Graves' Disease with Dissociation of Thyrotoxicosis and Ophthalmopathy*

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THERE are two characteristic, yet distinct, categories of symptoms in Graves' disease—the thyrotoxic and the ophthalmic. There is abundant evidence, both clinical and experimental, that eye involvement is not the direct result of thyrotoxicosis. On the clinical side there are the facts: first, that thyrotoxicosis can exist without eye signs; and, second, that eye signs, characteristic in all respects of Graves' disease, can exist with little or no thyrotoxicosis. On the experimental side it has been shown by several investigators that exophthalmos can be produced in thyroidectomized animals by the administration of extracts of the anterior lobe of the pituitary.[1,2]

None the less, clinical experience shows that usually thyrotoxic and ophthalmic manifestations vary in parallel. That is to say, they appear more or less together, get worse together, improve together, or remain stationary together.

Furthermore, it can be said that in the usual, classic or orthodox case of Graves' disease, the thyrotoxicosis constitutes the major therapeutic problem. If it is relieved, the eyes will take care of themselves. No special treatment is needed for them.

There are cases of Graves' disease, however, in which ophthalmopathy and thyrotoxicosis vary independently or inversely. The thyrotoxicosis may be lessening, or gone, while the eyes are getting worse. There may be a progressive ophthalmopathy at a time when the patient is in a frankly hypothyroid phase. In some cases there seems to be no thyrotoxicosis at all, but an important ophthalmopathy.

Such cases, which in our experience constitute perhaps four per cent of all Graves' disease, are of peculiar interest both on the theoretical side, because they may broaden our understanding of the morbid mechanism involved in Graves' disease, and on the practical side, because the treatment in them should, we believe, be quite different from that in the classic form of the disease. In them the eyes, not the thyrotoxicosis, present the major therapeutic problem. We have come to look upon them as consti-

*This paper is in the nature of a preliminary report. A complete report with statistical material is in preparation. Read before the Annual Meeting of the American Association for the Study of Goiter, Boston, Massachusetts, May 12 to 14, 1941.

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tuting a definite subspecies of Graves' disease. We do not claim that this subspecies is etiologically distinct from the classic type, though this is possible, but merely that its natural history follows a different pattern.

Within this subspecies we would include cases described in the literature under such terms as "malignant exophthalmos,"[3] "preoperative exophthalmos following thyroidectomy,"[4] "exophthalmic ophthalmoplegia,"[5] "postoperative progressive exophthalmos with low basal metabolic rate."[6] None of these terms is broad enough. The course is not always malignant; the development is not always postoperative; there is not always ophthalmoplegia. We have, therefore, sought a more inclusive label, and the best we can produce so far is that of "Graves' disease with dissociation of thyrotoxicosis and ophthalmopathy."* Because of the clumsiness of this term, however, we may henceforth, for convenience, refer to the "special ophthalmic type" in contrast to the "classic type" of Graves' disease.

The major clinical characteristics of the special ophthalmic type are as follows:

1. Prominence of ophthalmic symptoms. These patients often first consult the ophthalmologist, thinking there is nothing wrong with them save their eyes.

2. Mild to absent thyrotoxicosis. When present, ease of control of thyrotoxicosis.

3. Usually rather little thyroid enlargement. Sometimes none.

4. Relatively more frequent in males. Instead of a ratio of about four females to one male which pertains in our clinic for all toxic goiter, the ratio in the special type of Graves' disease is three females to two males.

5. Superstandard iodine response, often to minus levels of basal metabolic rate.†

6. Ophthalmopathy tends to become aggravated after thyroidectomy.

7. Sometimes at least, ophthalmopathy improves on the administration of thyroid.

In addition to these clinical characteristics, certain laboratory evidence has been obtained which also sets the special ophthalmic apart from the classic type.

8. Collection of administered iodine by the thyroid gland, as measured by means of radioactive iodine, has been shown by Hertz and Roberts[9] to fall at a significantly lower level in the special than in the classic types. Urinary excretion of administered labelled iodine is greater in the special type.

9. Bioassay for thyrotropic hormone in the urine has been found by

*This term has been criticized as denoting merely the eyeball, whereas the lesion involves the entire contents of the orbit. We find, however, that ὀφθαλμός means eye, and that eye means the organ of vision. We submit that "organ of vision" includes not only the eyeball, but its appurtenances as well. We shall use the term in that sense.

†By standard iodine response we mean the type of response shown by the family of curves in Means and Lerman, 1938,[7] or Means, 1937.[8]

Hertz and Colver[10] to be persistently positive in cases of the special type, but negative in classic Graves' disease and in normal persons.

10. The protein-bound iodine level of the blood in cases of the special type has been found by Salter and Hertz[11] to be essentially normal, whereas it is characteristically elevated in the classic type.

The kind of eye signs prevailing in the special ophthalmic type of Graves' disease tends to differ from that in the classic type. In the classic type the most conspicuous features are exophthalmos, lid lag, lid retraction and signs of the sort described in the older literature. In the special type the accent is on edema and irritative phenomena. There may be relatively slight proptosis, but marked periocular edema, chemosis of the conjunctivae, sometimes with massive swelling. Injection of the conjunctivae is common and the patient complains of smarting and excessive tearing. Often a thick ridge of edematous tissue above the upper lid, projecting like a finger toward the inner canthus, as described by Naffziger,[12] is present. Opthalmoplegia is common in the special ophthalmic type and resulting visual symptoms such as diplopia.

The *pathogenesis* of the ophthalmopathy in either the classic or special ophthalmic type of Graves' disease is obscure. The weight of evidence is against its being the direct result of sympathetic overactivity in either type.[13,14,15] That fluid accumulation in the orbit, or edema of orbital tissues, plays an important role was suggested as early as 1860 by Jones,[16] and in 1891 Boddaert[17] concluded that edema of the retrobulbar tissues, secondary to hypervascularization, causes the protrusion. Of recent years the edema, or swelling, theory has gained ground steadily. Moore,[18] in 1920, in a case of the malignant variety, incised the conjunctiva and scooped out as much orbital fat as possible. This seemed to him edematous and the extrinsic muscles were greatly swollen. Thomson,[19] also in 1924, who obtained histologic evidence in three cases of the malignant sort, concluded that "exophthalmos in exophthalmic goiter is due to a localized edema in the posterior part of the orbit which for some unknown reason, if sufficiently prolonged, is followed by connective tissue proliferation and permanent thickening of the orbital tissues." The edema, it seems, becomes brawny. Thomson's work clearly indicates that the ophthalmopathy, which obviously for a time is capable of improvement, or recovery, may finally reach an irreversible stage—the fibrosis which he finds being the sign of irreversibility. Naffziger,[12] who in 1931 described the operation for decompression of the orbit, reported great swelling of the extrinsic muscles in cases of malignant exophthalmos,* and Benedict,[22] in 1939, remarked that "the only logical explanation of exophthalmos in hyperthyroidism yet proposed is that of edema of all the soft tissues or the orbit outside of the eyeball." He was not able to suggest a reason for this collection of fluid.

It seems to us that the reason is to be sought by identifying the ele-

*Subsequently similar eye muscle lesions have been produced experimentally by injection of T. S. H. by Smelser,[2] Paulson[20] and Aird.[21]

ments involved in the total endocrine imbalance, which we believe Graves' disease to be. Certainly there is a balance between the anterior pituitary and its thyrotropic, or thyroid-stimulating hormone, which following Rawson[23] we may call T. S. H., and the thyroid and its hormone, which in addition to its better known actions has of late been shown to exert an inhibiting effect upon the pituitary.[24]

When the balance between these two hormones, which undoubtedly exists in health, becomes disturbed in disease, various results are possible. Either an excess or diminished supply of thyroid hormone may be delivered to the tissues, with resulting hyperthyroidism on the one hand, or hypothyroidism on the other. The hormones in question, however, are concerned not alone with rate of metabolism but also with water balance. T. S. H., like certain other hormones such as estrin, promotes water storage. Thyroid hormone promotes diuresis.*

Undoubtedly the ways in which hormonic balance can be upset in disease are several, and we do not find it difficult to believe that in certain cases of Graves' disease the nature of the imbalance is such that its most conspicuous result is water storage, which in the case of the orbit, because of the confined nature of the space, has particularly disastrous consequences. Final identification of the nature of the imbalance in any form of the disease will depend upon measuring the rate of manufacture of the several hormones, their concentration in the blood stream, and the capability of their end-organs to be stimulated by them. Work along these lines is in progress. In the meantime much can be learned from the clinical study of the varied relationships of eye signs to thyrotoxicosis and sooner or later it may become possible to fit the phenomena observed into a known hormonology.

The *plan of treatment* which we have been following in the special ophthalmic type of Graves' disease of late years, is based upon the theory of pathogenesis just outlined.

The therapeutic attack, we believe, should be aimed to relieve orbital swelling, not thyrotoxicosis, which as we have said may be absent, and this attack furthermore should not be by local measures alone, but by measures designed to break the vicious circle and restore hormonic balance. More specifically, measures promoting depletion seem indicated and those promoting water retention, contraindicated.

The agent most definitely indicated is thyroid hormone and the measure most definitely contraindicated is thyroidectomy. The former causes diuresis, the latter promotes water retention. We concede, of course, that sometimes a significant degree of thyrotoxicosis, one demanding treatment

*Pertinent in this regard is the as yet unpublished study by R. H. Williams and J. L. Whittenberger, at the Thorndike Memorial Laboratory, Boston City Hospital, in which it was shown that total body water is (a) increased in rats by thyroidectomy; (b) increased in thyroidectomized rats by the administration of T. S. H.; and (c) that the actions of T. S. H. and thyroid hormone on the total body water of such rats are antagonistic.

per se, may coexist with what seems clearly a malignant type of ophthalmopathy. Under these circumstances there is no gainsaying that thyrotoxicosis must be dealt with. But even so, we should prefer irradiation of the thyroid to ablation, because its effect is exerted more slowly, thus giving more time for readjustment and consequently subjecting the eyes to less risk of acute exacerbation of their disorder.[25] We would resort to thyroidectomy when faced with a bad eye situation only when forced to it by failure to control thyrotoxicosis by other means.

If the theory of the role of T. S. H. is correct, irradiation of the pituitary would be logical. We have seen striking benefit from this in one case—the only one so treated—but whether it was a matter of cause and effect or chance association, we are not prepared to say. The patient in whom we used it developed a progressive ophthalmopathy following thyroidectomy at a time when the basal metabolic rate was definitely subnormal. Bitemporal hemianopsia was demonstrated and interpreted as due to anterior pituitary swelling. Normal fields were obtained following the irradiation to the pituitary.

If thyroidectomy is contraindicated in these special ophthalmic cases, then preoperative recognition is very important. This differential diagnosis, the special ophthalmic from the classic type, we now routinely try to make. It depends upon the criteria enumerated earlier.

Having made the diagnosis of the special ophthalmic type, our usual treatment would be first to hold the basal metabolic rate as low as it will go by iodine administration and add to this as large a ration of thyroid as can be given without producing hyperthyroidism. The metabolic action of the two agents cancel out, but it is the diuretic action of thyroid we are after, and that is not opposed by iodine.

At all times the eyes must be safeguarded in every way. Their condition must be carefully followed and local measures used as indicated. If and when either the integrity of the conjunctiva or cornea is threatened, or if vision is diminishing, then orbital decompression should be resorted to. This is, of course, a palliative procedure, but it may be eye-saving and even life-saving.

In conclusion we would like to record the opinion that while subtotal thyroidectomy after full iodinization is probably the best treatment now available in most cases of Graves' disease (those conforming to what we have called the classic type), it may be bad treatment in the small group for which we have used the term "Graves' disease with dissociation of thyrotoxicosis and ophthalmopathy" (special ophthalmic type). Usually in these there is no need for thyroidectomy to correct the thyrotoxicosis, and there is considerable evidence that it is more likely to injure than help the eyes. We have indicated how the special type may be recognized preoperatively.

REFERENCES

1. Marine, D. and Rosen, S. H.: Proc. Soc. Exper. Biol. & Med., 30:901, 1933.
2. Smelser, G. K.: Am. J. Ophthal., 20:1189, 1937.
3. Jensen, V. A.: Acta Ophthalmologica, 18:1, 1940.

4. Thomas, H. M., Jr. and Woods, A. C.: Bull. Johns Hopkins Hosp., 59:99, 1936.
5. Brain, W. R. and Turnbull, H. M.: Quart. J. Med., 7:293, 1938.
6. Ginsburg, S.: Ann. Int. Med., 13:424, 1939.
7. Means, J. H. and Lerman, J.: Ann. Int. Med., 12:811, 1938.
8. Means, J. H.: The Thyroid and Its Diseases, Philadelphia, Lippincott, 1937, p. 339.
9. Hertz, S. and Roberts, A.: Abstract J. Clin. Invest. Proceedings of Am. Soc. for Clinical Invest., 1941. In press.
10. Hertz, S. and Colver, T.: Bioassay for Thyrotropic Hormone in the Differential Diagnosis of Two Types of Graves' Disease. In preparation.
11. Salter, W. T. and Hertz, S.: Blood Iodine Determinations in Two Types of Graves' Disease. In preparation.
12. Naffziger, H. C.: Ann. Surg., 94:582, 1931.
13. Pochin, E. E.: Clin. Sci., 4:79, 1939.
14. Pochin, E. E.: Clin. Sci., 4:91, 1939.
15. White, J. C. and Smithwick, R. H.: Autonomic Nervous System. Anatomy, Physiology and Surgical Application, 2nd Edition, New York, 1941.
16. Jones, C. H.: Lancet, 2:562, 1860.
17. Boddaert, R.: Bull. Acad. Roy. de Med. de Belg., 5:690, 1891.
18. Moore, R. F.: Lancet, 2:701, 1920.
19. Thomson, E. S.: Am. J. Ophthal., 7:27, 1924.
20. Paulson, D. L.: Proc. Soc. Exper. Biol. & Med., 36:604, 1937.
21. Aird, R. B.: Arch. Ophthalmol., 24:1167, 1940.
22. Benedict, W. L.: In discussion on Paulson, D. L.: Proc. Staff Meet. Mayo Clinic, 14:832, 1939.
23. Rawson, R. W.; Sterne, G. D. and Aub, J. C.: Changes in Thyrotropic Hormone Activity after In Vitro Exposure to Thyroid and Other Tissues. In preparation.
24. Membrives, J. R.: Hipofisis y Tiriodes, Buenos Aires, 1938.
25. Soley, M. H.: Exophthalmos in Patients With Various Types of Goiter (Presented at the Annual Meeting of the Association for the Study of Internal Secretions, Atlantic City, May 2, 1941).