Some Points

ON

THE ETIOLOGY, PROGNOSIS, AND TREATMENT OF GRAVES'S DISEASE.*

WITH PARTICULAR REFERENCE TO THE ADRENAL GLANDS AND THE VALUE OF READ'S FORMULA.

BY

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It is not my intention to attempt to deal fully with the several aspects of Graves's disease, but rather to touch on certain points in etiology, prognosis, and treatment which in my opinion are worthy of some consideration.

The subject is one of which our knowledge is steadily growing, and about which there is much variation in opinion and practice. This is as it should be, for there is plenty of scope for trial and observation in many directions in this disorder at the present time, but little excuse for dogmatic assertions or rule-of-thumb procedures.

ETIOLOGY.

A tenet which has materially delayed advance in our understanding of Graves's disease is that hyperthyroidism is a sufficient explanation. The conception is a simple one, and suggests a simple remedy. If the symptoms and effects are due to hyperthyroidism, let us cripple the thyroid in some way or other, and necessarily the symptoms must abate. Such a simple conception, entrenched as it is in the textbooks by the use of Graves's disease and hyperthyroidism as synonymous terms, we know now is untenable, and must be modified in various ways. The discovery and preparation of a product of thyroid activity—thyro-iodin or thyroxin—led to its being regarded as the peccant substance to excess of which the symptoms are due, but Williamson and Pearse¹ have shown that disturbance of the iodo-colloid function has only an indirect relation to the thyro-toxicosis. These workers have demonstrated that the thyroid gland has two distinct functional activities—one the production of thyro-iodin, the other of a secretion—and that it is this latter which is directly related to the thyro-toxicosis of Graves's disease. Even so, the question we must answer before we can approach the preventive medicine of Graves's disease or remain satisfied with its present treatment is: "Why is the secretory activity enhanced?" When the correct answer to that question is provided the present methods of treatment, directed towards destroying the activity of the gland by local means, will be a subject chiefly of historical interest. I do not wish to attempt to belittle the present-day value of such methods, but I feel that it should be our aim to minimize the need for their employment, which will assuredly be attained when we can explain the overproduction of thyroid secretion. This part of the field of etiology is, then, well worthy of exploration, and one likely to yield results of the greatest practical value.

Stimulation of Thyroid Activity.

It is generally agreed now that the thyroid reacts to toxic factors, as well as to sympathetic stimulation, by increasing its functional activity. Another stimulus arises from the sex glands in the female, probably from the uterus, for there is slight but noticeable enlargement of the gland at puberty, during pregnancy, and even during menstruation in many subjects; whilst with the termination of the climacteric the opposite is prone to occur, the gland shrinking and perhaps becoming so insufficient as to permit of the development of myxoedema. Perhaps this extra duty of the thyroid in the female may explain the greater incidence of Graves's disease in women, especially during the child-bearing period.

* Read before the Hampstead Division of the British Medical Association, March 14th.

Despite the careful work of McCarrison and others, the conception of the thyroid as an antitoxic gland was long in gaining credence, though it seems now to be acknowledged. I believe this activity to be of great importance in the etiology of Graves's disease. Like others, I have been especially impressed with the frequency of tonsillar sepsis in my experience. This has led me to make particular inquiry and investigation into the point in my last 50 cases of Graves's disease. In 22, or 44 per cent., I obtained a definite spontaneous history of severe recurrent sore throats or quinsies. In 8 of these (16 per cent.) an attack occurred while the patients were in the wards. It must be emphasized that simple sore throats were disregarded in these figures, and only severe and recurrent tonsillitis or quinsies were considered.

Stimulation of the thyroid gland by toxins, either acting alone or in combination with other exciting influences, seems to me to be among the most important causes of thyro-toxicosis or Graves's disease. It is tempting to suppose that the effect of local sepsis, such as that of the tonsils, is to create a demand for the iodo-colloid secretion, but that by this demand the whole gland is stimulated, the true secretion being also increased. It is this excess of true secretion which provides the symptoms of Graves's disease. Bearing upon these points it must not, however, be forgotten that hyperplasia of the secretory tissue of the thyroid seems to hold in check the development of iodo-colloid, for removal of some of the hyperplastic tissue is followed by a re-accumulation of iodo-colloid in the alveolar spaces (Williamson and Pearse).

The Adrenals in Graves's Disease.

The part played by the adrenal glands in Graves's disease cannot be ignored, but is not easy to assess. Psychical causes, such as worry, excitement, mental stress, and fright, have long been recognized as precursors. Moreover, the clinical picture of the disease is the very presentment of fear—the starting eyes, the flushing, the tachycardia, the tremor, even the diarrhoea and the hyperglycaemia, together delineate the features of fear. But fear and the preparation for fight or flight we believe to be intimately connected with activity of the adrenal gland, the hormone of the medulla of which hurries up the heart, braces up the blood vessels, and mobilizes sugar for immediate effort (Cannon). When Graves's disease begins abruptly, following a period of excitement and alarm such as a motor accident, it is difficult to exclude the adrenals in its production, for the increase of adrenaline which arises, by stimulating the sympathetic system, must provoke also increased thyroid secretion. During the war one saw many examples of men who, after exposure to danger, presented a picture which during time of peace one had been accustomed to recognize as mild Graves's disease, for they showed tremor, tachycardia, flushing, slight staring of the eyes, with retraction of the upper lids and visible sclerotics below them. In most instances these symptoms subsided quite quickly, being gone in a few hours or days, but occasionally true Graves's disease followed and persisted. There was, I believe, a notable increase in Graves's disease in London during the war period, which has been ascribed to the air raids (Langdon-Brown). If we accept the modern physiological explanation of the reaction to fear, the prominent part played by the suprarenals in the inception of Graves's disease in these cases can hardly be denied.

A more difficult question is as to how long this adrenal activity persists, and how far it contributes to the picture of the developed disease, for it must not be forgotten that administration of thyroid alone in excessive doses is capable of producing nearly all the symptoms. Yet it is reasonable to infer that with overaction of the thyroid there is accompanying overaction of the adrenals, for thyroid secretion stimulates the sympathetic, which in turn stimulates the adrenals. Assuming that my contention is right that suprarenal activity precedes that of the thyroid in response to psychical disturbances in certain cases of Graves's disease, it is easy to see how a vicious circle may be set up. The outpouring of adrenaline stimulates the sympathetic, which in turn stimulates the thyroid and the suprarenal itself, whilst the increased thyroid secretion for its part stimulates the adrenals still more.

Experimental Study of the Suprarenal Gland.

There are several interesting observations and experiments which bear upon this problem. W. Cramer² points out that the suprarenal gland is unusual in that its own secretion stimulates it to further activity through the intermediation of the sympathetic, a process which, unchecked, would inevitably lead to exhaustion of the gland. He finds that injection of adrenaline or of whole adrenals in a mouse produces characteristic changes in the adrenal medulla, which he believes effect a control of the gland. The changes in the gland are an apparent hyperplasia of the deeper part of the cortex, at the expense of the medulla. Hoskins³ and Herring⁴ found enlargement of the suprarenal cortex as the result of prolonged feeding with thyroid. Possibly, as Cramer suggests, an explanation of Graves's disease is to be found in a breakdown of this controlling mechanism.

The experiments of Marine and Baumann⁵ are especially suggestive. After suprarenalectomy, or after freezing the adrenal cortex with ethyl chloride in rabbits, they found that 88 per cent. (of 31 rabbits) showed markedly increased heat production (which corresponds to a raised basal metabolic rate) for months, loss of weight, and "a picture resembling the symptom-complex of exophthalmic goitre." These results did not occur if the thyroid gland was previously removed—an observation strongly indicating a controlling action of the suprarenal cortex against thyroid secretion and its failure in Graves's disease.

McCarrison has shown that inanition provokes hypertrophy of the suprarenal cortex. May not this hypertrophy be a protective mechanism to control metabolic activity by opposing the thyroid? Jaffe⁶ has shown that suprarenalectomy causes rapid enlargement of the thymus, and we know that thymic hyperplasia is a constant accompaniment of Graves's disease. Marine states that thyroidectomy hastens involution of the thymus, whilst suprarenalectomy delays it.

Shapiro⁷ has given a glycerin extract of ox suprarenal cortex in cases of Graves's disease, and records considerable benefit, especially upon the asthenia, dysmenorrhoea, diarrhoea, nutrition, heat production, tachycardia, and blood pressure. He believes that the suprarenal cortex exerts an inhibitory or regulating control over the thyroid, and that its functional insufficiency plays a fundamental part in the development of Graves's disease. He points out that suprarenal cortical injury and Graves's disease have many features in common, for both show increased metabolism and appetite, thyroid hyperplasia, lymphoid hypertrophy, including that of the thymus, asthenia, increased sexual activity, hypersensitiveness to toxins and drugs, and increased peristalsis. Marine's work on the high metabolic rate after excision of the suprarenals is not entirely confirmed by Scott,⁸ and Bornstein and Holm,⁹ who found much increased ventilation of the lungs, to which they ascribe the results.

Finally, Obregia¹⁰ has treated Graves's disease with glycerin extract of whole suprarenal glands of sheep, pigs, or calves. He records rapid amelioration of the condition, and states that all the patients have recovered. With adrenaline alone by the mouth he obtained improvement, but this was less pronounced than with the whole gland.

A clinical feature of interest in regard to the suprarenal cortex being a possible factor in Graves's disease is the pigmentation. In Addison's disease the pigmentation is generally regarded as due to cortical rather than to medullary defect, and a somewhat similar pigmentation occurs in Graves's disease. Feeding of birds with thyroid, on the other hand, causes disappearance of pigment.

To sum up the etiological part of my remarks there is, I think, good reason to believe that:

1. Hyperthyroidism is an incomplete definition of Graves's disease.
2. An important provoking antecedent is local sepsis, especially of the tonsils.
3. The suprarenal glands play an important part in the etiology and clinical manifestations.
4. There is a good deal of evidence to show that suprarenal cortex exerts a controlling influence on thyroid activity, and that its failure to control is an important factor.

PROGNOSIS.

Estimation of the severity of a case and a forecast of its probable outcome is based best on the assessment of many factors, and should not, in my opinion, depend entirely on the basal metabolic rate. The degree of tachycardia, the pulse pressure, the cardiac rhythm, the severity of nervous symptoms, the degree of general weakness, the existence or not of diarrhoea are all factors of great importance. The age of the patient is another pertinent consideration, for with the intervention of the menopause amelioration is to be expected. Occupying a prominent, perhaps the most prominent, position is the value of the basal metabolic rate, but it should be taken in conjunction with other features, and should not be used as a direct index of severity as though it possessed mathematical accuracy. The plan of deciding upon the treatment, whether operative or non-operative, by the reading of the basal metabolic rate alone is one which is less often adhered to than formerly, for it is recognized that slight variations in the records alter the final estimation exceedingly, that errors in technique are easily committed, that slight psychical disturbances profoundly modify the result, and considerable fluctuation may occur within a comparatively short period. If, however, we can disabuse our minds from regarding the rate of basal metabolism as an unflinching signal owning mathematical exactness, it remains an index of great value. A serious drawback to its use is the difficulty of estimation, considerable practice being needed to obtain accurate and comparable readings; indeed, the necessary apparatus has found its way into the armoury of few practitioners in this country. Some simple formula would be valuable if it approached the basal metabolic rate estimation in the degree of its accuracy.

Read's Formula.

A formula introduced by Read is not difficult to work with. It is as follows:

$$\frac{1}{2}(\text{P.R.} + \frac{1}{2} \text{P.P.}) - 72$$

where P.R. is the pulse rate, and P.P. the pulse pressure. Taking a normal patient with, say, a pulse rate of 72 and the pulse pressure of 40 the sum is thus:

$$\frac{1}{2}(72 + 30) - 72, \text{ which is equal to } +3.$$

To test the degree to which Read's formula approximates to the basal metabolic rate Dr. T. C. Hunt, recently of the St. Mary's Hospital Medical Unit, has compared the two in a limited number of cases: 54 were examined in all, but of these 4 were rejected, the basal metabolic rate being regarded as unreliable in view of excitement, nervousness, or other cause. Of the remaining 50, in 27, or 54 per cent., the two agreed within 10; in other words, they gave results which for practical purposes may be considered as equal. In only 3, or 6 per cent., did Read's formula give a result higher than the basal metabolic rate by over 10. (This agreed with the opinion of Eason, who states that Read's formula agrees with the basal metabolic rate in 50 per cent. of cases.) In 6, or 12 per cent., Read's figure was between 10 and 20 less than the basal metabolic rate; in 8, or 16 per cent., between 20 and 30 less; and in 6, or 12 per cent., it was more than 30 less. These last 6 were all cases with high basal metabolic rates, the average value being +73.

Dr. Hunt draws the following conclusions:

1. Read's formula will very seldom give appreciably too high an estimate of the basal metabolic rate, but often gives slightly lower figures.
2. A very marked discrepancy suggests an error in technique.
3. The basal metabolic rate in very bad cases is probably fairly considerably higher than Read's formula suggests.
4. Iodine treatment appears to improve the circulatory system as shown by Read's formula more definitely and more permanently than it improves the basal metabolic rate, which does not appear to be reduced for long by the comparatively small doses given (up to 20 minims of Lugol's solution daily). With this exception Read's formula has shown improvement with treatment exactly parallel with that shown by the basal metabolic rate.
5. Read's formula should be applied under basal conditions, but does not seem to vary so much as the basal metabolic rate from food or other external factors. In some cases it is quite impossible to gauge the latter accurately.

Within limits it would seem that the figure obtained by this formula is an accurate guide to progress, and differs widely from the basal metabolic rate figure only in the severest cases. It has a particular field of usefulness when for some reason estimation of the basal metabolic rate is not practicable.

TREATMENT.

The psychical and toxic factors in the causation of Graves's disease suggest at once two lines of treatment. The value of rest and freedom from mental excitement is too well known to need emphasis here. Removal of a focus of sepsis is also clearly indicated if the importance of such in the etiology be conceded. Unfortunately these two lines of treatment are in part antagonistic, for such an operation as tonsillectomy, for example, in an adult who has had repeated quinsies is no light one, and cannot be undertaken in a case of severe Graves's disease without anxiety. It finds its chief place in early cases, or those in which the thyro-toxicosis is slight. The question of focal sepsis should be borne in mind whenever an early case is encountered, or at a stage when the full clinical picture is still lacking. Its detection and consideration at this stage may be of great value as a preventive measure.

The modern treatment by administration of iodine, especially in the form of the French tincture or of Lugol's solution, has largely replaced earlier drug treatment. There can be no doubt of its potency, for within a very short time definite improvement is obvious in many cases, whilst the thyroid gland can be felt to become firmer. Unfortunately there is less certainty about the permanence of the good effect. Most English, German, and American observers hold that prolonged treatment is unsuccessful. Many French authorities, however, are of the contrary opinion. Thus Dautrebande,¹¹ Labbé,¹² and Boudreau¹³ state that iodine must be administered over many months, with gradually increasing dosage up to 0.5 or 0.6 gram of metallic iodine, given five or six times daily. These are truly heroic doses compared with the 2 to 10 minims of Lugol's solution, three times daily, customarily employed in this country. The rationale of iodine treatment is ambiguous, and, indeed, iodine would appear definitely to be contraindicated if it were true that Graves's disease is hyperthyroidism, and that its toxicosis is caused by excess of thyroxin. The recognition, however, that the thyro-toxicosis is related to excess of other secretion, and not to that of the iodo-colloid substance, suggests another explanation. May it not be that administration of iodine relieves or assists the thyroid in its reaction to toxins, and thus indirectly, by lessening its functional activity, reduces the output of the secretion which causes the thyro-toxicosis? In view of the unsatisfactory experience of others I have treated only a few patients by persistent and prolonged iodine therapy. The chief results have been gain in weight and lessened excitability and tremor, but there has been little beneficial effect upon the basal metabolic rate or the cardio-vascular symptoms. It must be confessed, however, that I have not yet had the temerity to use the large doses so forcibly recommended by some French writers.

About symptomatic treatment I shall not particularize as I have little new to advance. There are many occasions for such measures during the course of the disease. A mixture containing digitalis and bromide is, of course, one which has been very generally employed to combat the tachycardia and fibrillation, and to procure sleep and reduce the mental excitement. My belief is that digitalis should be used only with great caution in Graves's disease, for in this condition it may do serious harm.

There remain to be considered the two destructive procedures, which are used to cripple the over-activity of the thyroid gland—namely, x-ray therapy and operative procedures. There is no doubt that both may produce great amelioration of the symptoms, and may hasten recovery, though I think that in neither is one justified in using the word "cure." In a disease in which, under medical treatment, the tendency of the majority is slow progress in the direction of recovery, it is difficult to compute the precise value of surgical treatment unless its effects are immediately or rapidly curative. Nor is it easy to find any agreed statement as to which cases are considered by surgeons particularly suitable for surgical

treatment. There are many who regard all cases as suitable, except during an acute phase; there are others who are disinclined to operate at all. It must be acknowledged, however, that the tendency in recent years has been more and more towards operation, and the operative mortality has fallen in expert hands to a very low figure. On the other hand, x-ray treatment has become somewhat less favoured since it has been recognized that its effects cannot be controlled with precision, and that it interferes seriously with subsequent operative procedures. The common practice of preceding operation by a course of treatment by physical and mental rest, and by the administration of iodine, has certainly lessened the danger of surgical intervention. At my hospital we have no enthusiasts for surgical treatment, and it is seldom employed on my patients. In mild cases it seems to me to be unnecessary, and in very severe cases too dangerous, while of the intervening cases improvement by medical treatment is what one is accustomed to expect. In patients near the menopause, also, relief before long is to be anticipated. Perhaps I am influenced by the belief that surgical treatment for this disease is only treatment of a secondary condition, and that our chief hope lies in being able to discover and treat the primary causes. In the meantime, surgical treatment, though it may represent only a temporary phase, has undoubtedly a sphere of usefulness. To employ it as a routine measure is, I believe, irrational, but when medical treatment fails or falters it shortens the period of invalidism, which is so serious a consideration in many patients that it more than counterbalances the added risk.

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THE IMPORTANCE OF POST-NATAL MATERNAL CARE.

COMPRISING A REVIEW OF THE ORGANIZATION AND WORK OF THE POST-NATAL CLINIC OF THE EDINBURGH ROYAL MATERNITY HOSPITAL.*

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It is the common experience of those whose work is concerned with the treatment of diseases peculiar to women that parturition is ultimately responsible for a considerable proportion of the disability with which they have to deal. The importance of childbirth in this regard is reflected in the large number of gynaecological patients who refer their complaint to a previous pregnancy or labour. It is an obvious corollary that the degree of skill and care with which the process of childbirth is conducted is an important factor in a woman's subsequent well-being. The prophylaxis of future invalidism, however, requires from the accoucheur not only that pregnancy and labour be so managed as to reduce to a minimum the incidence of trauma and infection, but also such careful supervision of the patient's convalescence as will best assist the processes of involution and repair and restore a maximum degree of bodily efficiency.

Whereas the claims of the expectant mother have of recent years attracted, and rightly so, a full measure of consideration, the need for a similar attitude of guidance and

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