedure a marked reduction in mortality and the almost complete elimination of postoperative complications particularly thyroid crisis It would be repetitious to give a detailed description of these drugs their indications their dosage the frequency of their administration and the complications which may attend their use (see Chapter XXXVIII) From our experience it may be well to state that methylthiouracil and 1 methyl 2 mercaptoimidazole have proved eminently successful and in our hands are now preferred to either thiouracil or propylthiouracil Although malignant neutropenia has not been reported to follow the use of any of the imidazoles in the therapeutically effective doses it is best to discontinue the chemical at least one week prior to the anticipated date of surgery and to give Lugol's solution for ten to fourteen days preoperatively In addition to avoiding the possibility of an always serious agranulocytosis in the immediately postoperative period this regimen aids in decreasing the friability and vascularity of the gland thus facilitating surgical procedure and diminishing the loss of blood during the operation While the above is our usual practice we have also given both the thio compounds and iodine up to the date of operation without materially altering the problems surgically encountered Some question exists as to whether or not the thyrotoxic state is thus more satisfactorily controlled from the standpoint of anesthesia and the incidence of postoperative complications

In the small group of patients in whom preparation with iodine alone is indicated we must carry out the meticulous routine that was once indicated for all toxic patients This group includes those patients in whom (1) there is a serious toxic reaction to an antithyroid drug

(2) there is failure to respond to such a compound (3) the time element is an important factor, although we doubt that it is ever sufficiently important to gamble on the uncertainties of iodine in contrast to the completeness of control achieved by antithyroid compounds of the thio group (4) a cooperative attitude cannot be achieved to permit adequate observation and supervision of treatment and (5) the mildness of the thyrotoxic state affords an opportunity for safe and rapid preparation for operation without the need of long continued administration of an antithyroid compound These patients are best hospitalized placed on Lugol's solution and operated upon as soon as they have met the criteria described below

The patient with a nontoxic goiter is usually safely operated upon without previous treatment by either iodine or an antithyroid drug In our experience there will be a few who exhibit one or more ill defined symptoms of thyrotoxicosis and occasionally such patients will develop a mild postoperative storm Therefore we feel that any patient falling within the group of nontoxic goiters should be given the benefit of Lugol's solution for seven to ten days preoperatively Not only will this reduce the incidence of unexpected postoperative thyroid crises but it often makes the procedure technically less difficult by reducing the friability and vascularity of the gland

Preoperative Orders for Thyrotoxic Patients Requiring Hospitalization and Preparation With Iodine —To summarize the preoperative preparation it may be well to list the preoperative orders as used at the Flower and Fifth Avenue Hospitals and affiliated institutions It must be remembered that these orders are to be interpreted with due regard to the individual needs of the patient and are more of a guide than a rigid routine

1 As in all patients a meticulous history shall be taken noting particularly and carefully all symptoms referable to the endocrine and cardiovascular systems and to the metabolic status At the time of the physical examination the size consistency symmetry and mobility of the thyroid gland shall be carefully noted and recorded Examination shall include inspection for tracheal deviation and examination of the condition of the vocal cords laryngoscopically The status of the cardiovascular system must be evaluated

2 The patient shall be assigned a quiet private room and adequate bed rest assured The number of visitors shall be limited both pre and postoperatively and this order shall be extended to preclude frequent and unnecessary examinations by both the attending service and the house staff The same special nurses shall care for the patient during the entire hospitalization if possible

3 The diet shall supply at least 60 calories per kilogram or in any event should be sufficient to effect a gain in weight Proteins and fats

of high quality are desirable Supplements of milk and fruits reinforced with as much lactose as they will dissolve add much to the caloric value and little to the bulk of the diet The addition of vitamins and calcium to the regime is of value Spices coffee and tea should be eliminated

2 Temperature pulse and respiration shall be recorded at four hourly intervals Blood pressure and weight shall be recorded daily

3 Laboratory procedures shall include a chemical and microscopic examination of the urine the determination of hemoglobin red blood count white blood and differential count blood cholesterol and cholesterol esters and a Wassermann test The patient shall be typed and cross matched and blood banked for the day of operation Although not essential the following procedures are of value in selected cases blood sugar urea nitrogen and creatinine plasma or serum proteins calcium phosphorus prothrombin level protein bound iodine value and glucose tolerance and hippuric acid hepatic function tests

6 Roentgenological examination of the lungs and cervical region

7 An electrocardiogram

8 The basal metabolic rate shall be taken prior to the administration of any therapeutic agent When the patient is being prepared for surgery by iodine as the sole agent it shall be repeated every four to seven days

9 The internist cardiologist and anesthesiologist shall work as a team to which the patient early becomes accustomed so that visits from any or all of them cease to be exciting events

10 Specific medication with Lugol's solution shall be given 1 cc three times daily for a period of 10 to 21 days depending on the response of the patient and the patient's ability to meet the criteria for operation In addition phenobarbital 60 to 90 mg three times daily is usually helpful and necessary Quinidine hydrobromide 100 mg three times daily for three days preoperatively has in our hands proved of value in controlling and preventing the development of cardiac complications during operation

11 If sham anesthesia is used it shall be given daily by the same nurse or anesthesiologist who will administer the basal anesthesia on the day of operation Care shall be exercised by all concerned not to disclose the date of operation either by word or action

12 A light meal shall be given the night preceding the operation and fluids shall be withheld for six hours preoperatively

13 Preoperative medication usually consists of morphine sulfate and scopolamine 1½ hours preoperatively Avertin is the preferred basal anesthesia

14 The operative field is prepared in the usual manner except in those patients undergoing sham treatment in which case preparation shall be deferred until after the administration of the basal anesthesia

(2) there is failure to respond to such a compound (3) the time element is an important factor although we doubt that it is ever sufficiently important to gamble on the uncertainties of iodine in contrast to the completeness of control achieved by antithyroid compounds of the thio- group (4) a cooperative attitude cannot be achieved to permit adequate observation and supervision of treatment and (5) the mildness of the thyrotoxic state affords an opportunity for safe and rapid preparation for operation without the need of long continued administration of an antithyroid compound These patients are best hospitalized placed on Lugol's solution and operated upon as soon as they have met the criteria described below

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2 The patient shall be assigned a quiet private room and adequate bed rest assured The number of visitors shall be limited both pre and postoperatively and this order shall be extended to preclude frequent and unnecessary examinations by both the attending service and the house staff The same special nurses shall care for the patient during the entire hospitalization if possible

3 The diet shall supply at least 60 calories per kilogram or in any event should be sufficient to effect a gain in weight Proteins and fats

7 A reduction in the basal metabolic rate of at least 50 per cent and a progressive decrease in consecutive tests
8 A rise of cholesterol and cholesterol esters toward normal

Extent of the Operation.—Staged operative procedures should be considered in those patients whose toxic status could not be controlled by therapy. Under such circumstances it has been our experience and it has been repeatedly emphasized by others that staged procedures reduce mortality and morbidity rates. The extent of the operative procedure should be determined by the degree of toxicity present at the first examination and not by the extent of toxicity present after preparation. A decision to perform a hemithyroidectomy where subtotal resection was originally planned should be based upon the following danger signs:

1 Excessive loss of blood
2 Increasing pulse rate during operation
3 Increasing pulse pressure
4 An increased demand for anesthetic agent and/or an increasing oxygen consumption
5 Any interference with the maintenance of a normal airway

Operation should be cancelled if there is failure to respond to preoperative medication and the patient arrives in the operating room in a hyperexcitable stage or if there is a prolonged or difficult period of induction of anesthesia.

Preoperative Orders for Patients With Nontoxic Goiters or Patients With Toxic Goiters Hospitalized After Control of Toxicity by Antithyroid Drugs —

1 Light diet shall be given the night prior to operation, fluids by mouth are withheld for six hours preoperatively

2 Laboratory data shall include a urinalysis a hemoglobin determination, a red blood count and white blood count with differential typing and cross matching Most of the essential laboratory data have already been obtained while these patients are ambulatory

3 Roentgenological examination shall be made of the lungs and cervical region

4 The last basal metabolic rate taken 21 to 48 hours before admission shall be +15 or less

5 The formerly toxic patient shall continue to receive Lugol's solution up until the time of operation As previously indicated we also prefer to administer Lugol's solution 1 c c three times daily to all nontoxic patients Phenobarbital or quinidine is not often indicated

It is rather clear from the simplicity of these orders that we do not need to exert special effort to bring the patient to surgery who has been prepared by an antithyroid compound of the thiouracil or imidazole group We have no hesitancy in letting them know beforehand the day and hour at which the procedure will be carried out No prolonged preoperative hospital stay is necessary We usually admit the patient 12 to 24 hours prior to the time of operation just long enough to complete the preoperative examinations Sham therapy is not necessary anoci association is not important Thyroid crisis is to be little feared *we have not seen the condition if the patient has been properly treated* with the antithyroid compound

Criteria for Time of Operation —*For the patient prepared by antithyroid drugs* there should be complete control of all symptoms and signs and laboratory evidence that there is no toxicity before operation is performed Until this is accomplished the patient should continue to take the drug Failure calls for postponement of the operation and preparation with iodine

For the patient prepared for operation with Lugol s solution there shall be

1 Iodinization for 12 to 21 days with evidence of a good response
2 Emotional status good or at least improved
3 Stabilization of the pulse rate preferably below 100 while the patient is resting
4 A diminishing or stationary pulse pressure
5 A gain of weight and preferably restoration of weight loss
6 Evidence of myocardial competency is evidenced by the response of pulse and blood pressure to exercise the breathing test and the electrocardiogram

The pyramidal lobe is present in about 40 per cent of all pathological specimens It arises from the isthmus or lateral lobe more commonly the left It is a thin strip of gland occasionally double seldom median and usually deflected toward one side It may consist of fibrous tissue only or of fibrous tissue and muscle and is sometimes called the ligamentum suspensorium or muscle levator glandulae thyroideae of Soemmerring The muscle may be present independently of the pyramidal lobe The thyroglossal duct (canal of His) may connect the apex of the pyramidal lobe to the foramen caecum at the base of the tongue

The Fascial Covering—The thyroid gland in addition to possessing a capsule of its own is covered by a sheath of pretracheal fascia derived from the deep cervical fascia The thyroid capsule is inseparably connected with the gland The space between the capsule and the sheath of pretracheal fascia is crossed by the thyroid vessels and contains areolar tissue One median and two lateral extensions of the pretracheal fascia form ligaments securing the gland to the cricoid and thyroid cartilages and to the upper rings of the trachea

Arteries—Each lateral lobe of the thyroid is supplied by the superior and inferior thyroid arteries and in 10 per cent of subjects by the thyroidea ima as well

The superior thyroid artery is the first anterior branch of the external carotid artery It arises at the level of the cricoid cartilage ascending toward the greater cornu of the hyoid bone lying on the inferior constrictor muscle of the pharynx It then passes forward beneath the sternohyoideus and at the medial aspect of the apex of the gland usually terminates in three branches In addition to its terminal branches the branches of the superior thyroid artery are hyoid superior laryngeal sternocleidomastoid and cricothyroid Mastin (1923) describes the trifurcation of the thyroid artery (1) an anterior branch passing over the anterior surface of the gland as far as the isthmus and anastomosing with its fellow of the opposite side (2) a posterior branch passing along the posterior lateral surface and communicating with the inferior thyroid artery of the same side and (3) a small and variable terminal arising between the anterior and posterior branches and immediately entering the substance of the gland The superior thyroid artery usually the left supplies a branch to the pyramidal lobe if it is present

The inferior thyroid artery arises from the thyrocervical trunk a branch from the first part of the subclavian artery The inferior thyroid artery ascends along the medial border of the scalenus anticus muscle emerging behind the carotid sheath at the junction of the lower and middle third of the posterior border of the thyroid gland The recurrent laryngeal nerve ascends in front of behind or between

Chapter XLIV

THE SURGICAL ANATOMY OF THE THYROID GLAND

The thyroid is a ductless gland occupying the visceral compartment of the deep cervical fascia in the neck. It consists of two lateral lobes connected by a median lobe or isthmus and in about 40 per cent of the cases a pyramidal lobe. Not uncommonly the thyroid gland is horseshoe shaped. The average weight is 30 to 40 grams although it may be as much as 60 grams in the absence of gross or histological evidence of goiter. It is larger in women than in men especially during menstruation pregnancy and lactation. In the aged it *decreases in* size and becomes *more firm*; it may even contain calcareous plaques.

Lobes.—The *right lobe* of the thyroid gland is usually larger than the *left*. The lateral lobes are pyriform in shape and rise as high as the oblique line on the sides of the thyroid cartilages which marks the point of the insertion of the sternothyroid muscles. The superior thyroid vessels enter at the apex of the lobes and the surgeon when ligating these vessels should remember that just above and posterior to *them* lies the external ramus of the superior laryngeal nerves.

The superficial surface of the lobe is convex and lies between the trachea and the carotid sheath. It is covered by skin platysma deep cervical fascia and the sternohyoid sternothyroid the anterior belly of the omohyoid and sternocleidomastoid muscles and the *pretracheal* fascia. The deep surface is concave. Medially this surface is firmly attached to the trachea and lies in relation to the larynx esophagus recurrent laryngeal nerve superior and inferior thyroid vessels the cricothyroid and inferior constrictor pharyngeal muscles. The anterior border is thin and is in relation to the isthmus and to the lateral lobe of the opposite side.

The posterior border is thick and behind it lie the parathyroid bodies and carotid sheath (carotid arteries internal jugular veins and vagal nerves). The base may extend retrosternally and retroclavicularly and come into contact with the innominate and subclavian vessels the thoracic and right lymphatic ducts and the pleura. The inferior thyroid vessels *penetrate the base of the gland*.

The isthmus or middle lobe connects the lower thirds of the lateral lobes and is firmly attached to the trachea as it crosses the second and third tracheal rings.

From this point the course of the two recurrent laryngeal nerves is practically identical each ascending in the pretracheal fascia of its respective side via the esophagotracheal groove posterior to the thyroid gland Each then passes behind the cricoid origin of the inferior constrictor muscle of the pharynx to enter the larynx through the thyrohyoid membrane The nerve supplies all the intrinsic muscles of the larynx except the cricothyroid and the interarytenoid structures and yields branches to the mucous membrane of the lower portion of the larynx

Lahey (1938 1941 1944) has repeatedly emphasized the variable course taken by the recurrent nerve showing that (1) it may pass directly from the vagus to enter the larynx an undescended nerve ' or (2) it may arise from the vagus at the level of the inferior thyroid artery and hook under the artery to gain its position a partly descended nerve The relation of the nerve to the inferior thyroid artery is also variable (1) the nerve may pass posterior to the main trunk or all of the branches (2) it may pass anterior to the trunk or all its branches or (3) it may pass through the branches of the inferior thyroid artery

the branches of the inferior thyroid artery The artery divides into an ascending and descending branch The ascending branch anastomoses with a branch of the superior thyroid artery The descending branch passes to the inferior pole and then turns forward onto the anterior surface of the gland

The thyroidea ima usually arising from the innominate or occasionally from the arch of the aorta, is found ascending in front of the trachea to pierce the thyroid gland at or near its lower border

Veins —*The superior thyroid vein* accompanies the superior thyroid artery and empties into the internal jugular vein

The middle thyroid vein lacks a companion artery From the lower part of the thyroid gland it extends horizontally beneath the infrahyoid muscles and across the common carotid artery to end in the internal jugular vein

The inferior thyroid vein joins the left innominate by passing down in front of the trachea

The veins take their origin from a venous plexus on the gland Extensive venous anastomosis is effected along the borders of the isthmus When the gland is large accessory veins are present in considerable numbers The accessory veins of Kocher lie between the middle and inferior veins and usually drain into the internal jugular vein

Lymphatic Vessels — Lymphatic vessels anastomose freely efferents passing to the deep cervical glands a few descending to the pretracheal lymph glands and thence to the retrosternal glands

Nerve Supply —The nerve supply of the thyroid is from the middle and inferior cervical ganglia of the sympathetic with the addition of a few filaments from the vagi

The superior laryngeal nerve arises from the vagus at the ganglion nodosum descends behind the internal carotid artery and then passes medial to lie on the superior constrictor muscle of the pharynx It divides into an external and internal branch The external branch lies just above and behind the superior thyroid artery and vein and the nerve may be injured when ligating the superior pole vessels The external branch supplies the cricothyroid muscle The internal branch penetrates the thyroid membrane with the superior laryngeal artery and innervates the mucous membrane of the larynx

The right recurrent laryngeal nerve arises from the vagus and passes below and behind the right subclavian artery to reach the right side of the trachea

The left recurrent laryngeal nerve arises from the vagus in the thorax to the left of the arch of the aorta passing below and behind the arch to enter the neck on the left side of the trachea

Care is exercised not to injure the anterior jugular veins The upper flap of skin and platysma is raised from the deep fascia to a point above the thyroid notch A piece of gauze over the finger will usually accomplish this so that a minimal amount of sharp dissection will be required *The lateral portions of the flap do not need to be as* highly elevated as the central portion The upper flap is retracted by a rake The lower flap is not elevated The midline is accurately located to insure opening the deep cervical fascia in the avascular plane between the prethyroid muscles

The vertical incision through the deep fascia is carried down to the capsule of the thyroid upward to a point above the thyroid notch and downward to a point 1 or 2 cm above the sternal notch The anterior communicating branch of the anterior jugular veins may be avoided by not carrying the incision too low The next step is separation of the sternohyoid and sternothyroid muscles from the gland A gentle spreading motion with a hemostat of the Kelly type will facilitate the freeing of these muscles from the lobe Adequate exposure is obtained by retraction of the muscles laterally with a Brewster type *of retractor It is seldom necessary to cut the strap muscles transversely* but if advisable they should be divided at a high level

The next step in thyroidectomy is careful exposure of the trachea above the isthmus This necessitates dividing the suspensory ligament of the thyroid gland The medial clear space (cricothyroid space) lying between the superior pole of the thyroid gland and the cricothyroid muscle is exposed by blunt dissection Great care must be exercised at this point not to injure the cricothyroid muscle as troublesome bleeding will occur Failure to enter the space correctly may result in injury to the superior laryngeal nerve The lateral clear space lying between the carotid sheath and the superior pole of the thyroid is then entered keeping close to the gland until the cervical vertebra can be palpated When the medial and lateral clear spaces are carefully opened the superior thyroid vessels are readily sectioned between paired hemostats without fear of injuring the superior laryngeal nerve Completion of this maneuver makes possible the complete delivery into the wound of the superior pole of the gland Once the superior pole has been detached the lateral thyroid veins are divided between paired hemostats Sectioning the superior thyroid vessels and the lateral veins permits delivery of the lower *pole together with any retroclavicular or* retrosternal extensions A ring of paired hemostats are now placed on the posteromedial surface of the lobe This procedure permits the operator to resect the lobe intracapsularly A thin slice of thyroid tissue is preserved in the tracheoesophageal groove Avoidance of *injury to the recurrent laryngeal nerves* is usually thus assured

The recurrent laryngeal nerves are not visualized during the operation as advised by Lahey (1938) and the inferior thyroid artery is

Chapter XLV

THE TECHNIC OF SUBTOTAL RESECTION OF THE THYROID GLAND

The technic of thyroidectomy cannot be acquired by reading a text but must be developed while working at the operating table with well trained and experienced thyroid surgeons The procedure followed by the leading clinics throughout the world represents the culmination of years of experience by master surgeons who by trial and error have evolved the basic concepts exemplified in a so called model' technic

When applied to the management of thyrotoxicosis such concepts envisage (1) the removal of from two thirds to nine tenths of the abnormally functioning tissue enough to control the symptoms without producing thyroid insufficiency (2) careful hemostasis (3) avoidance of trauma to near by structures (4) adequate attention to drainage in an effort to prevent sepsis and (5) coaptation of tissue in such a manner as to ensure a satisfactory cosmetic effect There are many minor variants in the manner of procedure all consonant with the attainment of these objectives so much so that a perusal of the literature on the subject of thyroidectomy leaves the impression that there are many roads to Rome Without prejudice toward any accepted technic of thyroidectomy we employ the method used successfully by Coller (1937) The essentials of this excellent technic with but minor modifications are as follows

Intratracheal anesthesia is preferred The head of the table is slightly elevated a sandbag is placed between the patients shoulders the head is held perfectly straight and the neck is hyperextended The operative field is prepared and draped in the usual manner The skin incision must be symmetrical bilaterally It is made transversely 2 cm above the sternal notch and slightly curved so that its lateral angles are 3 to 3 5 cm above the clavicles It should be placed higher in very large goiters The incision is carried through the skin subcutaneous fat and the platysma to the deep cervical fascia

Crile (1919) believes that the upper flap should consist of skin and subcutaneous tissue only and thus excludes the platysma Roeder (1922) leans to the other extreme and extends his collar incision through the skin subcutaneous tissue platysma and deep fascia and elevates the whole as his upper flap

Chapter XLVI

POSTOPERATIVE CARE

Under present day procedures for the preparation and operation of a patient for thyroidectomy there should be little need for highly specialized postoperative care Following thyroidectomy the general or systemic complications most likely to appear are psychological invalidism acute psychosis hypothyroidism hypoparathyroidism and thyroid storm or crisis Those complications which result from a technical error are few in number and include hemorrhage respiratory stridor and hypoparathyroidism

"Systemic" Complications—The first two of the systemic complications psychological invalidism and acute psychosis may usually be avoided through proper preoperative advice and care by the internist The third hypothyroidism appears commonly after partial thyroidectomy for chronic thyroiditis and is to be expected following complete removal of the thyroid Hypoparathyroidism is rare when partial thyroidectomy is performed but may occur even in those cases in which careful sectioning of the removed tissue fails to reveal the presence of any parathyroid cells Thyroid crisis does not occur postoperatively in the subject who is properly prepared with antithyroid compounds These postoperative complications with systemic manifestations have been discussed at length elsewhere (Chapter XXXVII) and have been kept in mind in setting up the routine postoperative orders still in force at the Flower and Fifth Avenue Hospitals as summarized below

Complications Due to Technical Difficulty or Error—*Postoperative bleeding* usually produces clinical symptoms and signs within twelve hours after the completion of the operation Localized manifestations due to pressure rather than the blood loss per se makes this always a serious complication The patient complains of tightness of the bandage and upon inspection and palpation of the neck the extravasation of blood is usually self evident Pressure symptoms may include difficulty in breathing alterations in voice and late in the course cyanosis secondary to the respiratory obstruction

The conditions which usually give rise to this complication are an exceptionally vascular gland and residual tissue which is firmly fixed to the trachea thus making the satisfactory ligation of bleeders excep

divided within the capsule of the gland, the trunk is not ligated extracapsularly Resection is carried from the lateral side toward the trachea and at all times exact orientation in relation to the trachea is essential In removing the isthmus from the trachea and in working near the tracheo esophageal groove, hemostats are placed across the trachea from its mesial aspect Mobilization may elevate or rotate the gland to such an extent that placing the hemostats from the lateral aspect may injure the recurrent laryngeal nerve The amount of thyroid tissue to be left will vary in each individual case Hemostasis is accomplished with No 00 black silk for the superior thyroid vessels and No 0000 black silk for all remaining ties Precise and complete hemostasis must be obtained before the incision is closed

Drains are placed in each fossa crossing the midline as they pass between the muscles and are brought out at the lateral angles of the skin incision The sternothyroid and sternohyoid muscles are sutured as two layers with interrupted No 0000 black silk Four or five sutures of interrupted black silk sutures approximate the platysma and subcutaneous tissue The skin is approximated with Michel clips

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days postoperatively The dose should then be decreased or discontinued as advised by the internist If patients are unable to take this medication by mouth during the first 24 hours it may be given intravenously as sodium iodide 0 9 Gm in a 10 per cent solution or as Lugol's solution 2 0 c c in 50 c c of water as a retention enema

11 Quinidine hydrobromide or ergotamine may be of value in controlling cardiac complications (tachycardia and arrhythmia)

12. Change the dressing within 24 hours and remove the drains One half of the skin clips are removed after 48 hours the remainder loosened and then removed within 96 hours

13 Early ambulation should be practiced the patient may be out of bed the day following operation and discharged from the hospital within 4 to 6 days

14 The following signs are to be especially watched for and reported

i Bleeding from the wound

ii Any of the following signs of respiratory obstruction or anoxia

a Excessive secretions in the nasopharynx

b Persistent coughing

c Respiratory stridor

d Cyanosis

e Any difficulty in the use of the voice

15 The above signs indicate respiratory obstruction and may be due to any of the following causes and call for immediate action by the surgeon or his agent

i Local obstruction due either to the tongue falling back or to the accumulation of secretions in the upper respiratory tract

ii Concealed hemorrhage within the wound

iii Laryngeal edema

iv Recurrent nerve injury

v Tracheal collapse

tionally difficult If such conditions are encountered in the operating room, special attention should be paid postoperatively to reducing the movements of the neck to a minimum If postoperatively bleeding is observed or suspected the patient must be returned immediately to the operating room the incision reopened the clot evacuated, and hemostasis completed If possible any general anesthesia for this procedure should be withheld until the pressure symptoms are relieved by the removal of the clot

By far the commonest cause of *respiratory stridor* is the paralysis of one or both vocal cords Laryngeal edema secondary hemorrhage collapse of the trachea and postoperative tetany are less common but difficult problems In the absence of edema the paralysis of one vocal cord is usually not serious but bilateral involvement is almost invariably an urgent indication for tracheotomy In this connection it may be emphasized that a decrease of as much as one sixteenth in the diameter of the laryngeal or tracheal structures means a reduction of one-fourth in the volume of air which can be inhaled The early administration of pure oxygen or of oxygen plus a lighter inert gas such as helium may obviate the necessity for shortcircuiting the airway but if relief is not prompt tracheotomy should be done without further delay

Postoperative Orders —In order to minimize postoperative difficulties and to deal with emergencies promptly should they arise the following orders are routinely employed in our work

1 Tracheostomy set in the patient's room

2 Oxygen 6 to 8 liters per minute by intranasal catheter

3 Demerol 50 to 100 mg every four hours used with extreme caution In view of the bulbar effects discontinue as soon as possible and substitute phenobarbital 30 to 90 mg three times daily

4 Catheterize or have patient void at least once in 12 hours

5 Place in Fowler's position when fully reacted from the anesthesia

6 Chart blood pressure pulse and respiration every ½ hour for four hours then every two hours for the first 24 hours Chart temperature every four hours

7 Aspirate secretions from the nasopharynx whenever necessary

8 Clear fluids by mouth after nausea has ceased diet as desired after 24 hours

9 Maintain adequate fluid balance to insure a urinary output of 1 000 to 1 500 c c every 24 hours and administer fluids intravenously if necessary

10 Patients who have received Lugol's solution preoperatively should receive Lugol's solution 0 3 to 1 0 c c three times daily for 5 to 7

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