ETIOLOGY OF GRAVES' DISEASE

The trend of the literature of recent years is toward a conclusion that Graves' disease is essentially a hyperthyroidism. Various lines of evidence point to this conclusion and many well informed writers use the terms interchangeably. Perhaps the most significant fact justifying this practice is that the nitrogen metabolism runs high both in the disease and in true experimental hyperthyroidism. On the other hand, hypothyroidism, whether experimental or clinical, is characterized by a reduced nitrogen metabolism. The reduced metabolic level of a cretin can be raised by the feeding of thyroid substance or by such a purified derivative as thyroxin.

The simplest explanation of these facts would be that the thyroid furnishes a hormone which serves as a general cell stimulant. In the lack of this stimulant the cells function at a reduced rate. On teleologic grounds, however, such a belief is difficult to justify. Why should an organism or a cell be intrinsically adjusted to a low level and be dependent upon a more or less gratuitous stimulant to keep it up to "normal"? It would seem simpler that the cells would spontaneously function at the proper level. The real explanation is probably not so simple.

The crucial experiment to determine whether or not Graves' disease is actually the result of, or equivalent to, pure hyperthyroidism would obviously be to reproduce the symptomatology of the disease by the administration of thyroid material. Crotti, in his recent monograph, concludes that this has been satisfactorily done. Carlson, on the other hand, was unable in a series of careful experiments to produce the

picture of Graves' disease experimentally either in man or animals.

One observation which is apparently well attested renders untenable the conception that Graves' disease is a simple hyperthyroidism. This observation is that the disease may exist simultaneously with hypothyroidism. Thyroid secretion cannot be both augmented and depressed at the same time any more than can a physical object be simultaneously up and down. Various labored explanations of the paradox have been offered but they have the defect of leaving the contradictory fact still standing. Moreover, cases in which thyroid medication has proved beneficial in Graves' disease have been repeatedly described. The blood picture—a reduction of neutrophils, lymphocytosis and mononucleosis—is the same in both Graves' disease and myxedema. It would seem, then, that there is some element in common in the etiology of the two conditions.

The literature bearing upon this problem has recently been reviewed by Janney (1) in an extensive article in which an alternative theory is proposed. If, as he says, the hyperthyroid theory is discarded we have remaining as the only possible explanation dysfunction of the thyroid as the cause of Graves' disease.

The central idea in Janney's theory is that there is a toxic element in Graves' disease, the toxin being derived possibly from the thyroid hormone. This, according to Kendall, (2) contains the indol nucleus and might readily be split into intermediate decomposition products, one or more of which may be toxic. Under ordinary circumstances the hypothetical toxic

body would be further acted upon in the thyroid gland itself and be discharged only in some harmless or even beneficial form. On the other hand, the toxic body might be produced as a substance antecedent to the hormone proper. "It is possible that various factors might disturb the normal synthesis of the hormone, the result being the premature discharge of the toxic intermediary product into the circulation. The factors producing this condition might be disturbances in the nervous control of the thyroid metabolism, such as could be produced by fright, emotion, shock or direct organic injury such as trauma, thyroiditis, or again, histologic and gross changes in the parenchyma of the gland; that is, the well-known causes of exophthalmic goiter.

"The result of the premature discharge of the hypothetical toxic intermediary product would be an impoverishment of the gland of the thyroid hormone, which would explain the fact that Graves' disease goiters are poor in iodin, and especially in the active alpha-iodin proteins. The decreased production of the normal hormone due to the cause mentioned would tend to be accompanied or followed by signs of thyroid insufficiency."

It is on these grounds that Janney accounts for the occurrence in Graves' disease of such conditions as goiter, cutaneous symptoms (atrophy, pigmentation, scleroma, brittleness and loss of hair, trophic nail changes), abnormal depositions of subcutaneous fat (rare), osseus changes (imperfect ossification and epiphyseal union) fatty degeneration, especially of the heart and somatic musculature, mononucleosis, metabolic disturbances similar to or identical with

those in hypothyroidism—delayed glucose assimilation, creatinuria and growth disturbances in youthful cases. Certain symptoms such as weakness, loss of weight and creatinuria may properly be ascribed to either the presence in the blood of the hypothetical toxin or to a deficiency of the normal hormone. In exophthalmic goiter showing deficiency symptoms, judicious thyroid medication would, according to these views, be indicated. As to whether there actually is a toxic substance present in the blood of Graves' disease the evidence is relatively meager and not very convincing, but the matter is at least worthy of further careful research.

In any case, Janney's work will serve as an effective challenge to that numerous class of writers who use the terms Graves' disease or exophthalmic goiter and hyperthyroidism interchangeably. The trouble in Graves' disease may be that the chemical inlet to the thyroid is blocked rather than that the outlet or the gland capacity is enlarged.

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