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Projection of the thyroid-pituitary-ovarian axis in terms of iodine

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A PROJECTION OF THE THYROID-PITUITARY-OVARIAN AXIS IN TERMS OF IODINE

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"And if so be any man object unto me that this discourse is only compiledе together of certayne rapsodyes of antique Chyrugians I willingly heere confess and acknowlegge that in thise treatise there is verye little or nothing at all, of myne own Invention."

Jaques Guillemeau
A. D. 1594

INTRODUCTION

The choice of this subject for a thesis was influenced much more by the force of circumstance and coincidence than by premeditation. This paper represents the end result of many concessions to a subject as vast, as complicated, as unsolved and the solution of which is as beset with technical and theoretical difficulties as any in modern medical science.

The first case which I was able to observe clinically in my student career, was one of severe thyrotoxicosis. The course of the disease in this patient demonstrated graphically almost all the phenomena observed in the disease; the classic signs and symptomology; the initial transitory remission of symptoms in response to iodine therapy; subsequent "escape" from iodine due to delay in surgery; and, finally, death from an acute violet exacerbation of symptoms after surgery, the so-called "thyroid storm" or crisis. During the progress of the case several questions arose in my mind. First, when the patient became worse after previously responding well to iodide therapy, the dose of Liquor iodi compositus was doubled. Could such a procedure be expected to reinduce a remission of symptoms? Second, a clinician, in discussing the condition, mentioned the "jodbasedow" effect which was new to me and had several stimulating implications. Finally, when the patient became moribund after surgery, she was treated with massive intravenous doses of iodide. How, where and in what manner was this substance expected to act on the organism?

Later, I saw several so-called pluriglandular syndromes, involving as far as could be determined clinically, pancreas, gonads, pituitary, adrenals, and thyroid, totally or in part. There I encountered the exciting and mysterious problem of endocrine interrelationship. Of all the advances made in medical thought and knowledge, perhaps the

most arresting is the elucidation of the concept of "endocrine balance". Thousands of investigators the world over have worked tirelessly for years to tabulate the actions of these various glands, and answer the questions that each new discovery concerning them brought up. Much is known to be sure, but one cannot deny that their work has yielded as many questions as answers. One of the chief reasons for this is the definite limitations placed on them by the tools which they use. Much of their work must be done by biological observation and is subject to all the limitations placed on it by such inexact and uncontrolable means.

One of the most exact sciences on the other hand intimately related to medicine is chemistry; its tools are precisional and its results are governed by strict natural laws. It would be desirable, then to reduce all the variables concerned in endocrine balance to their simplest common denominators, so to speak, and to proceed with endocrinological investigation by means of chemistry. This however, is not possible in the dimness of our present knowledge. That the various hormones are chemical compounds, we are certain, but we can only speculate on many of their chemical properties, and are without adequate means of determining quantitatively their presence in organs and fluids.

We are aware of many truths concerning endocrine balance in a qualitative sense and have been able to adapt many of these to clinical usage. It is still to be desired, however, that we may, in the future, be able to express obscure clinical manifestations in terms of precise laboratory determinations. With this aim in mind, many workers have proceeded, but as yet, their results offer no final answer.

The most carefully studied and one of the best known endocrine

glands is the thyroid. Since the dawn of medical history enlargements of this gland, and later, symptoms associated with the enlargement have, in the minds of clinicians, been associated with iodine. As a result, a vast amount of work has been done on this ion and on compounds of which it is a part.

Elmer has presented the classic work on this subject. His "Iodine Metabolism and Thyroid Function" (20) has correlated most of the work done in the two fields and will serve as an excellent starting point for a student interested in the subject. It remained for Salter (67) to crystallize the problem and make a significant attempt to express endocrine balance in terms of something besides observations on biologic material. I am inestimably indebted to him, both as a source of material for this paper, which is largely an incomplete recapitulation of his ideas, and as a professional inspiration. It is unusual to find an accomplished clinician who, at the same time, has made himself a true scientist. He stresses the paradoxical truth that man or beast may suffer less from the loss of several glands than from losing a single one, and states that the practicing consultant and the laboratory investigator both, must henceforth think in terms of integrated hormonal effects, and must look to precise chemical mechanisms whereby parent organs react upon one another.

Recent advances in the chemistry of the sterols have served to emphasize the community in composition of the adrenal and the gonads. The results of this work has served to segregate reproduction and sex by assigning the first to the gonads which are dispensable, and the latter to the adrenal cortex which is necessary for life. In strictly chemical terms, nonetheless, there is evidence that these hormones overlap and are interchangeable to a certain degree.

Of more importance than this minor entente is the balance of power throughout the whole league of endocrines. A simple answer cannot be given to this problem and certainly no complete description, but part of the problem can be projected in terms of iodine. This approach according to Salter (68) is justified on several findings. First, the concentration of this element is phenomenally high in several glands, one of which can trap and store it. Second, in the athyreotic organism other glands lose their iodine as they cease to function and regain iodine as health is restored. Thirdly, at least one hypophyseal tropic activity is influenced by iodine. He concludes that for these and other reasons, iodine balance commonly reflects endocrine balance.

This work has always been complicated by a lack of suitable techniques and precise analytical methods as regards the low iodine concentration found in most biological systems. In late years, however, this situation has been much improved, though demanding a high degree of technical skill more reliable techniques are now available. They are still crude considering their objective but have, nevertheless, developed to a point of dividing the minute quantities of biological iodine into characteristic fractions, "organic" and "inorganic".

Since there is no appropriate place in the body of the paper to answer the three questions posed earlier, as such, I will discuss them briefly now. The first, is there any value in increasing iodine dosage when the so-called escape has occurred, needs but a brief consideration because the evidence is cited in detail later. Means (54) denies "refractoriness to iodine" and admits "escape" only as observed when iodide therapy is halted. Salter's concept (69) of "endocretion" would favor a true refractoriness. Many clinicians feel that whenever this phenomenon occurs, called by whatever name,

the indications are for cessation of iodide, bed rest and sedatives until the iodine stores of the satiated thyroid are again depleted and new response to iodide may be expected, and not for continued iodine administration.

The second question, that of the "jodbasedow" effect of iodothyrotoxicosis, is also not answered completely. The existence of this phenomenon is doubted by Means and Lerman (56) but many European clinicians are cautious in administration of iodide. Rabbits affected with cabbage goiter may be thrown into a thyrotoxic state by iodide administration according to Webster, Marine and Cipra (86). It is possible, perhaps, that a latent trend to hyperthyroidism may be made more evident by iodine therapy. The work of Thompson (76) and Marine (20) indicates that very low dosage of iodide (1.5 mg. per day) in thyrotoxicosis may increase the severity of the symptoms while a dosage 100 times as large produces prompt clinical improvement. In the light of such observations, the existence of such a danger regardless of its mechanism, should not be disregarded.

The final question, is there any indication for post-operative administration of iodide either when crisis exists or prophylactically has been answered to my satisfaction by the recent work (1939) of Davidson and Arie s (17). On the basis of a small, but well controlled series, they concluded that iodine has no effect on circulating hormone whether exogenous or endogenous, and that no chemical combination between iodine and thyroid hormone occurs in the blood stream. They carefully studied a large series of cases of Grave's disease in Cook County Hospital and could demonstrate no advantages from such treatment if the patients were properly prepared by preoperative iodine therapy. In another series in which fatal cases of "thyroid crisis" were considered, they decided that iodide administration resulted in

no improvement. According to their report, thyrotoxicity is directly proportional to (1) the inadequacy of preoperative preparation, (2) amount of gland left after surgery, and (3) the amount of hormone flushed into the blood stream by manipulation of the gland during surgery. They suggest that any improvement noted after intravenous iodide results not from the effects of the iodine but the dilution of the hormone so produced. Finally, they propose as routing practice in "crisis", the massive infusion of fluids, oral and parenteral, and sedation. Iodides are useful only when the residual tissue requires further protective iodinization or where the storm occurs before surgery in a patient who has not received iodine.

The problem of endocrine balance and the attempted projection of it into indine balance was not nearly as satisfactorily culminated. I was forced, first of all, to limit the endocrines considered, and gaps are present which should be filled in. The problem of the neural regulation of the hypophyseal hegemony was perforce ignored. Withal I am inclined to believe that I have dealt with fundamental considerations, however superficially. In the concluding paragraphs I have attempted to correlate the facts and conjectures mentioned earlier.

Iodine as a Physiological Constituent of the Organism

The iodine content of the whole human adult is very small; it varies, according to Sturm andBuchholz between 20 and 50 Mg (75). How small an amount can be appreciated when we realize that this is equivalent to less than 10 minims of liquor iodi compositus U.S.P. Of this minute total, the muscles contain one-half, the skin one-tenth, and the skeleton one-seventeenth.

The blood iodine of normal fasting individuals is probably less than 10 gamma per cent, and makes up one-tenth of the iodine in the human body. The thyroid gland in the human normally holds at least one-fifth of the total iodine, while the mass is only about one-five-hundredth that of the whole body. Thyroid iodine (40,000 gamma per cent) is, then a thousand times as concentrated as muscle iodine (30 gamma per cent). Lower values for all tissues may be encountered when the iodine intake is low, but the normal thyroid maintains its capacity for the preferential trapping of iodine even when the amount of ingested iodine is greatly reduced (20).

Concentrations of the next highest order are found in other glands of internal secretions, (11) including the anterior pituitary, ovaries, epiphysis, parathyroids and adrenal cortex (20). In general, the iodine concentration of these organs is some fourfold that of other body tissues which contain only 20 to 30 gamma per cent. This higher concentration in these organs largely disappears after thyroid-ectomy while the iodine in skeletal muscle and other tissues remains relatively the same (75). This fact raises thepossibility that the iodine in these glands is of thyroidal origin.

Iodine as a Physiological Constituent of the Thyroid

Rienhoff (66) describes micro-dissection methods by which fresh thyroid follicles may be teased apart, and the intrafollicular colloid, as a viscid, colorless, albuminous liquid withdrawn from them. This crude colloid is adulterated by varying amounts of nucleoprotein (8). Such intrafollicular nucleoprotein has, however, no known significant physiological function and is thought to originate from secreting, or disintegrating cells of the follicular wall.

The total iodine in the whole thyroid of apparently normal adult men may vary from 2 to 28 mg. of iodine (extremes 1.5 - 27.8) (20). In fresh tissue theiodine concentration varies from 1.1 to 166 mg. per cent. Marine (46) believes, however, that human tissue outside the limits of 0.1 to 0.55 per cent (dry weight) should not be considered normal and values below usually are associated with marked hyperplasia. It is, however, very difficult to assign normal values when it is known that iodine concentration varies with diet, season, age, and endocrine balance. Furthermore, if iodine intake is low, not only is the content of the thyroid low, but compensatory hyperplasia of the tissue further reduces the gross iodine concentration and exaggerates the deficiency. Of the iodine so stored about one-third normally is in "thyroxine-like" form although in some animals (Argentine sheep) the value may approach two-thirds (68). Stated differently than the major part of the iodine incorporated in normal human thyroid protein has reached the diiodotyrosine stage but has not yet been built up into the more complex thyroxine. When the gland is secreting hormone at full capacity, its total iodine reserve may be depleted to less than one-tenth of the normal average, in addition

its "thyroxine-like" reserve may nearly disappear, presumable because it is removed as fast as it is synthesized (68).

Iodine and Pathological Thyroid States

The total amount of iodine in the gland at any time is a balance between intake and output, and when changes in functional activity occur, the balance may be altered and quantitative changes take place in the stored colloid. These fluctuations may be translated into simple physiological mechanisms.

A decreased secretion of thyroid hormone and resulting hypothyroidism may occur because of a disturbance in the gland itself, or because of decreased stimulation from the pituitary gland in the form of thyrotropic hormone (54). When the latter case appertains the gland retains a normal amount of colloid but appears shrunken and the concentration increases about 50 per cent (29).

In untreated moderately severe thyroxicosis the iodine is usually low because the excessive secretion produces a depletion of the colloid falling to about one-third normal value. Mildly toxic nodular goiters may contain 6 to 7 times the normal amount (7). Even in these hyper-active states there is no appreciable inorganic iodine in the glands. Distribution of iodine between cells and colloid does not change but analyses of organic fraction shows that although both components, i.e. diiodotyrosine-like and thyroxine-like, the former falls to a greater degree than the latter (81). If it is considered that the hyperactive gland probably continues to manufacture hormone during hyperthyroidism and is more easily able to make diiodotyrosine than to complete the synthesis of thyroxine, as a result, more of the former is present (29).

Since Plummer reintroduced iodide therapy in Grave's disease (63) many ideas have been put forth as to the mechanism involved in production of favorable results. Probably the best so far proposed is that of Salter (69) postulating internal secretion into the follicles rather than secretion into the blood stream. If this is true the process may be considered as one of pure storage. A hyperplastic gland with iodine available will secrete into the follicles until the mechanical disadvantage becomes too great. When this occurs or when iodine is not available, the flow is again in the direction of the blood stream. At any rate, in effect iodine reverses the direction of flow of the hormone.

In support of this statement, Means and Lerman (56) showed that when iodide therapy is instituted, basal metabolism falls in an inverse logarethmic fashion. This curve parallels that produced by thyroidectomy at a high metabolic level, and also by cessation of thyroid substitution in myxedema (4). The circulating hormone concentration is decreased (79) and the total iodine in the thyroid is increased (42). After a short time these changes fail to maintain themselves and the gland exhibits the well-known "escape phenomenon". Means' (54) views on the subject are interesting. He says: "In modern writings upon the action of iodine in Graves' disease, one finds such terms as 'escape from iodine control' and 'refractoriness to iodine'. The former is clear enough and a good descriptive label for what happens when the administration of iodine is stopped in the thyro-toxic person who has previously been receiving it. Ordinarily, a rather adrupt intensification of thyrotoxic manifestations takes place. Iodine apparently exerts its action in Graves' disease by imposing a resistance of some sort to the delivery of thyroid hormone from gland to body. When the administration of iodine ceases, this

resistance is removed and thyrotoxicosis is increased. Refractoriness to iodine would imply that although administration of the substance is continued, its ability to alter thyroid physiology becomes lost. That is to say that the patient becomes worse in spite of continued administration of iodine. It is certainly true that patients occasionally become more thyrotoxic while receiving iodine. It has been my experience that even so, they still exhibit what has been described as escape when iodine is stopped.

Their thyratoxicosis is augmented at a still more rapid rate. Therefore, I feel that these is no refractoriness to iodine in an absolute sense, but I will concede that there may be in a relative sense."

The effect of iodine therapy in frank classical exophthalmic goiter is to convert the thyroid from an iodine-poor state into a state of iodine affluence, distended with colloid. The beneficial effect of iodine seems to depend on the glands being empty. Thompson et. al. (76,77) have found that the maximal therapeutic effect requires a minimal daily dose of from 6 mg. iodine in Boston to 12 mg. in Chicago. This is much more than necessary to preserve iodine balance but is much smaller than that prescribed by many clinicians.

The total iodine content of simple goiter tends to be normal but the concentration is decreased (20), the rather wide variations observed are attributed to scatter. Elmer further believes that two stages occur in the development of colloid goiter. Many patients fail to eliminate normally in the urine, injected iodide showing an increased capacity for trapping iodide. The second, later phase is marked by degeneration or atrophy of the follicular cells. Glands of this latter type are ineffective in treatment of human myxedema (40). Perhaps the simple goiter may be regarded as being in a virtual hyperthyroid state struggling to maintain normal metabolism on a deficient iodine intake.

Iodine in Fetus and Newborn

Maurer* analyzed the thyroids of human fetuses from the seventh to the tenth month. His findings are reported to have ranged from 37 to 1400 gamma per cent of fresh tissue. He believes some of the material represents active hormone which might supplement maternal supply because it has long been known that thyroidectomized pregnant bitches may remain healthy until after delivery. Hudson's (33) work makes it clear that the maternal supply of ingested iodide may pass through the placental circulation to the fetal thyroid. In a region poor in iodine, Marine and Lenhart (47) studied the thyroids of puppies at birth. Unless the mothers were supplied with extra iodide during gestation, the glands of the offspring contained almost no iodine. When artificial iodine sources, however, augmented the maternal intake in the latter weeks of pregnancy, the young had considerable amounts of thyroid iodine.

Newborn babies contain from 2.4 to 48 gamma per cent of thyroidal iodine in percentage varying from 2.3 to 1450 gamma per cent of fresh tissue (Maurer) other tissues contain only from 12 to 46 gamma per cent. In hogs Fenger (22) found in per cent (fat free), 0.11 to 0.32; in sheep 0.09 to 0.36. The ratio of thyroxine-like to total iodine is the same as in the adult. The thyroidal iodine increases in total amount from birth to puberty, from then until twenty years it increaes rapidly. At this time it reaches its maximum value. After the fiftieth year it begins to decline. (5)

Total Iodine in Thyroid of Man and Animals

Where the ingesta (including medication) contains much iodine, the thyroid traps large amounts often yielding a concentration

*Cited by Salter (68)

exceeding 1.1 per cent by dry weight. On the contrary, if iodine intake is low the amount of the thyroid is low and compensatory hyperplasia of the tissue further reduces the percentage content. In mountainous countries the iodine content of the food is low and even the air contains little iodine at high altitudes. Here low values for the thyroid may occur. In maritime countries like Japan where fish and seaweed are consumed, the fresh thyroid may contain very high concentrations, e.g. from 79 to 109 mg. per cent of fresh gland (20). McClendon (49) found that seaweek contains at least a thousand times as much iodine as any other form of food, one plant may yield 26 mg. iodine. It is interesting to note in this connection the use of burnt sponge by the ancients for the treatment of goiter.

There are numerous references to the effect of the seasons on thyroid iodine. In the Mississippi valley Kendall and Simonsen (36) found that the total iodine is highest in midsummer and lowest in February. They also found that parallel fluctuations occur in the thyroxine-like and diiodotyrosine fractions. The "thyroxine" fraction may practically disappear in February. Various explanations for this cyclic variation have been advanced, among them the higher iodine in the diet in spring and summer and the greater secretion of thyroid hormone in cold weather, connected with changes of endocrine balance in the winter. Since the rise of iodine in the thyroid, and, likewise, in the blood, puts in its appearance in March, before iodine rich foods are available, many investigators favor the latter explanation (20).

Seasonal or other changes in thyroid iodine and thyroid activity effect are reciprocally influenced by the activity of other endocrine glands. In the summer when the sex glands of birds are hypertrophic, the thyroid is atrophic and contains little colloid. In hibernating animals, e.g. the hedgehog, bat, marmot, seasonal changes are most marked. Their thyroids show regressive histological changes during

hibernation, and an active histological picture in the summer. Indeed, thyroidectomized rabbits do not show an increased gaseous metabolism in summer, whereas normal rabbits show both increased gaseous metabolism and increase in total thyroid iodine (especially the thyroxine fraction) (68).

Iodine Compounds in the Thyroid

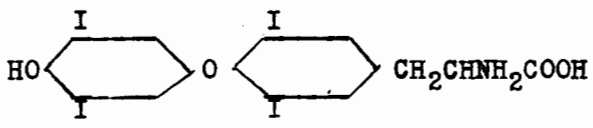
At the present time, tissue iodine is usually classified as (1) inorganic iodide, and (2) organically bound iodine, which may be (a) like thyroxine, insoluble in dilute aqueous acid, or (b) like diiodotyrosine, relatively soluble in dilute aqueous acid.

Inorganic Iodine in the Thyroid

In the thyroid itself, relatively little inorganic iodide is found, even after recent administration of iodide to the organism (29), when it may reach 10 per cent of total thyroidal iodine only to disappear rapidly when the medication has been assimilated. For this reason the organically bound iodine compounds are of much greater moment in this discussion.

Organic Iodine Compounds in the Thyroid

The chemical formula of thyroxine is $C_{15}H_{11}O_4NI_4$. It contains 65.4 per cent iodine, and 1.8 per cent nitrogen. The atoms are distributed thus:



Therefore, its precise chemical name is 1-b-(3,5-diiodo-4 3,5-diiodo-4' hydroxy phenoxy -phenyl) a amino-propionic acid. It is

isolated as a colorless, odorless microcrystalline powder which is very insoluble in water a physiological reactions. On rapid heating, it sinters at from 230° to 235°C. When precipitated from mildly acidic alcohol, it forms sheaves of rosettes of crystals. It forms mono- and di-sodium salts, likewise, mono- and di-potassium salts, silver salts and acetyl derivatives (2). The form made from natural thyroglobulin by the action of proteolytic enzymes is levorotatory (31,25). Thyroxine can be dissolved safely in cold dilute potassium or sodium hydroxide (up to 5N) and reprecipitated by acidification. The disodium salt is quite easily soluble in water. This fact is of importance from the standpoint of therapy (78).

Authorities differ somewhat in their estimates of apparent thyroxine in whole human thyroid, but, generally, the results are rather consistent, viz. from 0.2 to 5.9 mg. (39), from 3 to 5 mg. or from 0.9 to 7 mg (28). In dog thyroids Elmer (20) found 0.7 to 1.1 mg. of apparent thyroxine, in rabbits only 3 to 5 gamma. The corresponding figures for diiodotyrosine are 2.0 to 6.1 mg. iodine in human thyroids, 0.2 to 1.19 mg. in dog thyroids and 4 to 8 gamma in rabbit thyroids. These latter figures include inorganic iodide, which is presumed to be negligible.

Form of the Hormone in the Thyroid

Classical work on the active protein of the thyroid gland was done by Oswald and presented in a series of papers, the first of which was published in 1899. He found that practically all the iodine in the thyroid could be extracted with physiological salt solutions and that nearly all the iodine so extracted was chemically sound and, in fact, precipitable by heat coagulation. He treated such solutions with ammonium sulfate and found at half-saturation with this salt,

that the globulin so precipitated had carried down nearly all of the iodine. He purified this fraction further by dissolving it in dilute alkali and reprecipitating it with dilute acetic acid. This method has been used repeatedly with only minor modifications even up to the present time (29).

The general properties of the native protein first outlined by Hutchinson (34) have been confirmed and later described in detail by the more careful studies of recent years. This thyroglobulin exhibits the typical physiological effects of intact thyroid gland while the iodine free mother-liquor of the globulin is quite inactive. Thyroglobulins prepared from the thyroid of different species and from human thyroids in both normal and pathological conditions, have identical physical properties and resemble one another closely in elementary composition, apart from the iodine content which shows considerable variation (29). Eckstein has shown that, apart from its iodine content, thyroglobulin presents no conspicuous differences from other globulins of animal origin (19).

Because the physiological equivalent of the thyroid hormone can readily be produced outside the thyroid as demonstrated by their data (41), Lerman and Salter pose the following queries: (1) does thyronine (thyroxine minus all four iodine atoms) exist preformed in serum protein as an essential amino acid awaiting iodination; (2) does the process of iodinating the protein also change molecular configuration so as to produce physiological activity; (3) can the athyreotic organism synthesize iodothyronine molecules from other iodinated residues? Available data does not answer these queries.

Ordinarily, it is clear that the thyroid gland supplies the organism with the form of thyroid hormone which circulates in the blood. Much experimental work on this problem and not a great deal

has been positively shown, but there is considerable evidence which seems to point in this direction: that diiodotyrosine is the precursor of thyroxine and, later, is developed into thyroxine in the gland. Salter (68) believes that the gland contains 3,5 diiodothyronine in addition to the other two. Harrington and Randall (30) maintain, however, that with the errors in contemporary isolation methods, which are inefficient, thyroxine and diiodotyrosine could account for all of the organic iodide in the thyroid.

This premise holds good chemically, but when the thyroid hormone activity is studied pharmacologically, two puzzling facts arise. Kendall points out that certain samples of dessicated thyroid yield no crystalline thyroxine although they are physiologically highly potent (35). Secondly, dessiccated thyroid or fresh thyroglobulin may produce more caloregenic effects than warranted by the thyroxine they contain (31).

To explain these disturbing discrepancies, Kendall suggests that thyroxine is not the true hormone in the natural form and postulates a more potent precursor which breaks down during isolation processes or is converted into the less active thyroxine (35).

Two hormonal forms are spoken of by Kendall and Simonsen (36) --thyroxine as we know it, and "active thyroxine"--and they suppose that the latter is the physiologically active molecule, and may be a hydroxy-thyroxine. Thus in tissues, the former becomes the latter as the first step in its pharmacological metabolism. It is impossible, with our present knowledge to give a final answer to these speculations.

Production and Secretion of Thyroid Hormone

The iodine content of the thyroid has been discussed in previous pages, and now will be considered the manner in which this iodine has been incorporated into the gland, and various factors affecting its

fixation and subsequent release into the circulation as the thyroid hormone.

The thyroid gland can regulate iodine metabolism by fixing iodine and anchoring it to colloidal molecules, or by releasing such iodinated molecules or fragments thereof into circulation (64). The action of the gland depends largely on the properties of the blood which perfuses it. Foot, Baker and Carrel (24) have studied isolated human thyroids preserved in the Lindberg apparatus, and found that the final histological picture depended on the nature of the perfusate, not on the previous condition of the gland. With concentration up to 500 gamma per cent of iodide in the perfusing fluid, a demonstrable lower venous concentration resulted indicating removal of iodine from the perfusate. Above a concentration of 500 to 600 gamma per cent, a short period of iodide retention is followed within 20 minutes by iodine elimination, so that the iodine level in venous blood is higher than in arterial blood. Thus, the glands' iodine reserve is reduced and organically bound iodine is released. This latter situation seems highly abnormal, and probably has little direct physiological significance, but it does demonstrate that the storage mechanism is reversible. It is puzzling that organic preparations like "jodtropon" or thyroxine, when perfused through the isolated gland are not themselves stored, nor do they influence retention or release of thyroid stores. This finding suggests that iodine may enter the thyroid only in the inorganic form.

Influence of the Thyroid on Iodine Stores and Storage

In addition to its function of delivering hormone to the tissues at large, the thyroid serves as a reservoir for iodine, in which capacity it can regulate minor fluctuations in blood iodine. In myxedema, according to Perkin et. al. (61) the blood iodide remains

elevated longer than in the normal man after a single dose of iodine. Nevertheless, urinary iodide elimination is more rapid in myxedema (15). It would seems, then, that in the presence of the thyroid, the other tissues are able to fix iodine more effectively. This phenomenon will be considered further in discussing iodine in the ovaries.

When potassium iodide is administered, the response of the normal thyroid depends upon the route of administration, the state of the animal, the dosage used, the species and possibly even the external temperaure. When small doses are given, below 5 mg. or very large, continued doses, the gland may be suppressed. After cessation of iodine feeding at the peak of response, the thyroid returns to normal within a week (65). Where doses of 0.1 gm may produce 6,000 mitoses, only 200 mitoses appear after the administration of 0.01 gms. Prolonged feeding of iodide for one month, however, may suppress thyroid activity, rather than stimulate even when large doses of iodide are administered.

Many authors have assumed that a gland showing active mitoses was necessarily actively secreting hormone into the blood stream. Siebert and Linton (71) found however, that this is by no means true. Normal guinea pigs show no appreciable rise in basal metabolic rate after treatment with iodide and thyroidectomized guinea pigs show a slight fall in tissue metabolism. Salter and Lerman (69) have suggested that the active thyroid gland may secrete internally into its follicles (endocretion) depending on the polarity of the follicular cells and this would help to explain this phenomenon.

When diiodotyrosine is administered the normal thyroid showed only flattening of the endothelium and accumulation of colloid no stimulating effect is noted. Likewise the thyroid hormone depresses mitoses to one-fourth the normal number and "thyroidin" depressed

compensatory hyperplasia after hemithyroidectomy, probably resulting from diminution of tropic hormone output from the pituitary (71).

Van Dyke (82) has shown that the ability of the thyroid to take up iodine depends largely on the colloid content. The nearly empty follicle in thyrotoxicosis testify, therefore, to the avidity with which the gland removes iodide from the circulation. Elmer has shown, thenn, that iodide fails to accumulate in the blood and the iodine tolerance curve is low (20).

Under these conditions, in organic iodide accumulates in the gland and its transformation into iiodotyrosine begins under the influence of an enzyme system "iodose". This process was described by Baxter and Palmer (28) in the human gland and they noted progressive transformation of diiodotyrosine into thyroid-like material in a series of glands representing the first week of therapy. After that, a stable composition of the colloid was found, indicating that iodine accumulated no faster than the normal composition of thyroglobulin would permit, i.e. thyroxine-like iodine at one-third of the total iodine.

When large amounts of iodine are given, part of the inorganic iodide collected by the gland is turned back into the circulation and excreted. The rest is transformed gradually into thyroglobulin.

Two points in relation to the control of thyroid activity should be considered here. First, Gray (27) and Rabinowitch (65) found that thyroid or "thyroidine" inhibited the action of the thyrotropic hormone, probably per se and not due to its iodine content. This inhibitory action was greater than that of inorganic iodide. In this respect, the pituitary may be said to produce its own antagonist.

Secondly, the effect of iodide on the thyroid hormone is complicated. As stated previously, the thyroid responds to small doses

by retention, and to large doses by a sort of iodine catharsis. In vivo studies of pituitary tissues, thyrotropic activity indicates that iodide can directly affect the anterior pituitary. When doses above physiological amounts, but small from a pharmacological standpoint are given, the thyrotropic content of the pituitary is diminished. It is clear, however, that iodide does not prevent hyperthyroidism in man when thyroid hormone is administered from outside sources. Peripheral and organ action, therefore, must often be slight. (17).

It has been possible by administering thyroid hormone to athyriotic individuals to determine the daily secretion of the human thyroid gland, based on decay curves. These studies show that the gland secretes about one-third mg. of thyroxine or its equivalent in 24 hours. According to Elmer and based on iodine balance studies, the optimal daily amount is not less than 100 gamma iodine, nor more than 200 gamma iodine (20). Means reached the same conclusion after viewing his own data and that of others (52). After treating myxedema with purified thyroglobulin, Eppinger and Salter (21) confirmed his results.

The Pituitary Gland and Iodine Metabolism

The relation between the pituitary and thyroid glands has been demonstrated by many workers since Loeb and Bassett (44), more than a decade ago, described a thyro-activating principle in the pituitary gland. In the interim, the pituitary has occupied a dominant role in our interpretation of thyroid physiology.

A definite reciprocal relationship of the thyroid to the pituitary is no less true as illustrated by the morphological changes in the pituitary glands of animals that have goiter and in cretinoid states (58) and after thyroidectomy (70. The increased output of

urinary thyrotropic hormone after thyroidectomy is also suggestive (74).

Knowledge regarding the role played by iodine in this system is necessary for complete understanding of these interrelationships. Its undoubted integration with the physiology of the thyroid gland has been stressed by the early work of Marine and Williams (48). The part played by the pituitary must be established. The work of Loeser and Thompson (45), and the more recently expressed opinion of Marine (46), give the hypophysis a major role in the sphere of iodine metabolism as it relates to the thyroid. Before proceeding in this vein, however, it is necessary to discuss iodine metabolism as it pertains to the pituitary gland per se.

Iodine in the Pituitary Gland

The iodine content of the posterior pituitary is very small, 40 gamma per cent of the desiccated gland substance, in contrast to the content of the anterior lobe which was found to be 180-190 gamma per cent of fresh substance in the same laboratory (12). Also, following removal of the posterior pituitary, neither histological indications of hyperfunction, nor a characteristic curve of iodemia can be observed, whereas they appear after the removal of the anterior lobe. Similarly, after thyroidectomy characteristic histological changes can be found only in the anterior and middle lobes, not in the posterior lobe. Elmer further observed increased size of the pituitary in dogs and rabbits after thyroidectomy, and later noted a similar phenomenon in cretenism, myxedema and cachexia thyreopriva. On the other hand, it was found that destruction of the pituitary in tadpoles prolongs the larval state and results in a decreased deposition of colloid in the thyroid, while transplantation of adult frog pituitary is enough to evoke thyroid development and metamorphosis in tadpoles (20).

A more definite relationship was not suggested until 1922-1927, when P. E. Smith and I. P. Smith (73) reported that the extremely atrophic thyroid of hypophysectomized tadpoles could be restored to normal conditions by intraperitoneal extracts of bovine anterior pituitary. L. Loeb and Bassett (43) in 1929 produced hyperplasia of the thyroid in guinea pigs by means of anterior pituitary extracts, and these results have been repeatedly confirmed (83).

As further evidence of the relationship we may note: the existence of a pronounced iodine concentration in the anterior lobes; the influence of the thyrotropic hormone on the histological aspect of the thyroid, its clinical picture and the iodine level in the thyroid and blood; and, also, the influence of hypophysectomy on the iodine concentration in the tuber cinereum of the diencephalon; its remarkable ability to store thyroxine and finally, the action of iodine on the thyroid through the anterior pituitary lobe (83).

Pituitary Iodine

Estimates of the iodine concentration in the anterior pituitary vary somewhat, but are consistently high, as compared to other body tissues. Wells, in 1897 (88), found 0.05 mg. of iodine in 1.2 grams of dessicated human pituitary gland, or 420 gamma per cent. Kendall, (35) in 1931, reported 370 gamma per cent in desiccated pituitary gland, Class (12), also in 1931, found 80 to 190 gamma per cent, 400 gamma per cent in the desiccated gland.

Effect of Hypophysectomy on Behavior of Iodine Metabolism

In dogs, the weight of the thyroid generally decreases greatly after hypophysectomy. The absolute amount of iodine remains the same, but the concentration increases. This corresponds to the observed atrophy of the epithelium and of the parenchyma, and to the

retention of the iodine-rich colloid. For two weeks after hypophysectomy, the blood iodine rises slowly to about double its previous value, and, in the next two months, drops to slightly below normal, a level which it maintains. Simultaneously, there is noticed a fall in the basal metabolic rate of 80 per cent of normal where it remains, just short of clinical myxedema. The final hypoiodemia is quite clearly due to depressed thyroid secretion. During the stage of hyperiodemia, there is an increase in the urinary elimination of iodine up to three times the normal daily amount. Later, the iodine elimination becomes normal, but still subject to wide fluctuations, due to ingested iodine compounds (83).

Influence of Anterior Pituitary Tissue and Extract Administration

When thyrotropic hormone is administered, changes in reverse to those described above occur. Enlargement of the follicular cells takes place, and when the dosage is increased and maintained, this hypertrophy gives way to hyperplasia of the follicular cells. As these changes advance, the colloid becomes depleted and the picture resembles that seen in thyrotoxicosis. Despite the decrease in the colloid of the gland, the weight continues to increase due to the increased vascularity and the hyperplastic parenchyma (83).

Concomittant with these striking morphologic changes, chemical changes occur which indicate profound changes in the metabolism of the glandular tissue. The water and chloride content of the cells is increased, the colloid space reduced 50 per cent, and the oxygen consumption per gram of tissue is more than doubled, all this within 24 hours after institution of treatment (46). After six days of such treatment these values tend to approach normal.

The basal metabolic rate participates in these fluctuations, and

may rise to double its normal value. With this, the experimental animals show other symptoms of hyperthyroidism, cardiac arrhythmias, increased irritability, increased appetite, marked loss of weight; some species even show exophthalmos (26).

As in thyrotoxicosis, the gland's iodine stores, during these changes, are depleted, and the blood iodine rises (13). Despite the fact that continued small doses may depress thyroid function (14), it is clear that persistant hyperthyroid states may be produced with tropic hormone in adequate dosage.

Using radio active iodine as an indicator, Hertz and Roberts (32) compared the following criteria of thyroid function in rabbits injected with thyrotropic hormone: thyroid iodine content, acinar cell height, relative thyroid size and basal rate. Their results indicate that on approximately parallel variation of cell height, Basal Metabolic Rate and thyroid size occurs. Thyroid iodine collection varies with the other criteria, but not in a parallel fashion. The Basal Metabolic Rate, cell height and thyroid size show an initial rise to a maximum, with a subsequent decline which is accelerated by the administration of iodine, all except thyroid size reaching final values below normal. Therefore, they believe the result of thyrotropic hormone stimulation followed by: (a) involution, if iodine is administered, or, (b) functional depression after prolonged thyrotropic hormone administration. These data are in accord with the previously mentioned concept of varying ability of the thyroid to collect iodine at various functional levels, with higher thresholds corresponding to greater degrees of stimulation and decreasing thresholds during conditions of involution and functional depression.

When viewed from the standpoint of iodine metabolism, it has been shown that these histological changes are accompanied by marked and

consistent changes in iodine distribution. With the diminution in colloid, there is a loss of thyroid iodine amounting to 90 per cent of the total (13). The blood iodine may increase to three times normal. This rise is principally accounted for by organically bound iodine. There is an increase in urinary iodine elimination, the organism being in profound negative iodine balance.

The Effect of Iodine Containing Compounds on Animals Treated with Pituitary Thyrotropic Hormone

It is not surprising, in the face of the classic effects of iodine administration in patients suffering from thyrotoxicosis, that the effect of iodine on artifically induced thyroid hyperfunction has been carefully studied. As previously stated, the thyroid may be stimulated by administration of iodides, as well as by the thyrotropic hormone. If these are given simultaneously, however, Silberberg (72) has shown that the effects vary with the time of administration and the dosage used. These relationships cannot be expressed simply and with assurance because iodine affects both glands and as will be mentioned later, the tissues at large as well. Depending on dosage of both iodine may either inhibit or enhance the effect of the trophic hormone. The synergy is best demonstrated when large doses of hormone are given with small doses of iodide (72).

The Effect of Iodine on the Anterior Pituitary

That iodine depresses the tropic effect has been shown by several investigators, Elmer (20), Friedgood (26). How this is accomplished has not been explained, but iodine is thought to have three effects: (1) on the anterior pituitary and its hormone, (2) on the thyroid

gland, and (3) on peripheral "end-organs". Salter and Lerman (69) have considered the effect on the thyroid and believe it is a mass action of increased iodine concentration, which favors thyroid protein storage.

In discussion the beneficial effects of iodine in toxic goiter Cason (18) states "there is no proof that iodine acts as a direct sedative on thyroid cells . . . the evidence of primary diminution of secretory activity is lacking". Means (53), however, believes the action is directly on the thyroid cells. The results of Vanderloan and Logan (84) show that administration of iodine with thyrotropic hormone abolishes the increased metabolism of the thyroid gland, although the gland hypertrophies to about the same extent as it does in the absence of iodine. They interpret these results to lend support to Means contention stated above.

Earlier, the opinion of Marine (46) was mentioned, in which he expressed the belief that the pituitary was the final common path of factors affecting the activity of the thyroid gland. For several years, this idea has had many adherents and has never been seriously challenged. Stated again with reference to iodine, it postulates that the pituitary is influenced by the level of iodine in the body fluids and that through the pituitary, the thyroid and its integral activity in iodine metabolism are adjusted secondarily. If this holds true, then the basis for dysfunction of the thyroid and the metabolism of iodine must be looked for in the pituitary gland. Since an understanding of thyroid disease depends on a clear delineation of these relationships, an answer to the problem should be sought.

Chapman (10) presented observations on the thyroid glands of a series of hypophysectomized and intact animals maintained on high and low iodine diets. He found that the thyroid glands of intact animals

responded to the stimulus of low intake in iodine with an increase of weight, increase in height of acinar epithelium and an increased vascularity. Astonishing as it may seem, he found that the thyroids of hypophysectomized animals responded to low iodine stimulus in a similar manner to that of the intact animals. Responded indeed, with an increase in weight, increase in acinar cell height and an increase in vascularity which was proportional to that observed in intact animals. The conclusions drawn from this work, if it is satisfactorily confirmed, are inescapable--the thyroid is able to respond to the stimulus of low iodine in the absence of the pituitary. It is too early to predict what effect these findings will have on our previously held conceptions.

Effect of Thyroxin on Gonodotropic Hormone

The response in ovarian weight to injections of menopausal urine was studied by Tyndale and Levin (80) in three groups of animals: (1) normal rats; (2) hypophysectomized rats; and, (3) in hypophysectomized immature rats treated with thyroxine. Such treatment in normal rats results in marked stimulation of ovarian follicles due to the high gonadtropic titer in the urine. It is remarkable that simultaneous injection of thyroxine markedly decreases this characteristic response indicating a peripheral response.

In spite of these findings, there does seem to exist a constant regulatory relationship between these two glands. When one attempts to evaluate the conflicting evidence, the chief problem is the number of variables in the relationship. The pituitary-thyroid-iodine equation is, at best, three-dimensional, and many other factors must be considered.

The Ovaries and Iodine Metabolism

One need not go far to find considerable practical evidence that the ovaries and the thyroid are closely related, for commonly the thyroid enlarges during puberty, and shows periodic changes during the menstrual cycle. In addition to this, the thyroid enlarges during pregnancy and lactation and at the time of the menopause.

For almost 200 years, it had been known that the onset of puberty and pregnancy might precipitate the development of goiter where there is a high incidence of endemic goiter. This is not true in regions where the iodine supply is extremely low and goiter is practically pandemic. Where there is more iodine, but still a high incidence of endemic goiter, the sex effect is very marked. In a comparison of goiter on the Eastern seaboard, (Connecticut and Massachusetts) with Cincinatti and with Minnesota, Oleson and Taylor have made this point quite clear (59). There is a minimum of endemic goiter in the seaboard states, while Cincinatti has twice as much and Minnesota three times as much. McClendon's very complete reports (59) show that goiter incidence in these states corresponds to the iodine contents of the regions. The incidence of goiter in girls in these states is definitely higher than in boys. Careful examination of the group "moderate to marked enlargement" will show that at the peak there are no boys in Connecticut with goiter and only one per cent of girls, indicating an adequate iodine supply. Girls in Cincinatti begin to demonstrate effects of diminished iodine and 20 per cent show goiters, while only 4 per cent of boys are so marked, or 5 to 1. In Minnesota, where iodine lack is more acute, 36 per cent of girls and only 6 per cent of boys are noted, a ratio of six to one. It is also noted that girls show a higher incidence of goiter at a low degree of iodine lack than do boys at a much higher degree

of iodine lack, and girls also tend to have larger glands than boys on the same degree of iodine lack. When it is noted that the Basal Metabolic Rate in women tends to be lower than in men, this fact is remarkable. In girls, the onset of goiter is more closely related to puberty than in boys. Marine's extensive work (46) early emphasized the fact that iodine is the most important factor in the etiology of endemic goiter, and Kimball goes so far as to say that it is purely a deficiency disease, and therefore, readily preventable (37).

It is possible to continue this correlation in the consideration of exophthalmic goiter where statistics show an overwhelming preponderance of the female sex. Bram's (5) work gives the incidence of thyrotoxicosis as one boy to 20 girls in childhood, one man to five women in young adult life and one man to two women in old age. The decline in the ration as sex becomes less important is very interesting. Marine early noted (45b) that his characteristic cycle, he explains nodular goiter by discussing hypertrophy, hyperplasia and involution, is often precipitated by pregnancy.

Iodine in the Ovaries

As mentioned earlier, the ovaries show a very high iodine concentration as compared to other tissues; indeed, the highest of all tissues with the exception of the thyroid. Values reaching over 741 gamma per cent were reported by Maurer* but Sturm and Bucholz (75) found values for human ovaries from 30 to 100 gamma per cent. These figures and those variously reported by other investigators for other species, have been reviewed by Carter (6) and he calls attention to the fact that, in addition to the effect of ingested iodine, that the ovarian cycle is a potent factor influencing ovarian iodine. This will be referred to again at a later time.

*Cited by Elmer (20)

Carter also showed in regard to the quantitative nature of the iodine in the ovaries that there was no significant amount of thyroxine-like iodine in their organic fraction, but with an extract of the organs, he was able to produce metomorphosis in tadpoles. It is possible, therefore, that even if thyroxine is not present in the tissue combined as such a thyroxin derivative may be present. Consequently, Salter (68) believes that since the iodine content of the ovaries falls after thyroidectomy, the ovary may contain a specific form of iodine which is related to the thyroid, and which it extracts from the circulation.

Effects of Oopherectomy on Iodine Metabolism

Removal of the ovaries is followed by a relative increase in thyroid iodine (38). Within a little over a month, the thyroid iodine is increased by about one-fifth. Much of this increase is only apparent and is due to a functional atrophy rather than to a decrease in the total amount of iodine. This phase is probably the end result of thyroid readjustment, because Loeser and Thompson (45) have shown that immediately after oopherectomy, there is histological evidence of thyroid hyperfunction. This phenomenon is, however, only transitory. Many authors believe castration causes not only an increase in the secretion of gonadotropic hormone, but all other tropic hormones as well--the so-called "shot gun" effect. There is also an immediate rise in blood iodine and an increased basal metabolic rate. Beginning in the second week, the hyperiodemia decreased to the normal level in a month's time, and the metabolism also fell. No such effect was noticed in old bitches which were presumed to be postmenopausal. This effect was shown by Van Dyke (82) to be through the anterior pituitary, which produces increased amounts of tropic hormone.

According to Laqueur and Emge (38), however, withdrawl of ovarian hormones by castration in rats with hyperplastic-thyroids does not affect the degree of hyperplasia, nor is thyroid hyperplasia in castrates affected by parenteral substitution of estrogens.

Effect of Ovarian Hormones on Iodine Metabolism

It is generally accepted that removal of the goands is accompanied by definite castration changes in thyroid morphology characterized by a lowering of the epithelium of the follicles and an increase in colloid. According to Gumbrecht and Loeser* subcutaneous substitution with estradiol benzoate in castrated animals has no effect on castration changes, while Anderson (1) found that Ketohydroxyestrin restores the castration changes to normal and increases thyroid activity. The former also found, however, that when either estradiol benzoate or ketohydroxyestrin was administered by intra-uterine application, castration changes in the thyroid were prevented, provided substitution was made at the time of application. When castration changes were permitted to become well established before treatment was instituted, intra-uterine substitution effectively restored the normal morphology of the thyroid. It therefore seems that the route used in substitution influences the effect of a given estrogen on the thyroid.

When the estrogen level of a sexually intact animal was increased above the normal for brief periods not exceeding 5 or 6 days, a transitory increase in thyroid activity was noted. When, however, estrogen was administred for long periods, the thyroid showed definite evidence of atrophy. This seems to indicate that the length of a period of treatment also is an important factor in the ultimate effect on the thyroid (62).

*Cited by Salter (68)

Relatively little is known of the relation of the corpus luteum to the thyroid, and existing results are very contradictory and probably mean that the effects of progesterone on the thyroid like that of estrogen are subjected to modifications which require further classification. It has been shown, however, that thyroid hyperplasia in castrated female rats is decreased by parental administration of progesterone with or without estrogen.

The preceeding discussion deals with animals with normal thyroids. When a state hyperthyroidism is simulated by the administration of "thyroid hormone" in castrates, it was demonstrated that the action of parenteral estrogens is inhibited (87). A few years later (1933) Van Horn (85) reported that it required three times as much theelin to eliminate vaginal castration changes in mature female rats in a state of hyperthyroidism produces by desiccated thyroid than it did in castrates with relatively normal thyroids. He concluded that the increased rate of metabolism incident to the feeding of thyroid substance increased the speed of estrogen elimination. Weichert and Boyd (87) found that diestrous was prolonged when rats were fed desiccated thyroid for from 42 to 53 days. This they found to be accompanied by the formation of unusually large corpora lutea such as are seen in pregnancy and were able to demonstrate normal functional activity in these bodies by the production of "placentomata". The explanations given were that either the excessive supply of thyroid hormone stimulated the anterior pituitary to the production of unusual amounts of buteinizing hormone, or that the increased metabolism decreased the estrin level, permitting the persistence and overdevelopment of corpora lutea. In line with this latter explanation, Meyer and Wertz (57) stated that the demand for estrin increased with the increased thyroid hormone supply. All of this last

evidence cited points to the importance of the degree of thyroid function in estrogen utilization. That the thyroid hormone can alter the action of pituitary gonadotropius was demonstrated by Fluhmann in 1934 (73). He found that hyperthyroidism artifically induced by thyroxin or desiccated thyroid, inhibited the action of follicle stimulating hormone while hypothyroidism resulting from thyroidectomy increased the effect of parenterally administered pituitary gonadotropins on ovaries and uterus.

It is well known that the cessation of anterior pituitary function is followed by adrupt ovarian changes. Morphologically, this is characterized by three distinct phases: (1) failure of primordial follicles to mature, (2) persistence of corpora lutea, and (3) typical and constant changes in the appearance of the cells of the interstitial apparatus. Only replacement therapy by means of gonadotropic substances can arrest or reverse these changes (1). It may be taken for granted, therefore, that the presence of morphologic changes in the ovaries similar to those found after hypophysectomy are indicative of pituitary deficiany.

Emge and Laqueur (38) recently found such changes in the ovaries of non-hypophysectomized rats afflicted with thyroid hyperplasia and treated parenterally with estrogen. Thyroid hyperplasia in sexually intact female rats was not affected by moderate amounts of an estrogen, but is followed by an exhaustion atrophy when large doses are administered. From this, they deduced that thyroid hyperplasia disturbed the normal pituitary-thyroid-ovarian relationships.

To obtain further information they studied the effect of thyroid hyperplasia on the ovaries with and without additional estrogen supply. They concluded from this work that moderate thyroid hyperplasia induced by goiteragenic diet regardless of duration or the age of the host,

does not produce a deficiency reaction in the ovaries and they deduced that in rats the anterior pituitary apparatus is not ordinarily disturbed by moderate thyroid hyperactivity. Age they found to be an important factor in relation to estrogen administration in the presence of altered thyroid behavior, possibly because an estrogen overload depressing the gonadotropic apparatus occurs more rapidly in the presence of hyperthyroidism. This latter explanation fits with Fluhmann's observations (23) which revealed that the action of pituitary gonadotropins can be depressed when thyroid activity is increased by administration of thyroxine, also with the previously cited work of Tyndale and Levine (80).

Iodine Metabolism at Different Periods of Ovarian Activity

Elmer (20) relates that the thyroids of white rats show a decrease in iodine content during estrus and an increase during intervallum. This is also manifest by the histological picture of the thyroid at this time which shows colloid softening and enlargement of the blood vessels. These effects would appear to be evidence of increased secretion of thyroid hormone into the circulation. In agreement with this, the basal metabolic rate is increased by about 10 per cent at this time. During menstruation, the iodine level of the circulating blood is increased and Gley* early reported that the iodine content of menstrual blood was markedly increased. The urinary iodine excretion during menstruation is also found to be increased, although the cyclic variations in the urinary elimination do not run exactly parallel with those found in blood iodine (16).

Bokelman and Scheringer found that most cases of pregnancy begin to show a detectable rise in blood iodine by the third month, which increases to the seventh month. This level is maintained until shortly after delivery. There may be considerable variation, but often

*Cited by Elmer (20)

the blood level increases two or three times normal, late in pregnancy. After delivery, this hyperiodemia diminishes rapidly. Cole and Curtis (16) report increased urinary iodine elimination during pregnancy.

Much discussion has centered around the question of the activity level of the thyroid glands during pregnancy. The data cited above would favor a hyperfunctional state, if hyperiodemia, is an accurate indicator of thyroxinemia. If the thyroid hormone content of the blood could be measured accurately, this would have been solved long ago, but this is not the case. Clinical symptoms which favor thyroid hyperfunction are common; there is thyroid hyperplasia in 70 to 80 per cent of pregnancies, and the aggravation of a previously existing thyrotoxicosis is usually noted with pregnancy. The hyperplasia, notwithstanding, need not be connected necessarily with hyperfunction, for it may also be induced by iodine deficiency. This seems to be supported by the observation that iodine feeding to animals during pregnancy prevents these histopathological changes in the thyroid.

The histological picture of the thyroid indicates morphological changes of an inconstant character and intensity. Besides these clinical symptoms and the histology of the thyroid, attempts have been made to show thyroid hyperfunction during pregnancy on the basis of other phenomena which might indicate an augmented thyroxine level. In particular, investigations have been conducted based on gaseous metabolism, on the glycogen content in the liver, on determination of the level of acetone bodies and lactic acid in the blood, and on Reid Hunt and Gudernatsch tests. The evidence yet produced on such bases is so conflicting that a positive statement cannot be made at the present time.

Even if we admit that thyroid hyperfunction and hyperthyroxinemia during pregnancy from these results is an indisputable fact, its meaning in the organism and the presence of such remarkable variations as are noted require further elucidation. This increase in the blood iodine level can be partly explained if it is remembered that the fetus requires iodine; both as an ion and as hormonal iodine. In correlation with the degree of the requirement the thyroid of the mother supplies by hyperproduction of its hormone the needs of the fetus for iodine. When the fetal thyroid functions insufficiently, the thyroid of the mother must secrete more actively in order to satisfy the fetal requirement, and thus, there appears in the maternal organism a higher blood iodine level and the other symptoms which result from thyroid hyperfunction are less pronounced (47).

With the onset of menopause, there is in the blood, a tendency to an increased iodine concentration. This slight increase early, however, tends to subside after several months. Cucco* continues that, whereas the level for women between 20 and 35 years of age was less than 10 gamma per cent, 36 out of 44 cases at the climacteric had values ranging from 10 to 22 gamma per cent. He found furthermore, that after the injection of ovarian extracts for two or three weeks, the blood iodine might drop from about 20 gamma per cent to about 15 gamma per cent, his normal value. By contrast, cases which showed no blood iodine increase did not show any effect from ovarian extract administration.

This increase in blood iodine may well be the result of increased thyroid activity produced through the anterior pituitary which secretes an excess of tropic hormone at this time.

Bischoff and Clarke (3) found that 41 days after thyroidectomy

*Cited by Salter (68)

the rat ovary is responsive to exogenous pituitary gonadatropic stimulation. The hormone dose, ineffective in normal rats, produced marked ovarian weight increase in thyroidectomized rats and they conclude when thyroidectomy exerts an influence to increase gonadatropic effect, the effect may be explained by a decrease in the rate of exchange of body fluids and a resultant decrease in the rate of hormone resorption. Williams et. al (89) in discussing hypothyroidism and ovarian function, state that the degree of true primary hypothyroidism necessary to produce significant changes in ovarian function is in their opinion, severe.

The importance of the ovary in iodine metabolism becomes even more clear when the recent work of Perkin and Brown is considered (60). They studied the blood iodine levels in male and female dogs. These animals were saturated with iodine and their blood analyzed at frequent intervals during several months. It was found that total removal of the thyroid in females had practically no effect on blood iodine. Before it was nearly 2.0 mg. per cent and afterward at least 1.5 mg. per cent. When, however, the male dogs were thyroidectomized blood iodine was markedly depressed i.e. from 1.5 mg. per cent to 0.5 mg. per cent. When, thyrodectomized bitches were subsequently castrated, the blood level fell almost immediately to as low as .25 mg. per cent. Perkin and Brown concluded, and their conclusion is almost inescapable, that the ovary is able in large part to compensate for lack of thyroid.

SUMMARY

In the introduction I stated that the neural mechanisms affecting iodine and thyroid function were to be ignored. I chose or was forced to do this because of the tremendous additional amount of material it would necessitate covering, and I questioned the wisdom of attempting so ambitious a task. Such a discussion would be less complete, however, without mention of some of the known facts concerning certain phases of the subject, and some conjectures regarding others.

The following short section was abstracted from Salter (68), who has presented an excellent resume of the subject. I offer it as nothing of my own invention, but only borrow it to round out this summary.

The reason for the confusion which exists concerning the problem is fundamental, namely, that it has not yet been clearly elucidated exactly what relation the nervous system and the thyroid hormone have on each other. The problem is at least twofold, because it involves first, the influence of the thyroid hormone upon the action of nervous tissue, and secondly, the action of nervous impulses of one type or another di- on the action of the thyroid, and directly, upon the pituitary axis.

The thyroid hormone does increase the activity of the nervous system and it speeds up reflex responses and irritability throughout the nervous system as a whole, probably by enhancing metabolic enzyme systems. This may not concern iodine per se, and be only a reflection of increased thyroid hormone. Iodine in high concentrations does depress nervous irritability much as bromides do, but to a far lesser degree.

The effects of the nervous system on the thyroid may be directly on the gland by means of neurone connections, or indirectly by increasing or decreasing the activity of the pituitary in the production of the thyrotropic hormone. There is considerable evidence to indicate that increased sympathetic stimulation may cause an increase in thyroid hormone production and also that thyrotropic hormone production may reflect cortical activity. Salter says, "in short complex neurological activity in the cerebral cortex may influence the hypothalamic region and thus set off discharges simultaneously, (a) through the sympathetic nervous system directly to the viscera, and also, (b) through the anterior pituitary, which translates them into tropic hormones which in turn, influence the

the activity of the endocrine glands, thus moderating their control of the tissues at large."

As concerns iodine this complex situation may be divided into two parts. When thyroid activity is enhanced there is a tendancy to metabolize more iodine. This is due to increased production of the thyroid hormone. As the concentration of the thyroid hormone rises the production of thyrotropic hormone is diminished. This latter mechanism is probably translated by the nervous system. Secondly, nervous impulses at the periphery may alter iodine metabolism in the tissues. Blood iodine rises after injection of atropine, while choline produces a transitory drop. Continued digitalis administration may produce hyperiodemia, and adrenalin causes a transitory rise, but finally a subnormal concentration. Transection of the cord causes a drop in blood iodine.

Probably the most that can be said of these considerations is that they add to completeness, but very little to our understanding.

It seems quite clear, after reviewing the material cited previously, that the thyrotropic hormone is the chief agent controlling thyroid activity, but numerous other factors have been shown to enter in. The relations are confused by such factors as the influence of

time, and attendant fluctuations in concentration and excretion. Until these are adequately controlled or measured we can only hypothecate as to other fundamental relations.

Remembering that a high concentration of thyrotropic hormone, as evidenced by an increase in acidophilic granules in the pituitary, and bio-assay determinations, may indicate increased storage and cessation of secretion rather than an increased outflow, and with an eye to the more clearly understood pituitary-ovarian axis, we are perhaps justified in piecing out the following hypothesis.

A decreased concentration of thyroid hormone is a stimulus to increased production of thyrotropic hormone, presumably through nerve centers in the diencephalon. When the concentration of thyroid hormone reaches a certain critical level the pituitary secretion is diminished. Iodine in moderate concentrations, likewise depresses production of thyrotropic hormone when administration is of long duration.

Estrogenic hormones administered over a long period of time will produce suppression of activity of the pituitary, probably due to a non-specific action.

Thyrotropism may be enhanced by several mechanisms.

Thyroxine or thyroid hormone in small doses will produce increased thyroid activity via the pituitary. Iodine lack causes the pituitary to respond by demanding still more hormone from an already over worked gland. This finally results in the familiar histopathological picture seen in colliod goiter.

The cyclic administration of estrin also has a stimulating effect on the pituitary. This should be noted because long term administration causes depression. If this non-specific effect on the thyroid is an index of the action of estrin on the pituitary-ovarian axis, it should always be acministered cyclically to produce a maximum effect.

The response of the pituitary to environmental and chronic emergency states is worthy of mention. Many such conditions seem clearly to cause an increased pituitary activity in the form of the thyrotropic hormone. Among these are: (1) chronic infection, (2) continued cold, (3) thyroidectomy, (4) lack of iodine, (5) chronic poisoning with cyanide derivatives, (6) pregnancy and lactation, (7) growth, (8) indiscriminate administration of endocrine products, (9) continuous goiterogenic diet, and (10) cretain clinical syndromes.

It would seem then, that the pituitary can affect

the thyroid by two routes, (1) directly, by means of the thyrotropic hormone, and (2) indirectly, through the action of other endocrines under its control. There is a third possibility, that of nervous connections through the sympathetic system.

The explanation of the thyro-ovarian relationship is even more nebulous in its present state. It is probable that two types of interaction occur, (1) sensitization of tissues to thyroid hormone by ovarian hormone, plus (2) an indirect effect mediated through other endocrines, including the pituitary.

The first action may well depend on the acceleration of the metabolism of other glands, as indicated by the previously cited work of Chapman (9), and Tyndale and Levin (80). Bischoff and Clarke attribute it to changes in the rate of exchange of body fluids which tends to increase or decrease the rate of hormone resorption and utilization (3). The second mechanism has been considered as regards the pituitary, but the actions of other endocrines, though admittedly important, were omitted.

It seems almost hopeless to attempt to evaluate the role which iodine plays in this vast humoral entente, and no simple explanation has been particularly satisfy-

ing. The high concentration of iodine in endocrine tissue testifies to its importance to the organism, and this is further emphasized by the fact that thyroidectomy causes these glands to lose all of their extra iodine. They regain this iodine as health is restored. Chapman (10) has presented evidence which he believes shows that iodine may play a role in body metabolism in the absence of the thyroid and postulates the production of a thyroxine-like substance in the tissues. The studies of Starr et al (74), and Laqueur and Emge (38) point to the fact that the thyroid can respond to iodine in the absence of the pituitary.

When determinations of iodine levels are made on blood and urine the variations so demonstrated will consistently reflect the balance between iodine intake and its metabolism. Indeed, Riggs et al (66a) state definitely that hyperthyroid patients all show an increased blood iodine, while those with myxedema present a consistent low level.

CONCLUSIONS

The indispensability of the element, iodine, to the organism, has been proven. The effects produced by deprivation of the organism of iodine have been demonstrated. The relation of iodine to the thyroid-pituitary-ovarian axis has been considered in the light of present knowledge. Finally, variations in blood iodine have been shown to be the results of either variations in amount of ingested iodine, or altered endocrine physiology.

I believe that the following statements regarding iodine may be justified by the material presented. The fluctuations observed in iodine balance are, to a large extent, a reflection of the state of functional activity of the thyroid gland. On the other hand, changes in iodine concentration and excretion are profoundly influenced by variations in the amount of ingested iodine. Obviously both of these factors may be in operation at the same time, and each may participate more or less, in the production of a particular state of iodine balance. For these and other reasons, iodine in the organism may be considered as the source, or the reflection, totally, or in part, of a great many interrelated and reciprocal interpolated factors.

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