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THYROTOXICOSIS: ITS MEDICAL ASPECTS*

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NOMENCLATURE

Despite the fact that some care was taken in choosing the title of this discussion, the term finally decided upon is perhaps still not very satisfactory. While the word "thyrotoxicosis" is sufficiently general to include in our deliberations, as was intended, conditions other than the syndrome which Graves described just one hundred years ago, it has the disadvantage that it postulates a basic fact which has never been established. There is no indisputable evidence that exophthalmic goitre owes its evolution in the main, or even in a lesser degree, to the circulation of disordered thyroid secretion. The same may be said of the symptoms variously classified under the terms "toxic goitre," "toxic adenoma." *Pace* certain textbooks whose authors or editors strive prematurely to substitute for non-committal names of diseases terms having precise pathological connotation, the postulate that exophthalmic goitre is an expression of hyperthyroidism is even less authenticated, whether on clinical or on experimental grounds. So long as this dilemma is recognized and due indulgence granted, I am unembarrassed.

Is There a Pathological Secretion?

I propose that we should consider under our heading of thyrotoxicosis the relation borne by the thyroid gland to the various clinical pictures met with as well as these clinical pictures themselves, rather than confine ourselves to the mere question of poisoning by a hypothetical thyroid dysfunction. Until we find some method of measuring the amount of thyroid secretion poured out into the blood stream—and at present we possess no such method—we shall not solve the main problem facing us in this matter.

There are facts which suggest that the thyroid hyperplasia which is the characteristic change in the fully developed picture of Graves's disease is not the primary, but a secondary, phenomenon. Certainly there is no quantitative relation between the degree of thyroid enlargement and the degree or the duration of the symptoms. These latter may be very severe and active in association with very little, or even with no, thyroid enlargement; but again, the symptoms may be mild and tending to quiescence in association with considerable hyperplasia. Nor is there any reason to believe that we have yet established any qualitative relation: by which I mean that there is no evidence that the secretion from gland tissue that is merely hyperplastic, diffusely fibrotic,

or the seat of adenomata, differs from that which is elaborated by a healthy gland. Nor, again, to complete the series of morbid anatomical changes in the thyroid which appear to have associations with metabolic increase and/or with sympatho-mimetic manifestations, is there evidence that the cells of an adenoma itself yield a pathological secretion.

PATHOGENESIS

In considering the pathogenesis of Graves's disease the use of the term "thyrotoxicosis," as already noted, lands us at the very centre of the problem. What is the *causa causans*? It remains hidden. As in so many other instances, Nature has revealed the results of a disease-process, but jealously guards the secret of the exact mechanism by which these results are evolved. We see the picture on the screen quite plainly, but the projector is hidden. That some poison is at work seems an irresistible conclusion. Especially suggestive in this connexion are the crises, often pyrexial, which are so alarming a feature and prognostically so serious. They surely give us a dramatic presentation of an intense toxæmia. There is no reason for believing them to be of microbic origin. Are they metabolic? Or are they due to the flooding of the circulation by some uncontrolled physiological hormone? What part in the pathogenesis of the disease is taken by iodine metabolism?

The removal of a large part of the thyroid gland in a chronic and established case of the disease, resulting, as it often does, in such a marked subsidence of the symptoms, suggests that the source of manufacture of the poison resides in the gland. But the actual proof of this hypothesis eludes us, despite painstaking research. Moreover, we must exercise great care in the argument at this point. Thyroidectomy may interrupt a vicious circle in the patient's interest, and so do good in quite another fashion than getting rid of the cause of the trouble. There are analogies bearing upon this possibility: splenectomy in "splenic anaemia" and the same operation in "acholuric jaundice." It is feasible that the missing clue may be found extrinsic to the thyroid. Indeed, such a possibility is generally regarded as probable. But it may be found to be extrinsic to the involuntary nervous system also, though it certainly appears as though this latter organ bulks largely in, at any rate, the earlier stages of the disease. Biochemistry linked with histology may be the solution—a field of discovery of enormous potential value, as we appreciate when we realize the unveiling of the reticulo-endothelial system, and its bearing upon the mechanism of Addisonian anaemia.

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Of the state of the thyroid gland itself, quite apart from the moot question of the exact relation which it bears to the syndrome in general, I do not propose to deal in detail. I accept, as being a convincing summary of the clinical and morbid histological findings, the conclusions arrived at by my surgical colleague who opens this discussion with me. The fact that so many different pathological conditions may be present in association with the syndrome we are discussing has induced some workers to discard the thyroid altogether as being indirectly concerned in a causative sense. Yet that the gland is intimately bound up with the pathogenesis of Graves's disease seems, on clinical grounds, indisputable. But the factor of metabolic increase has by some been discarded also. Indeed, certain of the recent analyses of this baffling syndrome remind me not a little of the devastating and uneconomical criticism of the cynical friend who gradually reduced the fishmonger's caption—"Fresh Fish Sold Here"—to no caption at all by the elimination of unnecessary words. There was no need for the word "fresh," he said, for surely he wouldn't sell stale fish; no need for the word "here," since his shop wasn't anywhere else; no need for the word "sold," because he didn't give the fish away; and no need for the word "fish," for it could be smelled two streets off. The exophthalmos may be only a symptom, the thyroid gland may be more sinned against than sinning, the involuntary nervous system may be stimulated from without and not from within, and the basal metabolic rate may be low rather than high. But the subtleties of too fine an analysis confuse, rather than clarify, our ideas, seeing that the basic data are as yet so meagre. The stubborn fact remains: Graves's disease exists for all to see: the syndrome repeats itself with increasing persistence and demands our attention. If we take our stand here we are on the sure ground of clinical medicine, and in my further remarks this is what I propose to do. I shall use the terms "Graves's disease" and "exophthalmic goitre" as synonymous.

The Clinical Picture

The known aetiological factors, the symptoms, and the course of the disease call for a few remarks. That there is a diathesis in Graves's disease is generally accepted. But whether the flaw resides in the involuntary nervous system or in the psyche, or in the endocrine balance, or in some other as yet unrecognized tissue or function, or in more than one of these, we do not know. Of the predisposing causes we know a little: sex, certain collateral familial conditions, and an "autonomic imbalance." Of exciting causes there are the sex epochs, there are psychic traumata, and there is focal sepsis. Or is it merely fashion which leads us to speak of the last-named? For myself, I have been very disappointed in the search for focal sepsis in Graves's disease, however thorough this search may have been. Associated endocrine defects are sometimes advanced as a contributory cause, but the evidence is entirely unconvincing. Is this fashion again? Or is the suggestion due to a desire to give support to the hypothesis that exophthalmic goitre is itself an endocrine disorder? Of this, however, there is no good evidence (*v.s.*).

To the original three symptoms observed by Graves—the exophthalmos, the tachycardia, and the goitre—Charcot added tremor. These constitute the cardinal features. Many others have been noted from time to time, among them various ocular changes, dermatoses, glycosuria, neuroses, psychoses, and manifestations of sympathetic instability such as flushing, sweating, and diarrhoea. Loss of weight is very common, though, as in diabetes, which is one of the familial associates, the patient may be fat rather than lean. Lesser degrees of

the disease are recognizable, and, given favourable conditions, these quite frequently abort.

An attempt has been made by some to segregate cases which present some of, or even all, the symptoms of Graves's disease, but which show no increase in the basal metabolic rate—a striking feature in the great majority of the established cases. It is proposed to use the term "autonomic imbalance" for those cases in which the basal metabolic rate is not raised. How far this segregation is justified, and what proportion of these cases pass on to what these observers would call true Graves's disease, remains to be seen. Granted that the basal metabolic rate, as a measure of metabolic activity, is of fundamental importance, too much weight must not be attached hurriedly to this criterion. The basal metabolic rate is raised in some conditions which are not, and do not tend to become, Graves's disease. On the other hand, some cases of Graves's disease, if we use the clinical standard, occur with normal, or even lowered, basal metabolic rate.

As regards the course of the disease, in the majority of cases the onset and the early stages are insidious. In a few cases the origin seems to be acute, or even abrupt; but here, as in some other diseases, such as diabetes and disseminate sclerosis, it is usually possible to trace a latent stage of the disease before the exacerbation arrives. When fully developed, and even when the patient is very ill indeed, the disease may subside completely and with no recognizable residues—a very striking experience. Or the established picture may remain long enough to render organic residues permanent, even though quiescence arrives. But, unfortunately, in a large proportion of the established cases the fire, even if it dies down somewhat, continues to smoulder. The patient becomes a chronic invalid, with at first functional and intermitting, and, later, organic and permanent, heart damage. In still other cases the fire, instead of dying out or dying down, blazes, and the patient succumbs to an intense and overwhelming toxæmia.

DIAGNOSIS

The diagnosis of Graves's disease may be very easy or it may be very difficult. The difficulty lies in a recognition of the early and the incomplete pictures. It is these which call for clinical acumen, and it is these which reward the observer so abundantly if he discovers them. The secret, if secret there be, lies in bearing the disease in mind when faced with an obscure case having nervous or metabolic features. Training in the observation of facies and behaviour is of paramount importance. Whenever these deviate from the average we should not rest until we have a positive, not merely a negative, explanation. The formula, "I failed to elicit any signs of organic disease," and the supposed comfort to be derived from it, have hidden many an early case of exophthalmic goitre, and will continue to do so for many years to come. In these days we tend to fall upon a patient too early after our first contact with him, so anxious are we to pass him through the mill of our routine examination of his various organs. Graves's disease in its early stages is a disease of the patient, and not of her organs. So let us give ourselves time to "stand and stare," as the poet has it. We shall then have a chance of observing if the patient is staring, and why. Be it observed that the "stare" is not merely, or perhaps not at all, a matter of exophthalmos: there are the enlarged palpebral fissures, the infrequency of blinking, the dilated pupils, and the immobile forehead. But there is also the manner of entering the room, the hot hand, quickly given and quickly withdrawn, the restlessness, the rapidity of movement, the lack of poise,

the excess of gesture, the record time spent in undressing and in dressing, the moist skin, and the flush on the neck and chest.

Unexplained loss of weight, especially in men who are past middle age, should always raise the question of Graves's disease. So also should certain changes in the patient's behaviour, whether noticed by others or—and this sometimes happens in highly conscientious and self-critical women—by the patient herself: unworried lack of control, irascibility, excessive show of the emotions, and the quick expenditure of an unaccustomed store of nervous energy without apparent fatigue.

Medical Treatment

In considering the treatment of Graves's disease the physician must concern himself with prevention whenever the diathesis is recognized: a thankless task, for, as a philosopher has truly observed, it is not to be expected that human beings will accept advice when they will not accept warning. And the fact that the potential victim of the disease is more often a woman than a man lessens the chance of much being accomplished in this direction.

The picture of the slighter manifestations of the sympatho-mimetic part of the syndrome—to use Dale and Barger's term—too often escapes detection, as already remarked. Yet if these "larval" types, or "formes frustes," are noted, the physician has a better chance than if committal symptoms had not declared themselves. Even so, his efforts seldom carry conviction. To some his suggestions savour too much of washing in Jordan; to others they constitute an intolerable interference with that round of excitement which entails so much psychological and nervous stress for many young people. The doctor is often accused of wanting to make his patient a cabbage. Yet for those who accept his control and co-operate with him there is undoubtedly a good promise of stabilization. The chief difficulty, next to the temperament of the patient, lies in securing the necessary relief for those who are forced by their economic position to earn their daily bread by jobs which make excessive demands upon their nervous system. Whenever possible—and this applies to all classes—the question of the patient's occupation should be carefully considered. Though it is not necessary that the patient should become a cabbage in order to attain physiological salvation, it may help him very materially to grow cabbages, or something equally useful. The more rustic the type of routine the better; it is no mere shibboleth that leads the doctor to preach the doctrine of "the simple life" to these patients.

If the symptoms persist in spite of controlling the patient's routine of life, and in all cases in which the full syndrome has developed, the degree of physiological and psychical rest should be absolute, and should be continued for at least three months. Bed is the only place where such rest can be guaranteed. A good deal of time can be wasted over compromises for the adoption of which most patients seek to win their doctor's sanction. To yield or not to yield is the test of the latter's experience of the disease. To secure rest of the mind a heart-to-heart talk of an entirely confidential nature is imperative, and it is best to assume the existence of some emotional hold-up, since this is so frequently present. The patient should be given confidence in her ability to get well, though the need for patience should not be concealed. It is better to discount anything by way of a royal road from the first.

If focal sepsis be present this should be eliminated as far as possible. Efforts at specific therapy based upon the hypothesis of the thyroid dysfunction, whether by the use of serum from thyroidectomized animals or from

animals inoculated with excess of thyroid secretion, have failed in the hands of most observers. There is no specific drug, though there are drugs that help: iodine certainly, and in all cases in which the thyroid is involved (but surely there is room for more research into the best methods of exploiting this drug to its best advantage); belladonna (introduced by Trousseau) in some; the bromides in others. Of quinine hydrobromide, which has had a vogue, I cannot myself give any good account. Digitalis appears to be unhelpful apart from cardiac dilatation.

Surgical Treatment

There remains the important question of partial thyroidectomy, a form of treatment which has so far justified itself of late years that debate on the main issue seems unnecessary. I am not unaware that this discussion has been staged largely in order that we may benefit from hearing the chief actor in the surgical drama. I will say at once that not only have I sought Sir Thomas Dunhill's expert help in this direction over a number of years but that I have learnt to value his judgement in the interest of my patients to a degree that sometimes quite seriously threatens to jeopardize my own! In what cases, therefore, and especially how, I shall leave my surgical colleague to consider. Suffice it to say that in my own experience the operation should be undertaken whenever the disease remains active after six months of carefully supervised medical treatment, and also in cases which relapse in spite of the patient's routine of life being adequately controlled. I agree, too, that the operation is indicated in all cases in which auricular fibrillation has developed, and that it is indicated still more absolutely when signs of congestive heart failure are present, whether the cardiac rhythm be so affected or not. To delay when any of these three criteria have arrived is to lose valuable time and to lessen the benefit which may otherwise be expected. The technique I leave in better hands. We should all desire that the procedure be as bloodless as possible, that every patient be allowed the benefit of her parathyroids, that the recurrent laryngeal nerves be left intact, and that as few cases of myxoedema be created as may be.

As for the immediate mortality, the difference between a patient being only chronically ill one day and very dead the next is so tragic and so striking—an experience that was not very uncommon until a few years ago—that it is a relief to know that this difference can be eliminated by careful preparation for the operation, by skilled technique in its performance, and by a form of anaesthesia which is competently chosen and as competently administered.

It is not without significance that the most striking results of thyroidectomy are seen in those cases which are advanced and in which the vicious circle is complete, always provided the load of the procedure is not more than the patient can carry. We must consider if the known benefits seen after total ablation of the thyroid in some cases of congestive heart failure throw light upon the rationale of subtotal thyroidectomy in Graves's disease. We must not omit to remember, in this connexion, the fact that surgeons tend to remove more and more of the gland, whether in one or two stages, and that some of them attribute to this change in stratagem and in the tactics involved the better results seen to-day as compared with those seen formerly. That I deal with the question of surgical treatment in even as much detail as I do is because I believe that if we can properly assess the criteria and the responses connected with this important procedure, we shall make a valuable contribution to the elucidation of what is at present a great mystery—the pathology of Graves's disease.