CONCERNING THE PATHOGENESIS OF THYROTOXICOSIS. PART I.

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INTRODUCTION AND CONCLUSIONS

The "hyperthyroidism theory" of Graves' disease, which dates from 1884, is commonly accepted at the present time. It explains thyrotoxicosis as the antithesis of myxedema and is supported by several striking arguments. However, complete belief in this pathogenic theory has been precluded by certain conflicting data such as the frequent existence of hypo- and hyperthyroid symptoms in the same individual. During the thirty-five years since the conception of this theory, the development of our knowledge of thyroid pathology, physiology and metabolism has, especially during the past decennium, rapidly advanced, bringing to light additional facts which demand a renewed consideration of the pathogenesis of thyrotoxicosis.*

In the present article, after a brief survey of the older theories of Graves' disease, a critique of the hyperthyroidism theory is given from various viewpoints.

The facts and arguments in favor of the dysfunctional or dysthyroidism theory of thyrotoxicosis are then presented in detail. It is believed that the phenomena of Graves' disease can be most adequately accounted for on the basis of abnormal metabolic processes in the thyroid gland producing toxic effects upon the various tissues and organs, together with the systemic results due to lack of adequate amounts of the normal thyroid hormone.

More than the present knowledge of the chemo-physiology of the endocrine organs as well as of cellular metabolism is, however, necessary before we may arrive at a complete and ultimate understanding of the pathogenesis of thyrotoxicosis. Much must still be learned of the factors controlling thyroid secretion; of the intermediate steps in the synthesis of thyroxin in the human organism, of its exact chemical function and reactions in the

*In the present article the term thyrotoxicosis (Plummer) is used generically to include all local and constitutional manifestations of thyroid toxemia, including Graves' disease, so-called hyperthyroidism, toxic adenomata, etc.

repair and replacement of protoplasm as well as the exact relationship of the thyroid to other ductless glands. So many new data yet require to be obtained and duly correlated that a very conservative attitude seems indicated at present.

REVIEW OF THE THEORIES OF THYROTOXICOSIS **

The Detoxication Hypothesis. After Moebius had called attention to the predominating rôle played by the thyroid gland in the production of the symptoms of Graves' disease, Notki, followed by Blum, evolved the detoxication hypothesis. The thyroid was regarded as serving to rid the body of certain toxins. The symptoms of Graves' disease were said to develop as a result of imperfect detoxication due to a pathologic thyroid gland. With the later recognition of the internal secretion of the thyroid and the necessity of this secretion to maintain cellular nutrition growth and development, this hypothesis became untenable.

The Toxic Hypothesis. Attempts have been made to show a relationship between a chemically altered water supply and thyrotoxicosis in a manner parallel with the supposed production of endemic goiter by water of high calcium content, etc. Further study, however, showed that exophthalmic goiter is not an endemic disease and it is now known that the presence of bacterial toxins and not a changed chemical constitution in an effected water supply is necessary for the production of endemic goiter (McCarrison). The toxic hypothesis is regarded as disproven.

The Infectious Hypothesis. This hypothesis gained some headway during the period of development of bacteriology of infectious diseases, having been supported by Virchow, Kocher and others. The hyperplasia and other changes were regarded as due to direct bacterial invasion. Extended investigation demonstrated, however, that thyrotoxic as well as other goiters are sterile. Again, evidence in abundance was adduced from the surgical side showing that thyroid hyperplasia also developed as a compensatory process after partial thyroectomy [Halsted (1) *et al.*]. The older infectious hypothesis of Graves' disease should not be confused with the modern view of the production of endemic goiter through toxemia of intestinal and probably ultimately bacterial origin (McCarrison).

**The older literature on thyrotoxicosis is given in Moebius, P. J., "Die Basedowsche Krankheit," Wien., 1906; Hölder, and Sattler, "Die Basedowsche Krankheit," Leipzig, 1909; Engelman.

The Neurogenic Theory. This theory relegates the cause of thyrotoxicosis to the central or peripheral nervous system as opposed to the "thyrogenous theory" in which the origin of the disease is regarded as being in the thyroid gland itself. Together these two theories and their modifications are the only ones receiving serious consideration at the present day.

The neurogenic theory is supported by older as well as certain new data. Charcot, Marie, Gauthier, Trouseau, Gerhardt, *et al.*, regarded exophthalmic goiter as a disease of the entire nervous system, calling especial attention to the symptoms and signs of increased central, peripheral and vasomotor stimulation present.

This theory then developed in two divergent ways, one school emphasizing lesions in the central nervous system, particularly the medulla; the other, in the autonomic.

The Bulbar Theory was ably supported by Sattler, an unusually thorough student of Graves' disease. Sattler inferred from the frequency with which the cardinal symptoms, goiter and exophthalmos, were associated, that pathologic processes in the medulla or in still higher portions of the central nervous system must be present. The well known experiments of Filehne (2), corroborated by others, showed that on sections of the *corpora restiformes* of rabbits, exophthalmos, thyroid hyperemia and tachycardia occurred. Unilateral bulbar lesions produced such symptoms on one side only. Sattler also calls attention to the cranial nerve palsies, which sometimes are met with in Graves' disease; also the glycosuria and speech defects, as possible bulbar symptoms. The muscular spasms, contractures and paralyses can also be accounted for by the bulbar hypothesis (von Leube).

Other adherents to the neurogenic theory regarded the *peripheral* nervous system, particularly lesions and degenerated areas in the cervical sympathetic ganglia, as responsible for the disease. Thus, lesions in the upper cervical ganglion would effect motor and secretory cells in the muscle of Mueller, the thyroid and heart; in the median ganglion, the thyroid and heart; in the inferior, the heart alone. Eppinger, Falta, Rudinger (3) and Eppinger and Hess (4) have supplied many experimental and theoretical data in support of this view. Its most enthusiastic adherents maintain that Graves' disease with fully

developed sympathicotonic symptoms is necessarily due to the above origin.

Support of this viewpoint from the pathologic side has been supplied by L. B. Wilson (5), who showed that experimentally produced lesions in the cervical sympathetic ganglia may cause histologic changes in the thyroid paralleling those found in the exophthalmic goiter. Wilson concludes that the thyroid is stimulated to abnormal function usually as a result of local infection in the cervical sympathetic ganglia. Cannon and Cattell (6) have also recently demonstrated the activation of the thyroid to secretion by the sympathetics.

Criticisms of the Neurogenic Theory. The neurogenic theory properly emphasizes the importance of the nervous system in the pathogenesis of thyrotoxicosis. It has, however, proven inadequate to withstand various criticisms which will now be mentioned.

From the clinical standpoint, the presence of an irritative ganglionic lesion is usually assumed to account for the exophthalmos (contraction of the Muellerian muscle) and tachycardia (stimulation of the cardio-accelerator fibers). But how account for the thyroidal hyperemia and hyperplasia, which are best explained by a paralysis of the vasomotor fibers and a direct metabolic stimulation from the blood stream (example, increase in the goiter and clinical symptoms due to iodine administration)? The absence of pupillary contraction and presence of dilatation which actually occur in exophthalmic goiter would make it necessary to accept a selective stimulation of certain autonomic fibers and paralysis of others, which is paradoxical and does not merit credence. Murray pertinently remarks that irritative cervical sympathetic lesions in order to account for the symptoms must necessarily be regarded as persisting for many years in most cases, which is inconsistent with the usual reactions of neuro-ganglionic tissue to pathological stimuli. Filehne's rabbit experiments, in which certain symptoms of Graves' disease were produced, have also been criticised by Marie, who declares that such are no more Graves' disease than is the glycosuria produced by bulbar puncture to be regarded as true diabetes mellitus. [See C. P. Howard's (7) excellent critique of the Neurogenic Theory.]

Pottenger (8), a close student of visceral neurology, has recently emphasized that many thyrotoxic symptoms are actually

parasympathetic in origin, viz.: Von Gräfe's sign, Dalrymple's sign, epiphora, sudorrhea, diarrhoea, hyperacidity and eosinophilia. The neurasthenia, change of psyche, and tremor are to be regarded as of central origin. The nervous stimulation is, therefore, considered a general one involving in varying intensity the several portions of the nervous system, central, peripheral and vegetative, and consequently not confined to the sympathetic ganglia.

We have, furthermore, direct clinical evidence that *thyrotoxicosis can arise without primary involvement of the nervous system*, in those cases in which the disease has developed as a direct sequela of acute thyroiditis or as result of trauma to the thyroid.

From the pathological side there is also serious objection to a purely neurogenic theory. Many careful autopsies on patients dying of exophthalmic goiter have failed to demonstrate the regular occurrence of lesions in either the medulla or the cervical sympathetic ganglia. Again, bulbar disease with demonstrable pathologic changes is not found associated with the symptomatology of thyrotoxicosis more often than can be regarded as mere coincidence, although, according to the bulbar hypothesis, the reverse should be true.

The chief question in point, it would seem to me, is whether Graves' disease arises endogenously in the thyroid gland itself or from neurogenic cause. An *exclusively* nervous origin of the disease is untenable as it has been demonstrated in many thousands of cases that the surgical removal of the major part of the thyroid gland is usually followed by subsidence of the signs and symptoms. From this general experience, the deduction is irrefutable that whatever indirect influence the nervous system may have in the production of the disease, the same evidently originates as a result of pathological changes in the thyroid itself. Persistence of the symptoms after thyroidectomy can be explained by pathologic and metabolic changes in the portion of the thyroid remaining after operation, together with permanent lesions in various organs due to previous effects of the thyrotoxic condition.

On the other hand, it is impossible to deny the marked influence of the nervous system, especially in those cases of thyrotoxicosis developing suddenly after fright and various other forms of mental shock. Cannon's recent demonstration of the

influence of psychic states and adrenalin upon the secretion of the thyroid secretion emphasizes the intimate relationship of the thyroid to the nervous and endocrine systems.

In résumé, then, of the value of a purely neurogenic theory of thyrotoxicosis this theory may be dismissed as untenable in view of present evidence without, however, recognizing that the fundamental metabolic disturbance in the thyroid gland in this disease may be set up and largely influenced by psychic, trophic and endocrine factors under nervous control; also that toxic products of thyroid metabolism selectively attack nervous tissue.

Crile's (9) *Kinetic Hypothesis* may be briefly mentioned in connection with the neurogenic theory. This distinguished surgeon endeavors to correlate the nervous symptoms and lesions with those of the thyroid gland by regarding the disease as one affecting "the motor mechanism of man, the same mechanism that causes physical action and that expresses the emotions." "A pathological reaction" between the brain and the thyroid is produced by various nervous factors causing the disease to develop. The arguments advanced in favor of this rather nebulous hypothesis are not capable of exact critical analysis.

THYROGENIC THEORY

The Hyperthyroidism Theory of Thyrotoxicosis. If then a purely neurogenic origin of the disease is discarded, the cause must be sought in the thyroid gland itself. The *thyrogenic theory* is capable of two chief conceptions, the "hyperthyroidism theory" which ascribes Graves' disease to hyperfunctional condition of the thyroid as opposed to a "dysfunctional" or "dys-thyroidism" state in which the secretion of the gland is regarded as qualitatively altered. At present we are concerned with the pure "hyperthyroidism theory."

This view was first promulgated in 1884 by Rehn (10), although it is generally first ascribed to Moebius (11) (1886), who, however, while emphasizing the importance of the thyroid in the causation of exophthalmic goiter regarded the disease as due to increased but qualitatively altered thyroid secretion. Eminent students of the disease soon accepted this standpoint in principle, although from the first many have adhered to the dysfunctional theory. Among those who have supported the hyperthyroidism theory are Kocher, Reverdin, Gauthier, F. Kraus, Falta, L. B. Wilson, Plummer.

The chief data supporting the hyperthyroidism theory are the following:

1. The thyroid tumor and histological evidence of hyperplasia.
2. Relief or cure of the disease by thyroidectomy.
3. Experimental production of hyperthyroidism in man and animals by thyroid medication.
4. Increase of symptoms of thyrotoxicosis on exhibition of thyroid preparations.
5. The contrast shown by the symptoms and signs of "hyperthyroidism" and hypothyroidism (Kocher) as well as by the metabolism.

The hyperthyroidism theory is therefore apparently based upon some of the best known facts pertinent to thyrotoxicosis. The clear explanation of the morbid picture afforded by this pathogenic conception has greatly aided its general acceptance up to the present time. As so frequently experienced in the difficult science of medicine, a definite explanation of otherwise a peculiarly confused clinical picture is so attractive that even an array of other facts irreconcilable with such a simple theory are often overlooked or disregarded by most physicians.* The inadequacy of the hyperthyroid theory to account for present knowledge of thyrotoxicosis can best be shown by criticising *ad seriatum* the above mentioned arguments supporting this etiologic hypothesis, prefixing such criticism with important *a priori* grounds for questioning the same.

CRITICISMS OF THE HYPERTHYROIDISM THEORY

Criticisms on a priori grounds. If viewed from a broad physiological viewpoint, it is questionable whether the conception of "hyperfunction" has a sound basis, however convenient and ingenious it may be. We may seek through the whole realm of organology without finding a single instance of an idiopathic hyperfunctional condition such as is claimed for the thyroid in Graves' disease. Hypertrophy, hyperplasia and hyperfunction only ensue under normal conditions when there is a cause and demand for such a reaction either by additional functional strain on a normal organ or through depression of normal function through disease. For example, the heart of the mountaineer hypertrophies and increases its power through circulatory

stimuli produced by the higher altitudes. Again, cardiac hypertrophy results from hypofunction due to toxic degeneration of the myocardium. Acromegaly might be advanced as an exception to this rule, but even here the excessive overgrowth is asymmetrical and abnormally confined to the jaws, hands, feet, etc. It is accompanied by decreased physical and psychic vigor and general degenerative processes. This antithesis is so marked that the most eminent students of pituitary disease, including Cushing, do not accept a "hyperfunctional" condition of the hypophysis. Indeed, it is very questionable whether the general credence given to the conception of hyperfunction as applied to various endocrine diseases or symptom complexes, including exophthalmic goiter, is justified by present knowledge. There are many more current beliefs in modern clinical medicine which are generally held without scientific foundation or substantiation.

The function of the thyroid gland is largely one of control of growth and development. In cretinism both are markedly deficient. If, then, we unreservedly accept the "hyperthyroidism theory" of Graves' disease, we must regard the thyroid in this condition to be in a state of continual hyperfunction. If cretinism is the antithesis of Graves' disease, then we must needs expect a state of over-growth and over-development to be found in young thyrotoxic subjects, while actually there is no true over-growth and at times slight signs of retarded development. The elongated limb bones observed in cases of youths suffering from Graves' disease have been erroneously regarded as evidence of over-growth, whereas this phenomenon is actually due to the delayed sexual maturity (failure of gonadal stimulation of closure of the epiphyses).

Pathological Evidence. The presence of hypertrophy of the thyroid gland in thyrotoxicosis has been used as one of the chief arguments for accepting an overfunction or overproduction of thyroxin as the cause of this disease. According to this view, the degree of hypertrophy present should be found to vary directly with the severity of the clinical symptoms. This, however, does not hold true. Some large goiters are accompanied by slight symptoms and conversely a very small goiter may be present in a very severe case of Graves' disease. Certain individuals show even marked symptoms without demonstrable thyroid hypertrophy.

Exophthalmic goiter is believed to follow great nervous and physical exhaustion or shock. It also occurs during or as a sequela to acute thyroiditis of bacterial origin, also various acute infectious fevers. In these exhaustive and depressant conditions, it is paradoxical to accept etiologically a hyperfunctioning organ which would actually demand unusually good, not poor, nutrition. In particular, it seems to the writer that the development of thyrotoxic symptoms in the course of an acute thyroiditis demands for their explanation, the recognition of morbid metabolic processes due to actual pathologic lesions in the secreting tissue, which a hyper-secretory hypothesis could but lamely explain.

Reasoning logically, one should expect marked hyperplasia of the thyroid to be regularly accompanied by the symptoms of thyrotoxicosis and conversely thyrotoxicosis to be as routinely associated with hyperplasia. In testing this assumption, we may refer to the most extensive and accurate pathological researches on goiter of the Mayo Clinic. According to Wilson's (12) and Plummer's (13) careful studies nearly all thyroidectomized patients had hyperplastic thyroids, but hyperplasia evidently does not necessarily lead to exophthalmic goiter, for of the non-hyperplastic goiters removed, 23.3 per cent were from patients showing thyrotoxic symptoms. Plummer (14) has, of late, remarked, "Areas of hypertrophy, 'some hypertrophy' (MacCarty), are present in such a percentage of all thyroids resected that this degree of hypertrophy has little, if any, tangible significance. In exophthalmic goiter, diffuse hypertrophy of the thyroid is rarely absent, but even in severe cases it varies from the most marked degree to the vanishing point." According to Boothby's (15) recent statistical report of 1,656 cases of goiter with histological studies, 254 were classified as non-toxic adenomata, i. e., as hyperplastic goiters without toxic symptoms, and 366 as toxic adenomata accompanied by thyrotoxic symptoms. Boothby states, "The pathologist, however, cannot distinguish adenomas which produce hyperthyroidism from those which do not." It is also shown from the numerous cases of this clinic that at least 16 years elapse from the development of adenoma to that of the appearance of thyrotoxic symptoms in the same individual. Marine and Lenhart (16) have also shown that there is no constant relationship between the degree of hyper-

plasia and the cardinal symptoms, exophthalmos and tachycardia. These authors also emphasize that hyperplasia is very common in simple goiters and other types of thyroid disease in which thyrotoxic symptoms are absent.

It follows from these amply demonstrated facts that the presence of thyroid hypertrophy and hyperplasia can have no direct etiologic bearing on the production of thyrotoxicosis, for hypertrophy and hyperplasia may be present without the development of thyrotoxicosis; the reverse may also be true.

Surgical Evidence. A chief argument for the acceptance of the hyperthyroidism theory has been the fact that surgical removal of the major part of the hyperplastic thyroid gland usually leads to cessation of the symptoms. This argument loses its apparent conviction, now that it has been shown that thyroid hypertrophy and hyperplasia cannot *per se* be responsible for the disease. Another explanation must be found for the hyperplastic processes in various thyroid diseases, including thyrotoxicosis (See below).

The surgical cure of the disease has indeed nicely demonstrated that the toxic excitant of the morbid process has its origin in the gland itself, but brings no proof that the varying degree of hypertrophy and hyperplasia is the cause of the disease. Surgical experience has, on the contrary, made it clear that the pathogenic processes do not necessarily depend upon the presence of an intact, hyperplastic and supposedly hyperfunctional gland, for in certain obstinate cases the symptoms may not subside so long as the tiniest rest of the toxic gland is allowed to remain. This not uncommon observation is excellent evidence that an intensive metabolic disturbance in the thyroid is at fault rather than a simple hyperfunction which would necessitate the presence of a large mass of thyroid tissue in order to produce the disease.

Clinical Evidence: The relation of the iodine content to the degree of hyperplasia is of interest in this regard. As iodine is organically combined in the thyroxin molecule the amount of iodine present in the gland can be properly considered a certain gauge of its metabolic activity, duly recognizing, however, that such determinations cannot comprehend the amounts of iodine secreted in molecular association in thyroxin. It has been found that hypofunctioning goiters accompanied by cretinism are

markedly deficient in the iodine content. According to the hyperthyroidism theory one may then expect to find more rather than less iodine in thyrotoxic thyroids. Actually, Kocher (17) has noted as little as $1/30$ of the normal amount present; Wilson and Kendall (18) from $1/50$ to $1/20$ of the normal. According to Marine and Lenhart's (19) studies, the iodine content of exophthalmic goiters varies inversely with the amount of hyperplasia present and shows in this regard no departure from the behaviour of the iodine content in various other thyroid conditions, normal and abnormal. Thus hyperplasia is known to decrease in non-toxic thyroid adenomata on exhibition of iodine or thyroid substance and iodine is stored in the gland. Precisely the same behaviour was observed by Kocher and Marine and Lenhart on administration of iodine and thyroid preparations to exophthalmic goiter patients. From these observations, it is evident that no evidence from the behaviour of the iodine content in exophthalmic goiter can be adduced in favor of the hyperthyroid theory.

Experimental "Hyperthyroidism": The similarity of the symptoms following the ingestion of thyroid material in excess of that of Graves' disease, also the well known aggravation of the disease by thyroid medication, constitute a further support of the hyperthyroidism theory. These statements are substantiated by experimental and clinical data which will now be analyzed.

From the experimental side, Klose (19) and Lampe, Liesegang and Klose (20) have reported the production of exophthalmic goiter symptoms, i. e., elevation of temperature, tachycardia, glycosuria, increased nervous irritability and, rarely, exophthalmos by feeding exophthalmic extracts to certain strains of fox terriers. These are among the very few experiments known to the writer in which exophthalmos, a cardinal symptom of human Graves' disease has been produced. Ballet and Enriquez (21), Baruch (22) and Kraus and Friedenthal (23) likewise report the production of exophthalmos by feeding thyroid preparations. Such results, however, merely demonstrate that extracts from the *pathological* thyroids of Graves' disease patients can produce a similar condition in animals, but do not prove that Graves' disease can be produced in animals by feeding large amounts of thyroid tissue or the thyroid hormone, which must be demon-

strated to prove the hyperthyroid hypothesis. Klose and his associates, however, failed to elicit the above symptomatology when extracts from normal thyroid glands were fed and they themselves interpreted their results as supporting the dysthyroidism theory.

A large number of workers have administered various iodine and thyroid extracts; also divers preparations from normal, goitrous, or thyrotoxic individuals without the appearance of a clinical syndrome capable of being designated as exophthalmic goiters. Among these may be mentioned Cunningham (24), Soupault (25), Hutchison (26), Gley and Claret (27), Gley (28) (who repeated Klose's work), Schoenborn (29), Fonio (30), Carlson, Rooks and McKie (31), Marine and Williams (32). Kendall (33) in injecting goats and dogs with large amounts of the isolated thyroid hormone gave the hyperthyroidism theory a severe test, but failed to observe the development of Graves' disease. This author states, "The general picture could not be differentiated from parathyroid tetany, idiopathic tetany or from certain phases of epilepsy." Though tachycardia and hyperpyrexia were produced, no exophthalmos was noted.

Summarizing then these data on the experimental causation of Graves' disease in animals, one must admit that the weight of evidence is against acceptance of the reproduction of this disease experimentally through use of thyroid preparations, including the thyroid hormone in chemically pure form.

DISCUSSION OF THE CLINICAL EVIDENCE IN FAVOR OF THE HYPERTHYROIDISM THEORY

From this side is reported the well known case of Notthafft (34) whose patient ingested 1,000 thyroid gland tablets within 5 weeks. There followed the development of the complete picture of exophthalmic goiter which gradually subsided when the thyroid medication was stopped. Several other similar cases have occurred in the literature. The writer has learned of still another by verbal communication of Professor Graham Lusk, New York.

It is, however, remarkable that, although over-dosage with thyroid preparations is of not uncommon occurrence, the number of such cases has remained extremely few. These rare instances in which toxicity does occur, it would appear, might be accounted for by the previous existence of a latent tendency to

thyrotoxicosis, which, on the stimulation by the thyroid preparations, thereupon developed. Proof of the hyperthyroidism theory by such means would also necessitate the demonstration of an unquestionably normal thyroid gland in such instances. This is lacking and impracticable as well. It is also a well established clinical fact that most cases of exophthalmic goiter develop severer symptoms after the exhibition of thyroid preparations [Cerioli (35), Kocher (36), Goldflam (37), *et al.*]. This aggravation of Graves' disease by thyroid medication can, however, only superficially be regarded as supporting the hyperthyroidism theory, for it is susceptible of other explanation. Thus the ingestion of large amounts of iodine and thyroxin may merely serve to provide a dysfunctioning gland with added material for the production of a toxic, imperfectly synthetized or anabolized thyroxin molecule, which may be the ultimate cause of the disease.

Finally, all experiments known to the writer on the experimental or clinical production of Graves' disease by thyroid preparations are subject to the same criticism; the question as to their interference with the normal thyroid metabolism with possible production of aberrant or pathological metabolites in the thyroid, which, themselves, cause the toxic symptoms. Convincing proof of the hyperthyroidism theory can only be brought by first excising the thyroid gland in experimental subjects and then producing *all* symptoms of the disease by introduction of large quantities of normal thyroid gland or, better, thyroxin. Such proof for the hyperthyroidism theory has not been forthcoming. One is here reminded of the inconsistency shown by the ready acceptance by many physicians of the experimental production of Graves' disease in animals on quite insufficient evidence, whereas the bacteriologist refuses to accept the bacterial cause of a given disease without its exact reproduction in animals or man.

The Contrast shown by the Symptoms and Signs of "Hyperthyroidism" and Hypothyroidism has been advanced in most text-books as a proof of the hyperthyroidism theory ever since the great emphasis put upon this apposition by Kocher. In regard to the value of the general clinical antithesis of these two conditions, McCarrison has shrewdly observed that the contrast shown by their symptomatology brings us no nearer the eluci-

dation of the *cause* of the morbid state of either. It seems to the present writer that it would be just as illogical to argue that acute mania is caused by "hyperfunction" of the higher cerebral centers because this form of insanity shows a diametric opposition, clinically, to acute melancholia. Such an argument would be regarded by every one as purely speculative.

Considered purely clinically, exophthalmic goiter presents a general picture of stimulation of the entire nervous system, a number of symptoms, viz., increased excretion of nitrogen and elevation of metabolism, the vagotonia, hyperpyrexia, nervous excitability, etc., differing only in degree from well known reactions of the organism to bacterial toxins, etc. On the other hand, the clinical picture of myxedema is one of widespread degeneration and consequent loss of function due to the loss of the anabolic action of the thyroxin on the tissues. The contrasting symptomatology of these two diseases is therefore most reasonably explained by a chemo-toxic effect in Graves' disease and loss of function in myxedema and cretinism, two essentially different pathological conditions producing, of course, differing symptoms.

Furthermore, a critical survey of the *complete* symptomatology of both diseases renders it evident that the clinical antithesis of Graves' disease and hypothyroidism is largely confined to certain prominent symptoms as shown by the contrasting facial expression, mentality, the pulse rate and the like. In fact, a number of identical symptoms and metabolic phenomena are present in both conditions. Even Kocher admitted the common presence of edema, dryness and loss of hair and hair color, cutaneous dryness and pigmentation, and diminution of the salivary secretion. In addition to these, there are other trophic and nutritional disturbances occurring in the two diseases but cloaked in the case of Graves' disease by the more striking evidences of general nervous excitation. To avoid repetition, reference can be made to the detailed consideration of the symptomatology from this standpoint developed in a later section.

Aside, however, from the identity of a number of the symptoms, a chief argument against acceptance of the hyperthyroidism theory has always remained the constant occurrence of a number of cases where clinically myxedema has been found accompanying Graves' disease. It is impossible to account for this condition on the hyperthyroid hypothesis. As Faure has em-

phasized, the conception of a thyroid gland in coincident state of hyper- and hypo-function is paradoxical. This fact alone would seem to the writer effectually to militate against the acceptance of the pure hyperfunctional theory.

Furthermore, myxedema is occasionally met with as a sequela of Graves' disease. Here may also be mentioned the not uncommon familial occurrence of Graves' disease and exophthalmic goiter. These facts would argue a common, not a diametrically opposite, etiology.

Metabolism in Graves' disease and the Hyperthyroidism Theory. The increased metabolism in Graves' disease and the decreased metabolism in hypothyroidism is another argument used in favor of the hyperthyroidism theory. In order to apply certain criticisms to this argument it is necessary to analyze known metabolic data in thyroid disease.

During the past few years, since the general introduction of basal metabolic rate determinations in the study of thyroid disease, the contrast of thyrotoxicosis and myxedema has been further emphasized by the marked differences in the height of the gaseous metabolism in these two conditions. This metabolic antithesis has been particularly brought out by Plummer and Boothby, *et al*, of the Mayo Clinic in numerous articles which have served, on account of the large number of such metabolic studies reported and the prominence of their source further to strengthen the case of the "hyperthyroidism theory" among the medical profession at large.

The great assistance afforded the clinician by metabolic rate determinations in the diagnosis and treatment of thyroid disease has, however, led to overestimation of the importance of basal metabolism determinations in the diagnosis of these conditions. The influence of the thyroid as a regulator of oxygen consumption and of energy production has thus been thrust into the foreground without due consideration of the importance of thyroid function in cellular nutrition. Exception is here taken to the definition of the thyroid hormone advanced by Plummer and Boothby (38), influenced by Kendall's chemical viewpoint. They regard thyroxin as "a catalyst that accelerates the rate of formation of a quantum of potential energy in the cells of the organism." It is questionable whether this definition can be regarded at present as more than purely speculative, inasmuch as we re-

main in considerable ignorance of the exact chemical reactions involved in the formation of the "potential energy" in question. The frequent quotation, however, of this hypothesis in recent publications seems sufficient proof of the seriousness with which it has been generally received by the medical profession at large. This is due to the prominence of the source of this view. It would likewise indicate the desirability of authoritatively advancing only such new theoretical viewpoints as are completely defensible, both by critical analysis of the pertinent literature and adequate experimental support.

The chief function of the thyroid gland is the regeneration of old and growth of new cells by aiding in the synthesis of protoplasm. An attempt at a more specific definition seems inadvisable at present. This *anabolic* function is of vastly more importance than its catabolic effect, i. e., the production of heat and energy through combustive processes requiring oxygen. Both anabolism and catabolism, however, require oxygen consumption with liberation of heat, energy and carbon-dioxide. *The metabolic rate is very probably influenced by the thyroid, not directly for the purpose of control of energy and heat production, but only to the extent that these processes are necessary in the chemical reactions leading to the accumulation of intermediary metabolites and their synthesis into old or new protoplasm by the aid of the thyroid hormone.*

This view of thyroid function, which should indeed be self-evident from the marked influence that the thyroid is known to exert upon growth, was first emphasized by the present writer (39) in 1916, and developed in a later paper (40).

Even athyroid individuals are capable of considerable release of energy and heat production through other agencies, probably other ductless glands, which also function in the general nutritive processes of the cells. In cretinism and myxedema, even when there is complete absence of the thyroid gland, the gaseous exchange is decreased at most to 40 or 50 per cent, so at least 50 to 60 per cent of the normal metabolism must be accounted for otherwise than by activity of the thyroid gland. It will also be remembered that the heat centers in the medulla are still functioning even in athyreosis, as evinced by their response with pyrexia when sufficiently stimulated by bacterial toxins.

It is indeed probable that the decrease in the basal metabolism in hypothyroidism is to some extent *a compensatory retardation of the chemical processes of the cells of the body, whose exhaustion and disappearance would be hastened, in absence of a normal thyroid, by normal metabolic processes.* This seems indeed probable by the observed drop in the metabolic rate in cases of inanition with intact thyroids to levels as low as those seen in severe cases of cretinism and myxedema. That the lowered metabolism in hypothyroidism is due at least in part to "hormone starvation" is suggested by the gradual fall of the basal metabolism after complete removal of the thyroid, though it is capable of other explanation.

In view, then, of this conception of the metabolism of hypothyroidism, the decrease of the basal metabolic rate in hypothyroidism is regarded as a measure of an accompanying metabolic phenomenon rather than indicative of failure of a fundamental thyroid function.

The conception of the increased metabolism in thyrotoxicosis as being due simply to increased energy production, through increased thyroxin production, *i. e.*, "hyperfunction" and "hyperthyroidism," is likewise subject to considerable criticism. Although a general indication of the severity of the disease, it has not proved possible to demonstrate an exact parallelism between the amount of "hyperfunctioning," thyroid parenchyma and the degree of elevation of the metabolic rate. Every internist of experience has observed cases of thyrotoxicosis still presenting considerably increased metabolic rates (for example, an increase of even 50 per cent) in individuals who possess but one-tenth or less of a toxic goiter largely removed through operation. Indeed, it is far more logical to explain the elevated metabolism in Graves' disease as a result of a general intoxication from abnormal products of thyroid activity. This reaction differs chiefly in degree from that produced by bacterial and other toxins in fevers, as has been stated. With regard to the increase in the metabolic rate observed after administration of large amounts of pure thyroxin, this observation fails to bring proof that the augmented gaseous exchange is not likewise due to a toxic stimulation, from the development of toxic intermediate products in course of the catabolism of amounts of thyroid hormone introduced experimentally in excess of requirements.

It by no means necessarily follows that the results ensuing after an ingestion of abnormal amounts of thyroid substance influence the basal metabolism *by the same means* in which it is held to the normal level by a normally functioning thyroid. Indeed, the very presence of a number of peculiar nervous and other symptoms in experimental hyperthyroidism would suggest a probable change in composition of the thyroid hormone responsible for the same. The long latent period reported by Kendall (41), as well as Janney and Isaacson (42) following the administration of a toxic dose of thyroxin can be considered as evidence in favor of some chemical transformation being necessary *before* the toxic outbreak with elevation of the metabolic rate can take place. Otherwise, one would expect an *immediate* rise of the basal metabolic rate which under normal conditions is one of the most labile of natural phenomena.

The Protein Metabolism. The known facts concerning other aspects of the metabolism of hypothyroidism as contrasted with Graves' disease do not bear out the suggestion made by the behavior of the gaseous exchange, namely, that the one process is antipodal to the other,—“hypofunction” versus “hyperfunction.” Although the nitrogen metabolism is generally decreased in the former and increased in the latter condition, still the writer's experiments (40) have made it probable that the decrease of nitrogen output in cretinism is due rather to decreased protein absorption secondary to a decreased ability to retain synthetically nitrogenous metabolites in the body; possibly also to nitrogen “sparing.” In thyrotoxicosis the increased nitrogen output is best explained as a toxic loss of protein and nitrogen. It may also be noted that Janney (40), as well as Halvarsen, Bergeim and Hawk (43), found it possible to obtain an increased nitrogen balance by administering thyroxin to Graves' disease patients, a procedure which, according to the hyperthyroidism theory, should always have the opposite effect.

Creatinuria is frequently present in both Graves' disease and myxedema. Although *hyperglycemia* is the rule in the former and *hypoglycemia* in the latter condition, there is little regularity in this. Speaking generally, the most we can state is that irregularity in the carbohydrate metabolism is present in both diseases. In view of these discrepancies, it is impossible longer to accept that contrast shown by the metabolism of thyro-

toxicosis and hypothyroidism is conclusive evidence of the validity of the hyperthyroidism theory.

Summarizing then the foregoing data, criticising the value of the contrasting behavior of the metabolism in hypothyroidism and thyrotoxicosis as a support of the hyperthyroidism theory, the following may be said.

1. As the chief function of the thyroid is the generation and regeneration of the tissues by action of thyroxin on protein metabolites, not that of a mere catalyzer for the combustive processes, the basal metabolism, however significant clinically, is not of fundamental importance in the theory of thyroid disease.

2. The lowered basal metabolism of hypothyroidism and the elevated metabolism of thyrotoxicosis are subject to other explanation than that of increased or decreased heat and energy production due to a simple kinetic hypothesis. The lowered metabolism of hypothyroidism may be caused at least in part by a compensatory retardation of metabolic processes in the cells to offset the decrease in amount of thyroxin, a hormone necessary for growth and repair of the cells and tissues. The increased gaseous exchange in thyrotoxicosis can be more reasonably explained by a toxic stimulation of the nervous and other tissues than by the effects of simple over-accumulation of the normally non-toxic synthetic hormone, thyroxin.

3. The characteristics shown by protein, creatin and carbohydrate metabolism in exophthalmic goiter and hypothyroidism are not such as can be satisfactorily explained by the hyperthyroidism hypothesis.

Summary of Criticisms of the Hyperthyroid Theory: In the preceding pages the chief data and arguments in favor of the "hyperthyroidism theory" have been analyzed and reviewed in the light of modern knowledge. Sufficient evidence, it is believed, has been advanced to show that this time honored theory is supported by superficial and, in part, conflicting arguments, which constitute but a fallacious explanation of the etiologic, pathologic, metabolic and clinical data of Graves' disease.

(To be continued)