THYROID DISEASE AND GLAUCOMA*†

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ONE of the earliest reports on the association of thyroid dysfunction and glaucoma appeared in the *Guy's Hospital Reports* when Brailey and Eyre (1897) described five cases of thyrotoxicosis in young women who all exhibited signs of glaucoma. An abstract appeared in the *Ophthalmic Review* in 1901 and the Editorial expressed scepticism of the findings. Further reports of an association between thyroid disease and glaucoma have appeared in the literature, but the association remains ill-defined, particularly as glaucoma has been associated at times with thyrotoxicosis and at other times with myxoedema.

It is not unreasonable to expect that thyroid dysfunction might influence intra-ocular pressure (IOP) since other hormones can do so—those associated with menstruation, pregnancy (Paterson and Miller, 1963), and hypercorticalism (Linnér, 1959; Bernstein and Schwartz, 1962; Alfano, 1963; Lerman, 1963; Perkins, 1965a) for example.

The possible ways in which disease of the thyroid might influence IOP are:

(1) Through thyroxine, which might have a direct influence on the IOP. In this case we should expect to find a difference between the IOPs of patients with hyper- and hypothyroidism, and also that the IOP would vary in the individual according to his thyroid function.

(2) The association of thyroid dysfunction and glaucoma could be a manifestation of some hypothalamic activity, either directly or *via* the pituitary, acting on both the thyroid and the eye at the same time. The following diagram sums up some of these possibilities:

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(3) Glaucoma and thyroid disease may occur in persons with a particular genetic make-up. The known familial incidence of both thyrotoxicosis and glaucoma suggests that genetic factors are important in both conditions.

Clinically it seems fairly well accepted that patients who develop congestive glaucoma fall into a broad category of so-called neurasthenics, and thyrotoxic patients have been similarly classed. Furthermore, the onset of thyrotoxicosis after an emotional disturbance is well recognized clinically. Using this as circumstantial evidence, Fridenberg (1920, 1924) speculated on the possibilities of endocrine imbalance as an aetiological factor in glaucoma. Using a similar argument, Magitot (1947) suggested a hypothalamic disturbance, a view still held by many ophthalmologists, particularly in Europe.

Of the evidence in support of an association between thyrotoxicosis and glaucoma, the report of Vasilieva (1965) is the most dramatic. He examined 53 cases of hyperthyroidism and found that all had raised ocular tension, which was proportional to the degree of thyrotoxicosis. Jain (1957) reported a case of thyrotoxicosis, the onset of which was almost simultaneous with that of glaucoma, and Ambrosio (1958) reported a case of bilateral congestive glaucoma following thyroidectomy. However, in Jain's case, the documentation was incomplete and the case was complicated by heterochromia, and the events in Ambrosio's case were open to other interpretations. Again, Saxena, Crawford, and Talbot (1964), reviewing a series of thyrotoxicosis in childhood, found a case associated with buphthalmos, an association of two rare diseases which suggested a common aetiology.

Leydhecker (1960), after reviewing the literature, came to the conclusion that the evidence for an association between glaucoma and thyroid disease was equivocal. Amongst the authors quoted was Léopold-Lévi (1931) who noted the hypotensive action of thyroid extract on the IOP of his glaucoma patients and quoted Hertel and Fuchs in support of this finding.

More recently Gördüren (1962) reported six cases of simple goitre in patients under 40 years of age, all of whom had ocular hypertension which did not amount to definite glaucoma. The basal metabolic rates of these patients were normal or raised but none required antithyroid therapy. Rogova (1964) reported a group of 105 patients with endemic goitre and found that 13 per cent. had a raised IOP which was directly related to the degree of hyperthyroidism. More recently still, McLenachan and Davies (1965) found that 45 of 100 cases of open-angle glaucoma had some form of thyroid dysfunction which was manifest at the time of diagnosis of the glaucoma. Of these, sixteen were said to be hyperthyroid and sixteen to be "myxoedematous". Unfortunately no details were published of the exact criteria on which the diagnosis of the thyroid conditions was based. The same authors went on to postulate that an alteration in the mucopolysaccharide in the inter-trabecular spaces might play some part in the aetiology of open-angle glaucoma. An acid mucopolysaccharide is deposited in myxoedema (Gabriclove and Ludwig, 1957) and in a localized form in thyrotoxicosis (Trotter and Eden, 1942; Watson and Pearce, 1949). Furthermore, there is evidence that those cases with pre-tibial myxoedema show the highest incidence of eye lesions such as exophthalmos and ophthalmoplegia (Hamilton, Schultz, and de Gowin, 1960). So far it has not been possible to demonstrate a mucopolysaccharide in the inter-trabecular spaces in

human eyes routinely and both Zimmerman (1957) and Ashton (1960) are agreed that it can only be found in eyes which have contained a melanoma. However, Bárány (1954) has shown that the resistance to the outflow of aqueous in animal eyes can be reduced by half if hyaluronidase is added to the perfusion fluid. Pending the examination of eyes from patients with myxoedema the problem remains unsolved.

There is no evidence that the hypothalamus directly controls the IOP although it can probably exert some influence on it. Gloster and Greaves (1956, 1957) found a small rise in IOP independent of changes in vasculature or extra-ocular muscle tone by direct stimulation of some areas of the cat's diencephalon.

It is also conceivable that the hypothalamus can act through the pituitary as an intermediary. Indirect evidence is mounting that the pituitary may in some way be associated with glaucoma. Zondek and Wolfsohn (1947) had remarked on the coincidence. Amongst cases referred to their Medical Clinic, they reported 22 of 'primary' glaucoma which had some form of pituitary dysfunction, including six cases of pituitary tumour. Recently, van Bijsterveld and Richards (1964) reported three cases of pituitary tumour with open-angle glaucoma and Howard and English (1965), reviewing 74 cases of acromegaly, found amongst them an incidence of open-angle glaucoma of 10 per cent., which is a good deal higher than the incidence of 2-3 per cent. in the general population.

It is now generally recognized that patients with endocrine exophthalmos often have a raised IOP as measured by tonometry. Both Pesme (1947) and Rosselet (1960) reported isolated cases which had developed glaucoma and malignant exophthalmos. Vanni (1959) claimed that, in oedematous forms of exophthalmos, one could observe masked forms of ocular hypertension, and he later tried to correlate the degree of ocular hypertension with the retrobulbar resistance. It was postulated that venous obstruction might play a part (Vanni and Vozza, 1960). That venous obstruction can be a factor in raising the IOP is supported by the finding of ocular hypertension in cases of mediastinal compression on the superior vena cava, which is improved by the relief of the obstruction (Lévy and Lobstein, 1958).

The problem has been further elucidated by Weekers and Lavergne (1958), who at first thought that there was an association between glaucoma and so-called thyrotrophic exophthalmos. They also found that the ocular rigidity in such cases was much lower than normal (Weekers and Lavergne, 1957)—comparable to the levels found in high myopia—in thyrotrophic as opposed to thyrotoxic forms of exophthalmos. Thus, when the correction for ocular rigidity was made, the number of cases with raised IOP was even greater. However, they soon realized that this was an erroneous finding due to the fact that the Schiøtz tonometer readings were taken when the eyes were in elevation (Weekers, Prijot, and Lavergne, 1959). In a subsequent study, they found that the ocular tension in these cases was normal until elevation was attempted (Weekers, Prijot, and Lavergne, 1960); this work has been amply confirmed by that of Draeger (1960) and Böck and Stepanik (1961).

Thus it would seem that, apart from Vasilieva (1965) and McLenachan and Davies

(1965), who found an association between thyroid dysfunction and glaucoma, the only other large groups showing this association comprised cases of endemic goitre in which the disorder is due either to a dietary deficiency in iodine or to a genetic factor and is not a disorder of the hypothalamic-pituitary-thyroid axis.

Material and Methods

In the present study, patients visiting an endocrine clinic were screened for the presence of glaucoma. Their optic discs were examined and the ocular tension measured using the hand-held applanation tonometer described by Perkins (1965b). A total of 155 patients was seen over a period of 6 weeks. Patients were selected at random and at the time of tonometry the diagnosis of the thyroid condition was not known to the examiner. Both new and follow-up cases were included and the findings were later compared with their thyroid state when this had been confirmed, if necessary by the result of laboratory tests. The usual tests used in this clinic were:

- (1) Protein-bound iodine (normal 3.5–6.8 $\mu\text{g./100 ml.}$).
- (2) Triiodothyronine uptake (normal 90–100 per cent.) (*cf.* Farran and Evans, 1965).
- (3) Radioactive iodine uptake as measured by the 48-hr urinary excretion.

The assessment of the thyroid state was based, apart from the clinical impression, on two or more laboratory tests. Of the 155 patients, 25 were thyrotoxic and the hyperthyroidism was easily definable. There were thirteen in the hypothyroid group but in only four was the hypothyroidism gross. The rest were euthyroid at the time of examination. 49 were originally thyrotoxic but had had either radioactive iodine ablation or thyroidectomy; thirteen were originally hypothyroid and were having replacement therapy; 43 had non-toxic goitres, the majority of which had been removed by operation. The rest attended for other reasons (Table I).

TABLE I
DIAGNOSIS IN 155 CASES

Total Number of Patients	Hyperthyroid	Hypothyroid	Euthyroid, originally		Simple Goitre with or without Operation	Carcinoma	Hashimoto's Disease	Other
			Hyperthyroid	Hypothyroid				
155	25	13	49	13	43	6	4	2

The average age for the whole group was 46 years. This is a little higher than one might expect in a thyroid clinic and the reason is that a number of those included were patients who had had radioactive iodine therapy and were attending the follow-up clinic. The average age for the thyrotoxic group was 40 (70 per cent. female), while the average age of the hypothyroid group was 54 (85 per cent. female) (Table II, opposite).

Results

The distribution curve of the ocular tension of the whole group of patients did not differ significantly from the general population and was Gaussian in character. The curve for the hyperthyroid group followed closely the curve for the group as a whole and though the number of hypothyroid cases was small the peak of the curve fell in the same range as the curves for the other groups (Figure, opposite).

TABLE II
MEAN OCULAR TENSION, AGE, AND SEX INCIDENCE IN 155 CASES

Group		Total	Hyperthyroid	Hypothyroid
Tension (mm. Hg)	Mean	16	16.8	16
	Standard Deviation	3.5	4	2.8
	Sample Variance	12.4	16.28	8.15
Average Age (yrs)		46.5	40	54
Sex Incidence (Per cent. Female)		81	70	85

The mean tension for the entire group was 16 mm. Hg (S.D. 3.5), for the hyperthyroid group 16.8 mm. Hg (S.D. 4.1), and for the hypothyroid group 16 mm. Hg (S.D. 2.8) (Table III). The standard errors of difference in means between the groups were as follows:

Whole v. Hyper group = 0.6
Whole v. Hypo group = 0.59
Hyper v. Hypo group = 1.001.

There is therefore no significant statistical difference between mean tensions in the three groups.

TABLE III
MEAN TENSION BY AGE GROUP

Age Group (yrs)	< 40	40-60	> 60
Per cent. of Whole Group (155)	35	43	21
Mean Tension	16.5	15.9	15.5
Per cent. of Euthyroid Group (117)	33.5	43	23.5
Mean Tension	16.3	15.6	15.7

In the whole group there were only two cases of glaucoma:

The first was a man who was known to have narrow-angle glaucoma discovered 3 years before the onset of thyrotoxicosis. At the time of examination the tensions were controlled on miotics.

The second was a man aged 54 who presented with thyrotoxicosis. Before having RAI therapy he was found to have tensions of 20 mm. Hg (right) and 34 mm. Hg (left), normal optic discs, and normal fields. The anterior chamber was deep in both eyes but gonioscopy revealed a prominent iris roll which obscured most of the left angle and some of the right. The outflow facility was 0.27 (right) and 0.09 (left), the latter being much reduced. The tension in the left eye was controlled finally on gutt. pilocarpine 4 per cent. and eserine 0.5 per cent.

There were seventeen patients with exophthalmos, which was unilateral in two, and all had a normal ocular tension with the eyes in the primary position. 56 per cent. of eyes showed an increase in tension of more than 4 mm. Hg and 25 per cent. an increase of 10 mm. Hg or more when elevation was attempted. All eyes with ophthalmoplegia showed this increase. There was one case of malignant exophthalmos which had oedema of the disc in both eyes and needed surgical decompression. Two other cases had had surgical decompression for malignant exophthalmos and both showed a rise in pressure of more than 4 mm. Hg on elevation even though the exophthalmos had been very much reduced. This is in accord with the observation of Draeger (1960).

Discussion

These results suggest that the distribution of ocular tension in a group of patients with thyroid disease does not differ significantly from that of the normal population. In 155 cases there were only two cases of glaucoma, which is within the incidence for the general population. Furthermore, the ocular tension of the hyperthyroid group did not differ significantly from that of the hypothyroid group although the number of patients in the latter was relatively small.

In our series the thyroid disorder had been present for more than 5 years in 31 per cent. of cases and for more than 10 years in 13 per cent. An extra-thyroid factor acting on the thyroid gland and the eye would be expected to continue to exert its influence on the eye in spite of treatment of the thyroid condition, but in the patients whose thyroid disease had commenced over 10 years previously (mean duration 17 years) and whose mean age was 57, the mean ocular tension was only 15 mm. Hg.

Failure to find any correlation between thyroid state and ocular tension does not exclude an association between glaucoma and thyroid disease. The incidence of ocular hypertension and glaucoma rises with age and, as the mean age of the patients seen in this study was 46 years, it is possible that the ocular changes have not yet become manifest. Only 21 per cent. of our patients were over 60 years of age, compared with 81 per cent. of the cases of open-angle glaucoma reported by McLenachan and Davies (1965) (Table III).

This survey suggests that a direct influence of thyroid or pituitary hormone on the ocular tension is unlikely, and that any link between thyroid disease and glaucoma is more likely to be genetic in origin, especially since it has been found that there is a higher incidence of PTC (phenylthiocarbamide) non-tasters in patients with multi-adenomatous goitre and in those with glaucoma.

Summary

The ocular tension of 155 patients with thyroid disease was measured with an applanation tonometer. No significant difference in mean tension was found between hyperthyroid and hypothyroid patients, and the distribution of ocular tensions in the group as a whole was similar to that in a normal population. Two of the 155 patients were found to have glaucoma, an incidence comparable with that reported in most population surveys.

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