COMMUNICATIONS

EXPERIENCES WITH MALIGNANT EXOPHTHALMOS*

RELATIONSHIP OF THE CONDITION TO THYROTOXICOSIS AND TO THE PITUITARY THYROTROPIC HORMONE

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Anyone confronted with a case of severe malignant exophthalmos, who searches the literature for guidance in therapy, must soon perceive the confusion of thought and experience that exists regarding this condition, the solution of which is one of the most pressing problems facing thyroid surgery today. By some, the administration of thyroid is claimed to cure the condition, while others recommend such measures as orbital decompression, the administration of sex hormones, and irradiation of the pituitary. None of these remedies, however, produces consistently good results, and there are authorities who will disclaim each one of them. Even the aetiological basis of the condition is in dispute. Undoubtedly there is a connection between malignant exophthalmos, the secretion of the pituitary thyrotropic hormone, and thyrotoxicosis, but the relationship seems to be indirect and the connecting linkages are unknown. The current theories concerning the condition will, therefore, be reviewed.

Fortunately malignant exophthalmos is uncommon. It may be defined as that type or phase of Graves' disease in which the eye component is more noticeable than the thyrotoxic (Means, 1948). In the common form of "exophthalmic goitre" there may be, besides a goitre and manifestations of thyrotoxicosis, a retraction of the upper eyelid which gives the appearance of stare. The degree of protrusion of the eyeballs however is slight, and not sufficient to endanger them. Further, the stare recedes after thyroidectomy pari passu with the relief of thyrotoxic symptoms; but in a very small minority of patients the protrusion of the eyeballs may increase and be associated with varying degrees of weakness of the oculomotor muscles (ophthalmoplegia). Indeed the protrusion may become so marked that the eyeball is endangered from exposure of the cornea. We then have the condition known widely as "malignant exophthalmos" (Rosenbaum, 1937; Robertson, 1945), and also under other
names such as "exophthalmic opthalmoplegia" (Brain, 1938; Mann, 1946), "hyperophthalmopathic Graves' disease" (Means, 1948), "progressive exophthalmos" (Naffziger and Jones, 1932; Haik, 1944), "thyrotropic exophthalmos" (Mulvany, 1944), "exophthalmos of endocrine origin" (Martens, 1947), "chronic orbital myositis" (Offret, 1939; Dunnington and Berke, 1943) and "pseudotumour of the orbit" (Hope-Robertson, 1947).

This range in nomenclature indicates that there are many variations in the way this condition may manifest itself. The term "malignant exophthalmos" seems to us appropriate because it is a fair description, and yet is non-committal regarding aetiology.

There are other distinctions between malignant exophthalmos and exophthalmic goitre. The former occurs at or close to the climacteric and affects males more frequently than females, whereas the latter occurs usually in young adults and is much commoner in women than in men (Mulvany, 1944; Martens, 1947). Malignant exophthalmos, although sometimes associated with a toxic goitre, can occur without enlargement of the thyroid and without thyrotoxicosis. Indeed, it quite often follows thyroidectomy for toxic goitre, the nervousness and irritability of thyrotoxicosis being relieved, but the ocular protrusion becoming exaggerated. Malignant exophthalmos and exophthalmic goitre therefore appear to behave as two distinct, although probably related, conditions.

Now the eyes signs of Graves' disease are of two distinct types. First is the stare produced by retraction of the upper eyelid, which characterizes exophthalmic goitre and which disappears when the thyrotoxic symptoms are relieved. There is no agreement as to its mechanism. Pochin (1939) considers it to be due to spasm of the levator palpebrae superioris, a striated muscle supplied by the third cranial nerve, and he believes that sympathetic over-activity has nothing to do with it. Mulvany (1944) however considers that lid-retraction is due to spasm of Muller's palpebral muscles, which are smooth muscles forming part of Landström's circular muscle and innervated by the sympathetic. Second is the state of true protrusion of the eyeballs. This protrusion is independent of lid-retraction, for after thyroidectomy it may actually advance while lid-retraction is receding (Soley, 1942; Salter and Soley, 1942; Mulvany, 1944).

Rundle and Pochin (1946), in analysing post mortem the orbits of seventeen cases of thyrotoxicosis, found an increase in the fat content, both within the orbital muscles increasing their bulk and within the fibro-fatty interstitial tissue. They felt it was this increase in fat which displaced the eyeball forward. Whether this same increase of orbital fat occurs in malignant exophthalmos as in toxic goitre remains to be confirmed, but it is attractive to feel that the condition in the former is but an exaggeration of what occurs in the
latter. Rundle and Wilson (1944) have added rather convincing evidence that the swelling of the eyelids so commonly seen in Graves' disease is also due to deposits of fat and not to oedema. Means (1948) however, in commenting upon this, points out that, although oedema may be absent during the milder phases of the exophthalmic process, it is certainly present in the orbital structures during the severest phases, no example of which is included in Rundle and Wilson's material.

That the extrinsic muscles of the eyeball are swollen in malignant exophthalmos to from three to eight times their normal size, and that this swelling by displacing the eyeball is the major factor in producing exophthalmos, was first shown by Naffziger who devised the operation of orbital decompression for the condition (Naffziger and Jones, 1932; Naffziger, 1933 and 1938). In Naffziger's material the muscles showed oedema and round-cell infiltration, often of a peri-vascular pattern, with loss and destruction of muscular fibres and an increase in the fibrous tissue, but some surgeons have not observed swollen orbital muscles during decompression of the orbit, nor have they seen appreciable benefit follow this operation (Robertson, 1945; see also our Case 6, p. 266).

Concerning aetiology, it is now well established that exophthalmos can be produced in experimental animals by the administration of pituitary extracts but not by thyroxin (Brain, 1938; Mulvany, 1944; Salter and Soley, 1944; Mann, 1946; Dobyns, 1946; Martens, 1947). Whether these results can be applied to Man, with his differently constructed orbit, is not certain. None the less, several authorities have argued that the proptosis of malignant exophthalmos is due, not to the thyroid hormone, but to an excess secretion of the pituitary thyrotropic hormone (Brain, 1938; Means, 1942 and 1944; Salter and Soley, 1944; Robertson, 1945; Mann, 1946; Martens, 1947). Thyroxin and pituitary thyrotropin are known to be antagonistic, both in vivo and in vitro, and several observers have reported remissions in cases of malignant exophthalmos after the administration of thyroid (Mulvany, 1944; Salter and Soley, 1944; Robertson, 1945; Mann, 1946), though others have seen no benefit from thyroid therapy (Thomas and Woods, 1936; Means, 1948). Again, it should be remembered that in myxoedema, where an increase of pituitary thyrotropin usually occurs in the blood, exophthalmos does not develop. (Purves and Griesbach, 1949).

Recognizing these and other difficulties, Mulvany (1944) has attempted to distinguish two types of exophthalmos, which he designates as "thyrotoxic exophthalmos" and "thyrotropic exophthalmos" respectively. Thyrotoxic exophthalmos, he considers, is due primarily to excess thyroxin which leads to a myasthenic weakness of the extra-ocular muscles by causing a widespread
degeneration of the nerve fibres that supply them. This weakness, together with retraction of the upper eyelid consequent upon sympatheticotonia, permits the eyeball to slip forwards when the palpebral fissure is widened. Thyrotropic exophthalmos, he considers, is due to an excess of pituitary thyrotropin causing an inflammatory change in the orbital muscles that increases their bulk and so displaces the eyeball forwards. This latter type of exophthalmos occurs independently of thyrotoxicosis. Mulvany makes many points of distinction in the histological features and symptomatology of his two types, and also advocates different lines of treatment. For the thyrotoxic type he recommends, that treatment should be directed towards relieving thyrotoxicosis, either by thyroidectomy or by the administration of iodine solutions. In thyrotropic exophthalmos, however, thyroidectomy is contraindicated as it aggravates the condition, and instead treatment should be by the administration of thyroid substance or, when the eyeball is in jeopardy from exposure, by orbital decompression.

Mann (1946) accepts Mulvany's two mechanisms, but thinks that his two varieties of exophthalmos can co-exist or overlap. She divides cases of malignant exophthalmos into three groups as follows, depending on which mechanism predominates:

**Group I. Primary Deficiency of Thyroxin with Compensatory Excess of Thyrotropic Hormone.**—These cases are characterized by swelling and oedema of the eyelids and conjunctiva, and by a low basal metabolism. Lid-retraction and thyrotoxicosis are absent. The treatment recommended is the administration of thyroid substance together with tarsorrhaphy where required.

**Group II. Primary Excess Thyroxin as initial Symptom followed by Thyroid Atrophy or Removal, replaced by Excess Thyrotropic Hormone.**—In these cases there is an initial history of thyrotoxicosis which subsided, either spontaneously or after thyroidectomy, and was then followed by swelling of the eyelids, ocular protrusion, and ophthalmoplegia. The basal metabolic rate bears no constant relation to the eye condition, and is very variable, although usually low after thyroidectomy. Treatment is on the same lines as for Group I.

**Group III. Excess Thyroxin and Excess Thyrotropic Hormone arising simultaneously.**—In these cases signs of thyrotoxicosis co-exist with ocular protrusion, ophthalmoplegia, and swelling of the eyelids. The basal metabolic rate is consistently high. No definite treatment is recommended, other than that thyroid administration should be withheld.

Neither Mulvany's nor Mann's hypotheses were tested by assays of the pituitary thyrotropin in the blood, nor have they been established by other workers. Other methods of therapy recommended in the literature include irradiation of the pituitary gland or of the orbital tissues, the administration of testosterone and other sex hormones, the exhibition of Lugol's iodine solution, and the use of diuretics. All these treatments have had their advocates, usually on the basis of observations in one or two cases, and have then been tried by others without beneficial results. Most of these treatments
are based upon the hypothesis that an increase of the pituitary thyrotropic hormone is responsible for this condition.

There is thus no unanimity as to either the cause and mechanism of malignant exophthalmos, or its treatment.

**Case Reports**

We therefore propose to review our experiences in twelve patients with severe malignant exophthalmos. Our observations suggest that Mulvany's separation of cases into two types, thyrotropic and thyrotoxic, is faulty. No solution to the essential cause of the condition is offered, but it is suggested that the condition is self-limiting, that it is only indirectly related both to the thyroid hormone and to the pituitary thyrotropic hormone, and that the administration of thyroid substance, even in large amounts, will neither prevent nor stay the progress of exophthalmos. Such improvement as we have noticed in patients receiving thyroid substance can equally well be explained by the self-liming nature of the disease.

The clinical features of our patients are summarized in the Table (over-leaf). They were all advanced cases and were referred to a neurosurgical unit because exposure keratitis had appeared or was deemed imminent and the referring doctor had envisaged the need for orbital decompression. In five of the twelve cases the condition had followed upon thyroidectomy. Nine cases, including eight with corneal ulceration and one with marked chemosis and papilloedema, were submitted to orbital decompression, and in six of these biopsy specimens of the orbital muscles were taken for histological study. In eleven cases the concentration of pituitary thyrotropin in the blood was determined for us by Drs Griesbach and Purves*. In nine cases thyroid substance was given at some stage of the patient's illness, often in large doses, without any decisive effect being noted.

The various cases presented differing combinations of symptoms, and as our attitude to successive cases changed with experience, each will be described separately. They are arranged in chronological order in two groups, depending upon whether there was an antecedent thyroidectomy or not.

1. After Thyroidectomy

**Case 1. Bilateral Malignant Exophthalmos with Corneal Ulceration.**

Temporary recession after orbital decompression followed by a return of exophthalmos, which later subsided concurrently with thyroid administration.

A 35-year-old housewife, referred by Dr. W. A. Bird, had complained of nervousness and irritability for the past 8 months. Her signs included a slight diffuse goitre, a resting pulse rate of 100, but no tremor of the outstretched hands. Basal metabolic rate levels were +8 and +16 per cent. There was pronounced bilateral lid-retraction, slight protrusion of the eyeballs, and enlarged conjunctival caruncles on either side (Fig. 1a). A diagnosis of malignant exophthalmos with mild thyrotoxicosis was made, and thyroidectomy was carried out to relieve the latter. The histological report was "a diffusely hyperplastic goitre showing some reversion to the resting colloid state" (Dr. John Sutherland).

*This was done according to their recently published method (Purves and Griesbach, 1949), whereby injections of the patient's serum are given to young guinea-pigs whose own pituitary development is inhibited by the administration of thyroid digests, and the effect of any pituitary thyrotropic hormone contained in the patient's serum on the guinea-pig's thyroid is then determined.
### TABLE
SUMMARY OF CLINICAL FEATURES OF

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex and Age (years)</th>
<th>Degree of Exophthalmos</th>
<th>Thyroidectomy Performed</th>
<th>Other Features</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Goitre</td>
</tr>
<tr>
<td>1</td>
<td>F 35</td>
<td>Bilateral severe</td>
<td>1 month earlier</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>F 36</td>
<td>Bilateral severe</td>
<td>1½ years earlier</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>M 42</td>
<td>Bilateral severe</td>
<td>2 years earlier</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>F 32</td>
<td>Bilateral moderate</td>
<td>1 year earlier</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>F 44</td>
<td>Bilateral moderate</td>
<td>3 years earlier</td>
<td>Moderate</td>
</tr>
<tr>
<td>6</td>
<td>F 46</td>
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<td>—</td>
<td>Moderate</td>
</tr>
<tr>
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<td>M 57</td>
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<td>—</td>
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<td>10</td>
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<td>11</td>
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<td>Bilateral marked</td>
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<td>Slight</td>
</tr>
<tr>
<td>12</td>
<td>F 60</td>
<td>Bilateral marked</td>
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### TWELVE CASES OF EXOPHTHALMOS

<table>
<thead>
<tr>
<th>Effect of Orbital Decompression</th>
<th>Effect of Thyroid Therapy</th>
<th>Follow-up Period (years)</th>
<th>End-Result</th>
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<tr>
<td></td>
<td>Before orbital decompression</td>
<td>After orbital decompression</td>
<td>Without orbital decompression</td>
</tr>
<tr>
<td>Temporary recession</td>
<td>No definite influence</td>
<td></td>
<td>6</td>
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<tr>
<td>Marked recession</td>
<td>Progress of exophthalmos not checked</td>
<td>Large amounts tolerated without effect</td>
<td>5</td>
</tr>
<tr>
<td>Passive recession only</td>
<td>Large amounts tolerated without effect</td>
<td></td>
<td>4½</td>
</tr>
<tr>
<td>Marked recession</td>
<td>Progress of exophthalmos not checked</td>
<td>No definite influence</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Progress of exophthalmos not checked</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Slight recession</td>
<td>No definite influence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Passive recession only</td>
<td>Exophthalmos not prevented from developing</td>
<td></td>
<td>4½</td>
</tr>
<tr>
<td></td>
<td>No definite influence</td>
<td></td>
<td>4½</td>
</tr>
<tr>
<td></td>
<td>Exophthalmos not prevented from developing</td>
<td></td>
<td>1½</td>
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<tr>
<td></td>
<td>Exophthalmos not prevented from developing</td>
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<td>1½</td>
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<tr>
<td></td>
<td>Exophthalmos not prevented from developing</td>
<td></td>
<td>1½</td>
</tr>
<tr>
<td>Temporary recession</td>
<td>Progress of exophthalmos not checked</td>
<td></td>
<td>1½</td>
</tr>
<tr>
<td>Doubtful</td>
<td>No definite influence</td>
<td></td>
<td>½</td>
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</table>
After this operation her nervousness was allayed, and the B.M.R. fell to –22 per cent. with resting pulse rate of 90. The stare and lid-retraction disappeared, but instead the eyeballs protruded more than ever, and within a month chemosis of the conjunctiva appeared on either side. The caruncles also enlarged further, and early ulceration developed in the left cornea (Fig. 1b).

A bilateral orbital decompression of the Naffziger type was therefore carried out. As in all the subsequent cases this operation was performed under intratracheal anaesthesia through a coronal scalp incision located behind the hair line. After the scalp flap had been reflected forwards, a small frontal bone flap pedicled on the temporal muscle was then turned on each side. Next, on one side at a time, the frontal dural envelope was elevated off the anterior cranial fossa, thus exposing the roof of the orbit. This was then removed with nibbling forceps back to but usually not into the optic canal. In addition, the lateral wall of the orbit in the region of the pterion and temporal fossa was removed before the periorbita was incised and the orbital contents inspected. In this particular patient, the muscles appeared pale and broadened, but the orbital fat was not excessive, although it was under pressure. No biopsy specimens were taken. At the end of the operation there was a gratifying recession of the eyeballs, and within a few days the pouting folds of conjunctiva disappeared, and the caruncular swellings lessened (Fig. 1c).

On her discharge from hospital on the 20th day; we were confident that the patient had recovered. However, two weeks later, while in another city, a "bubble" rapidly appeared over the right cornea. She was admitted to a local hospital, again with pouting conjunctival folds, and after performing a paracentesis of the anterior chamber, an ophthalmic surgeon enucleated her right eyeball two days after admission. At the time her left eyelids were reported as oedematous, and were sutured together for four days. They then seemed all right again, and she was discharged from hospital 10 days after admission, with instructions to take by mouth 2 to 3 grains of desiccated thyroid daily. This she has done ever since.

When seen by one of us 13 months after orbital decompression, the left eyeball appeared healthy, but there was some swelling of the eyelids as well as a slight retraction...
of the upper lid. Her weight had increased by about 20 lb., and her facial appearance showed some coarsening, while the outer third of each eyebrow was thinned. Resting pulse rate was 70. An assay revealed a high level of pituitary thyrotropic hormone in her blood. She has since written (6 years after orbital decompression) saying that her left eyeball seems normal, and that her general health is good, while her weight has remained up (Fig. 1d).

Case 2. Bilateral Malignant Exophthalmos leading to Loss of one Eyeball and Corneal Ulceration in the Other.

Second eye saved by orbital decompression. No response to thyroid apparent even to very large doses.

A 32-year-old housewife, referred by Drs D. Y. Allan and J. D. Willis, had undergone thyroidectomy 15 months previously for mild toxic symptoms. Shortly afterwards her eyeballs started to protrude gradually but steadily. Beginning a month before admission to our Unit she was given thyroid substance, at first 3 grains daily, but increasing rapidly to 12 grains daily. However, the protrusion of both eyeballs continued to increase, the cornea became ulcerated, and finally the left eyeball had to be excised because of panophthalmitis. Next day she was transferred to our Unit.

This patient's appearance on arrival was alarming (Fig. 2a). From the eyeless left socket a large fold of conjunctiva pouted, while the eyelids themselves were swollen. On the right side a smaller fold of conjunctiva projected between similarly swollen lids, while the eyeball was protruded and the cornea ulcerated. The visual acuity was reduced to 6/36, although the optic fundus seemed normal. Yet in spite of all this she showed no signs of thyrotoxicosis, no enlargement of the thyroid, and no menstrual disturbance. The pituitary thyrotropin of her blood was much increased.
A right-sided orbital decompression was promptly carried out. The orbital contents were under pressure, the orbital muscles appeared pale and swollen (the cross-section of the levator palpebrae superioris being 1.2 cm. wide by 0.8 cm. thick), and a biopsy specimen showed a marked inflammatory reaction. The eyelash left orbit was not operated on. Immediately after operation the right eyeball receded considerably, but on account of the ulceration it was protected temporarily by stitching the lids together.

A fortnight later when it was uncovered, the right eyeball seemed normally placed, its corneal ulcers had healed, the swelling of the eyelids was less, the chemosis of the conjunctiva had disappeared and the visual acuity was normal (6/6). On the non-decompressed left side, the conjunctiva still pouted and the eyelids were still swollen. B.M.R. levels were -21 and +25 per cent., and resting pulse rate was 80 to 90.

The opportunity then arose for testing the effect of thyroid administration by observing its effect on the swollen eyelids and pouting conjunctiva on the left side. Six grains of desiccated thyroid were given daily, increasing rapidly to 18 grains daily, at which level the administration was maintained for 2 months. During the first month 15 minims of Lugol's iodine were also given daily. Two proprietary brands of thyroid tablets were used, both marketed by reputable and internationally known firms, and both used extensively by our medical colleagues with good results in myxoedema.

Yet in this particular patient there was scarcely any systemic effect. Her resting pulse rate was unaltered, her B.M.R. levels rose only to +35, +35, +46, and +42 per cent. as determined at sundry times during the three-month period, and her weight actually increased by 3 lb. Only a slight recession was noted in the swelling of the left eyelids and conjunctiva (Fig. 2b), and this slight recession might equally well be due to resolution of the traumatic swelling in the orbit consequent upon enucleation of the eyeball. So during her fourth post-operative month the pouting fold of conjunctiva was excised, and she was then discharged to her home (Fig. 2c).

This patient has been followed-up for more than 5 years, during which time she has taken 3 grains of desiccated thyroid daily. Her right eyeball and orbit remain normal, but in spite of the long continued thyroid therapy, there is still some swelling of the left orbital contents, and some features suggestive of myxoedema have appeared, such as coarsening of the face and sparseness of the outer parts of the eyebrows (Fig. 2d). A recent B.M.R. determination is -10 per cent. Mentally she is alert.

A point of great interest in this case is the apparent tolerance during the early post-operative period to very large doses of thyroid substance. During the third month an assay by Mr. F. H. Kennedy revealed a thyroxin-iodine level in the blood of four times the normal (16 micrograms per 100 millilitres as opposed to 4 micrograms per 100 millilitres— butyl alcohol extraction method). We presumed from this that the thyroid substance had been absorbed from the alimentary tract. Also of interest is that during the three-month period of intensified thyroid administration, the levels of pituitary thyrotropin in the blood fell gradually to normal.

Case 3. Bilateral Malignant Exophthalmos with Corneal Ulceration and Hypopyon in one Eye at first and only Slight Protrusion in the Other.

Little recession from orbital decompression. Marked resistance to massive doses of thyroid.

A 42-year-old man, referred by Dr. L. S. Talbot, had undergone thyroidectomy for 'toxic diffuse goitre' two years previously. Prominent eyeballs and lid-retraction had been noted before operation, but afterwards these signs became more marked, although they appeared to fluctuate. Three months before admission he developed a left corneal ulcer, and apparently some features of toxicity, for his B.M.R. was between -23 and -35 per cent. He was given 30 minims Lugol's solution daily for 2 weeks, and the B.M.R. fell to -6 per cent. The corneal ulcer apparently subsided.
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Then 4 weeks before his admission to our Unit his left eyeball again flared up, and when admitted he showed a grossly protruded left eyeball with corneal ulceration and hypopyon (Fig. 3a). The eyeball was surrounded by swollen folds of conjunctiva, and could perceive only light. The right eyeball was not inflamed, but the right upper eyelid was retracted. The eyelids showed little oedema on either side. There were no signs of thyrotoxicosis, the resting pulse rate being 80, and the B.M.R. levels +2 and +4 per cent. The thyroid was not palpable. An assay of the pituitary thyrotropin in the blood showed only a slight increase.

Fig. 3.—(a) Case 3. On admission, (b) Case 3. Three months later, shows pouting of conjunctiva a few hours after tarsal stitches were undone.

(c) Case 3. Four years later.

In view of our experiences with another patient (see Case 6), we deferred orbital decompression, and instead under local analgesia covered the cornea of the left eyeball with a flap of conjunctiva. By the fourth day, however, marked chemosis of the conjunctiva had appeared on the right side, and a bilateral orbital decompression was promptly carried out. On both sides the orbital fat bulged when the periorbita was incised, while the orbital muscles seemed pale and swollen (biopsy specimens showed slight inflammatory changes). When the operation was concluded, little recession of the eyeballs occurred, but we were able to stitch the eyelid margins together on each side without much tension.

The post-operative course was smooth, but it subsequently proved necessary to keep the eyelid margins approximated for about 7 months. This was done by means of silk mattress-stitches inserted through the eyelid margins and prevented from cutting into the skin by being threaded over tiny pieces of rubber tubing. Penicillin drops were instilled twice daily, and it was found that a set of stitches could usually be left in situ for from 10 to 14 days before the eyelids became very inflamed or the stitches had started to cut through their margins. The stitches would then be removed for 24 to 36 hours, during which time the inflammation in the eyelids would subside, and a fresh set of sutures could then be inserted under intravenous anaesthesia. Each time the stitches were undone, protuberant folds of conjunctiva would rapidly develop, so that by the end of the day the eyelids could no longer be closed (Fig. 3b). Several attempts were made by ophthalmological colleagues and ourselves to circumvent these repeated stitchings by permanent tarsorrhaphy, but without success for the lid margins would not adhere, presumably because of inflammatory changes.
Throughout this long period of 7 months, during which the eyelid margins were repeatedly stitched, various methods of treatment were tried:

(i) Desiccated thyroid was given by mouth, first 6 grains daily, and increasing to 10 days later to 18 grains daily, at which level the dosage was maintained for 3 weeks. There was no effect on the ocular state, pulse rate, or body-weight, and towards the end of this period, B.M.R. levels of -7 and -13 per cent. were recorded.

(ii) Lugol’s iodine solution was given in doses of 30 minims daily for 4 weeks. Again no general effect was noted, and B.M.R. levels of zero, +6, and +8 per cent. were recorded.

(iii) Massive doses of thyroid were given, first 50 grains daily for 10 days, again without effect, except that resting pulse rates ranged between 80 and 100. The B.M.R. was still -10 per cent. at the end of this course. Then for 9 days six intravenous injections of 10 mg. thyroxin were given. The total dose was thus 60 mg. thyroxin, the equivalent of about 500 grains of thyroid substance. Yet the B.M.R. readings on alternate days during this 9-day period were -9, -32, -11, -33, and -2 per cent., and the only general effect observed was a resting pulse rate of about 100 instead of 80. Again no benefit ensued to the eyes. The patient’s weight by now was 14 lb. heavier than on admission (10 st. 8 lb.). We concluded that, like Case 2, he had an abnormal resistance to thyroid, even when administered parenterally.

(iv) A month followed without any drug treatment, during which B.M.R. levels varying between -1 and -34 per cent. were noted, and resting pulse rates from 80 to 90. His weight increased another 6 lb.

(v) Testosterone propionate 30 mg. intramuscularly was given twice a week for 6 weeks, and again no definite effect was noted.

(vi) Methyl thiouracil, 100 mg. daily for 5 weeks, followed.

(vii) Stilboestrol 5 mg. twice daily until his discharge from hospital nearly 9 months after admission. With treatments (iv)–(vii), as with the thyroid, there was no significant general or local effect.

About the seventh post-operative month a slight but gradual improvement began, and we found that his eyelids could be left unstitched without oedematous folds of conjunctiva appearing, and that he could approximate his eyelids voluntarily. The lid margins were ragged from repeated stitching, and were subsequently trimmed by Dr. W. Manchester.

Four and a half years have now passed since his discharge, and during that time he has worked as a truck and grader driver. His eyeballs are still prominent (Fig. 3c), but less so than before. Lid-closure is good on the right side, while on the left he can cover the cornea with the upper eyelid, but is unable to bring the two lids together. The left cornea is opaque, possibly partly as a result of adherence of the conjunctival flap which was swung over the cornea in the initial stage of surgical treatment. Visual acuity in the right eye is 6/9, and in the left eye only hand movements. His weight remains stationary, and there are no signs of thyrotoxicosis. A recent assay shows no increase of pituitary thyrotropin in the blood.

**Case 4. Bilateral Malignant Exophthalmos with Marked Ophthalmoplegia which developed in spite of Thyroid Therapy.**

**Benefit from orbital decompression.**

A 32-year-old Maori woman, referred by Drs. L. W. Broughton and John Willis, had undergone thyroidectomy for toxic goitre 9 months earlier. Within 2 months her eyeballs had started to protrude, but when referred to our Unit she showed only a slight degree of exophthalmos with slight swelling of the eyelids (Fig. 4a). There were no signs of thyrotoxicosis and no palpable thyroid. B.M.R. readings were between
zero and +13 per cent. The blood pituitary thyrotropin was considerably increased. As her exophthalmos was mild, she was sent home with instructions to take desiccated thyroid by mouth. At first she took 3 gr. daily, but as her exophthalmos continued to advance, the dosage was increased to 12 gr. daily, at which level it was maintained for a month.

Three months later she was re-admitted with increased exophthalmos associated with marked swelling of the eyelids, slight chemosis of the conjunctiva, and a convergent squint (Fig. 4b). Exophthalmometer readings showed that the ocular protrusion had increased 2 mm. in each eye since her previous admission. During the same period her weight had increased by 14 lb. B.M.R. readings were now +22 and +24 per cent.

Bilateral orbital decompression was now undertaken. The extra-ocular muscles were pale and swollen, and biopsy specimens showed moderate inflammatory changes of the usual type. Also the orbital contents were under pressure and bulged markedly when the periorbita was incised. At the end of the operation her eyeballs had receded, and, when she was discharged home 2 weeks later, the exophthalmometer showed this recession to be 3.5 mm. on the right side and 5 mm. on the left side (Fig. 4c).

Subsequently her eyeballs remained receded, but the external rectus muscles became gradually weaker, and the convergent squint increased. She continued to take thyroid substance in amounts up to 4 grains daily without improvement in her general condition, although her was a slow and progressive loss of 2 stone in weight from an initial level of 13 st. 2 lb. Diplopia was troublesome, and her appearance of squint worried her. Finally, a year after the operation, she met her death as the result of an accident. A post-mortem examination was performed for the coroner, but histological studies of the orbits were not made.

Case 5. Bilateral Exophthalmos of Moderate Degree.
Progressed in spite of thyroid therapy, and possibly improved when thyroid administration was withheld. No orbital operation necessary.

A 44-year-old ex-servicewoman, referred by Drs B. Watson and D. Pottinger, had undergone thyroidectomy for toxic goitre 3 years earlier. Her eyeballs were considered
prominent before operation, but shortly afterwards became more so. Starting a year later when the protrusion was still mild, she had taken 3 grains of desiccated thyroid daily, except for a short period when the dosage had been 9 grains daily. Also at another period she had been given methyl thiouracil 0.4 mg. daily for a month in addition to thyroid tablets, but neither regime had benefited her, and the protrusion of her eyeballs had steadily increased.

When referred to our Unit her eyeballs were moderately protruded while the upper eyelids were slightly swollen and were retracted. She could close here eyelids. There was no chemosis and the external oculomotor movements were full. Mild thyrotoxic signs were present in the form of nervousness, increased sweating, and a resting pulse rate of 90 to 100, while a small amount of thyroid tissue was palpable. B.M.R. readings were -30. -8, and -12 per cent on consecutive days. The blood pituitary thyrotropin was increased. Menses were regular. As the eyeballs were not in jeopardy, we decided to withhold thyroid administration and to defer orbital decompression pending observation of her progress. She was therefore discharged home without any medication.

Four months later she described herself as slightly improved. Her nervousness was less, and her weight had increased by 6 lb. Exophthalmometer readings indicated that each eyeball had receded 4 mm. Her resting pulse rate was 72, and her B.M.R. readings were reported as -24 and -27 per cent. Three months later still exophthalmometer readings showed a further recession of 2 mm. on the right side but no further change on the left. A year after thyroid administration was stopped, she wrote to say that she was back at work after a lapse of three years, and that her eyes were satisfactory.

(2) WITHOUT THYROIDECTOMY

Case 6. Bilateral Malignant Exophthalmos with Bilateral Corneal Ulceration.

Death 2 weeks after orbital decompression.

A 46-year-old housewife, who once had been obese, had developed nervousness and irritability starting two years before her admission to our Unit, and has lost several stone in weight. A nodular goitre was noted at this time, and also a coarse tremor of her hands. She was treated with Lugol's solution, and her nervousness lessened, but her excess weight did not return.

For 6 months before admission her eyeballs had become increasingly prominent, and for 3 weeks they had been sore and painful. For 5 days she had been blind in her left eye. On admission both eyeballs were protruded and showed marked corneal ulceration, while the eyelids were swollen (Fig. 5). The left cornea had perforated, and the eyeball was disorganized with panophthalmitis. Vision in the right eye was J16. A nodular goitre was present. Yet she did not show any nervousness or tremor, although the pulse rate was 110. Moreover, the B.M.R. had been reported only a few days previously as -3 per cent. The blood pituitary thyrotropin was not increased.

Shortly after admission a right-sided orbital decompression was undertaken to save the right eyeball. The orbital contents were not under pressure, and the levator palpebrae superioris and superior rectus muscles, although pale, were not considered
enlarged. Biopsy specimens of these two muscles showed only slight inflammatory changes. After the operation the right eyeball could be pressed back into the orbit, and the eyelid margins were sutured over it. The left eyeball was eviscerated.

For the first few days after the operation she seemed to be progressing favourably, and the B.M.R. level on the 7th day was +21 per cent. During the second week, however, she developed an acute congestive heart failure, and she died on the 15th day of ventricular tachycardia (Prof. F. H. Smirk). The manner in which this cardiac failure developed suggested an "acute thyroid crisis".

A post-mortem examination was carried out by the late Dr. John Sutherland, all the contents of the right orbit being removed for study. To our amazement the various muscles, which at operation had been adjudged of normal size, were in reality markedly swollen, while in contrast to the slight changes seen in the biopsy specimens, histological examination of the post-mortem material showed gross inflammatory changes in most of the orbital muscles. Similar but less marked inflammatory changes were seen also in the lacrimal gland. The thyroid showed a nodular hyperplastic goitre.

Case 7. Bilateral Malignant Exophthalmos with Corneal Ulceration.

No striking benefit from orbital decompression, but a gradual subsequent recession of ocular protrusion, probably not influenced by either the decompression or thyroid therapy.

A 57-year-old man, referred by Dr. J. S. Monro, had noted for the past 6 months increasing prominence of his eyeballs associated with diplopia. Two weeks before admission both corneae became ulcerated, the right side being more affected, and his eyelids were stitched together with interrupted silkworm-gut stitches. On his arrival the stitched eyelids were swollen and inflamed, and on the right side one silkworm-gut stitch had cut through the margin of the lower eyelid like a seton. The patient exhibited no signs of thyrotoxicosis and no goitre, but the blood pituitary thyrotropin was slightly increased. The B.M.R. was normal.

A bilateral orbital decompression was undertaken promptly. On each side the extra-ocular muscles were pale and swollen, but the orbital contents were not under increased pressure. Little, if any, spontaneous recession of the eyeballs was apparent at the end of the operation, but the eyeballs could be pressed backwards. A permanent tarsorrhaphy was attempted on each side, and was successful on the left side, but (mainly because of the gap in the lower lid and the associated inflammation) the right eyelids did not adhere. Otherwise the immediate convalescence was smooth. Three months later he was referred to a plastic surgical unit, but as the right cornea was scarred, diplopia was troublesome, and a repair of the lower lid seemed impracticable, the right eyeball was enucleated.

The left eyeball was saved, but over a year passed before it receded sufficiently to permit the tarsorrhaphy to be undone. During the first 6 months of this period, desiccated thyroid was taken by mouth, at first 3 but later 6 gr. daily. B.M.R. levels of +20 to +25 per cent. were recorded with the smaller dosage, and of +40, +41, and +44 per cent. with the larger dosage, these levels being associated with a good deal of nervousness, but no loss of weight. In the second six months methyl thiouracil was given, at first 0.2 g. daily, later 0.1 g. each second day, and coincident with this regime the B.M.R. fell to -6 per cent.

Throughout the first year, a slow and very gradual recession of the left eyeball occurred, and this apparently was not affected by either the thyroid or thiouracil therapies. On follow-up examination 2½ years after the orbital decompression, the left eyeball appeared normal and without any protrusion, but he was troubled by ingrowing eyelids. Shortly afterwards, a corneal ulceration developed without further protrusion, and lateral tarsorrhaphy was repeated by Dr. A. N. Talbot. When seen
again by us, 4½ years after the decompression, the left cornea was clear once more, and well protected by the tarsorrhaphy. There was no obvious exophthalmos nor oedema of the eyelids. The patient was in receipt of an old-age pension, but was able to look after his own home and garden.

**Case 8. Bilateral Malignant Exophthalmos with Corneal Ulceration, developed in spite of Long-continued Thyroid Therapy.**

Slight benefit from orbital decompression, followed by temporary worsening before further spontaneous improvement.

A 48-year-old housewife, referred by Dr. John Willis, had been taking 2 to 3 grains of thyroid substance daily for 5 years on another doctor's advice in order to keep her weight down. During this period her weight had fallen by 3 stone to 10 st. 10 lb. Six months before admission both eyeballs began to protrude, and thyroid therapy was continued except for a period of a month when thiouracil was tried instead. On admission both eyeballs were markedly protruded, and the palpebral tissues were swollen, while the left cornea was ulcerated and surrounded by oedematous conjunctiva. There was no lid-retraction (Fig. 6a). Exophthalmometer readings: right eye, 23 mm.; left eye, 24 mm. Moderate-sized nodular goitre. There was slight nervousness, irritability, and tremor, but the B.M.R. was disproportionately high (+ 60 per cent.). Resting pulse rate was 76. There was some sparseness of the outer eyebrows, and marked elevation of blood pituitary thyrotropin.

Fig. 6.—(a) Case 8. On admission. (b) Case 8. Three weeks after orbital decompression.

Bilateral orbital decompression was performed. The extra-ocular muscles were pale and swollen, but the orbital contents were not under pressure. Muscle biopsies showed mild inflammatory changes. At the end of the operation the eyeballs had not receded, but the eyelids were possibly a little more easily approximated than before the operation, and they were fastened together with mattress stitches, as in Case 2.

This closure was maintained for a period of 5 weeks. A reinsertion of the stitches proved necessary about 3 weeks after operation, and the stitches were removed for 24 hours, when it became evident that, although according to exophthalmometer readings each eyeball had receded 3 mm., the swelling of the eyelids and the chemosis of the conjunctiva had actually increased (Fig. 6b). After 3 further weeks of lid-closure, however, the swelling of the lids and the chemosis had subsided, and the patient could one more voluntarily approximate her eyelids on either side.
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After operation she remained under our direct observation for 3½ months before returning home. During this time her eyeballs further receded. Exophthalmometer readings: right eye 17 mm.; left eye 17 mm. No thyroid substance was given post-operatively although 15 minims Lugol's solution were given daily for a month without general effect. B.M.R. estimations made at frequent intervals throughout this period showed astonishing variations between +20 and +185 per cent., most of the determinations being about +40 per cent. Yet her pulse rate throughout was between 70 and 80, and she did not show any signs of nervousness or tremor. She was perhaps a little more tolerant of cold weather than the average patient, but no obvious thyrotoxic manifestations were present. Her weight increased by 5 lb. during the period. Her final B.M.R. readings were +36 and +40 per cent. Two other interesting observations were made. The first is that during the post-operative period her goitre gradually lessened, and the circumference of her neck decreased by nearly one inch. Secondly, 3 months after admission her blood pituitary thyrotropin had fallen to normal levels.

When seen again a year after operation, her eyes were satisfactory, although there was still some swelling of the eyelids (Fig. 6c). Her weight had increased a further 4 lb., but her pulse rate was 72.

Case 9. Unilateral Malignant Exophthalmos of Moderate Degree.

Resolved spontaneously.

A 65-year-old man, referred by Dr. N. B. Fisher, had first noticed 4 years ago, that his left eyeball was gradually protruding without any discomfort. This protrusion had increased until 3 months before his admission to our Unit, and after this it started to recede. There were no headaches, history of sinusitis, nervousness, or loss of weight. Examination showed a moderate unilateral exophthalmos associated with swelling of eyelids of the type seen in the previous cases, but no chemosis of the conjunctiva, goitre, or symptoms of thyrotoxicosis. B.M.R. was zero. Blood pituitary thyrotropin was not raised. Blood pressure 200/90.

The question of orbital decompression was deferred and the patient was sent home. During the next three months thyroid was given in doses decreasing from 3 to 1 gr. daily, the B.M.R. being +18 per cent. at the end of the first month, when slight tremor of the fingers was apparent. The protrusion continued to recede gradually, not only during this period of thyroid therapy but also after it was discontinued.

When seen by us about 18 months later, the exophthalmos had subsided completely. The patient's weight had increased by 7 lb., and the B.M.R. was —19 per cent., but he had no obvious signs of myxoedema. When he was seen again a further year later we learnt that there had been a slight and temporary return of ocular protrusion six months before. His doctor had given him 2 gr. desiccated thyroid daily for a month, and the ocular protrusion had disappeared within that time. Since then he had been taking 4 gr. thyroid each second day. There was no trace of exophthalmos when we saw him.

Case 10. Bilateral Malignant Exophthalmos of Moderate Degree.

Resolved spontaneously.

A 42-year-old woman, referred by Dr. K. J. Talbot, with a bilateral exophthalmos of similar degree to Case 9 but of only 3 months' duration. A period of nervousness and palpitations lasting 3 weeks had coincided with the outset of ocular protrusion, and she had lost 7 lb. in weight during that period, but had since regained it. No thyrotoxic symptoms were seen by us, and there was no goitre. B.M.R. normal. Both eyeballs were protruded, the right more than the left. Exophthalmometer—right eye +18 mm.; left eye 17 mm. Slight lid-retraction was present.
As improvement in the thyrotoxic symptoms had occurred, the patient was sent home without any specific treatment. When she was seen again 3 months later both eyeballs had receded to normal, and the stare had also disappeared. Exophthalmometer—right eye +16 mm.; left eye 15 mm. Eighteen months later it was reported that the eyeballs were still receded.

**Case 11. Bilateral Malignant Exophthalmos with Slight Corneal Ulceration.**

*Orbital decompression resulted in slight immediate recession followed by temporary worsening. Spontaneous improvement followed later.*

A 35-year-old woman, referred by Drs R. H. Q. Baxter and W. A. Bird, had complained for 10 months of gradually increasing ocular protrusion, at first in the left eye, and then in the right as well. For a short period she had been given 2 gr. desiccated thyroid daily, and during another period had evidently been given methyl thiouracil, but neither regime had benefited her.

On admission to our Unit, she showed bilateral ocular protrusion and moderate swelling of the eyelids. Exophthalmometer readings—right eye 21 mm.; left eye 22 mm. The external oculomotor movements were slightly restricted. She also exhibited signs of mild thyrotoxicosis, in that she was nervous and irritable, had a slight enlargement of the thyroid, a resting pulse rate of between 80 and 90, and B.M.R. of +58 and +51 per cent. The glucose tolerance test showed a mild diabetic curve. The blood pituitary thyrotropin was not raised.

Ten days after admission she developed chemosis of the conjunctiva and a slight ulcer of the left cornea. A bilateral orbital decompression was therefore carried out. The orbital fatty tissue bulged when the periorbita was opened, while the orbital muscles seemed pale and swollen. Muscle biopsies showed mild inflammatory changes. At the end of the operation, the eyeballs had receded nicely, but two weeks later they protruded again, even more markedly than on admission. Exophthalmometer readings: each eye 23 mm. For 6 weeks the lids had to be kept stitched together, as in previous cases, before the eyeballs started to recede again. We then undid the stitches, and found that she could close her eyelids. At night time they were strapped together with adhesive tape for added protection. Then 3 days later, to our horror, a large deep ulcer appeared over the lower third of each cornea. At first we were nonplussed as to the reason, for she could still close her eyelids. However, we found that the corneae were insensitive, and that her eyelids remained open during sleep, so it is possible that our adhesive tape had abraded the cornea.

This corneal ulceration was most unfortunate, for the ulcers subsequently healed with a marked opacity of the lower halves of each cornea. Lateral tarsorrhaphy was out of the question, because when the palpebral fissures were narrowed, these opacities came within the line of vision. We therefore made her wear close-fitting goggles of the type used by underwater swimmers, which kept the moisture in and prevented drying of the conjunctiva. She has worn these goggles continuously for the past 4 months, and during that period there has been a slow but steady recession of the eyeballs. Exophthalmometer readings: 18 mm. in each eye. This recession seems to have been spontaneous, because we have purposely withheld all medicinal therapy. The nervousness and irritability have disappeared, the resting pulse rate is between 70 and 80, and a recent B.M.R. is +9 per cent. The glucose tolerance curve is now normal, but a recent assay of blood pituitary thyrotropin has shown a moderate increase, which has occurred at a time when the eyeballs were apparently receding.

Right orbit decompressed but not left. This unilateral operation was followed by a rapid improvement on both sides.

A 60-year-old woman, referred by Dr. John Willis, complained that for the past 3 months, both eyeballs had steadily become protuberant. The onset of these symptoms had followed a severe mental shock occasioned by the sudden death of her brother. For 6 weeks she had complained of diplopia, and of difficulty in moving her eyes to either side, and for the past week the conjunctiva had been protruding on either side.

On admission both eyeballs were protuberant, and a fold of oedematous conjunctiva pouted below the cornea on either side (Fig. 7a). The eyelids themselves showed only slight swelling. There was a gross external ophthalmoplegia, for neither eyeball could be deviated more than a few degrees from the central position. Each optic fundus showed about 2 dioptres of papilloedema. Visual acuity: right eye 6/60, left eye 6/24. There were no signs of thyrotoxicosis and no goitre. B.M.R. was zero. The blood contained a moderate excess of pituitary thyrotropin.

Fig. 7.—(a) Case 12. On admission.

(b) Case 12. Six weeks after a right-sided orbital decompression.

As the exophthalmos seemed progressive and had reached a severe stage, bilateral orbital decompression was decided on, but the findings were most unexpected. At the operation (performed as usual under intratracheal anaesthesia) the right side was operated first, and after the roof and lateral wall of the right orbit including the optic canal had been uncapped, the periorbita was opened, but the orbital contents were not under pressure. A firm, rather bluish structure about 6 mm. thick by more than 10 mm. wide identified in the lateral part of the orbit, was considered to be the lateral rectus muscle. Endeavouring to obtain a biopsy, the surgeon (M.A.F.) nicked this structure, which immediately poured forth arterial blood under pressure, but without
arterial pulsation. The leak was sealed with a muscle stamp, and the surgeon then demonstrated to Dr. R. P. Wilson and other colleagues how red blood could be freely aspirated from this structure, and how the puncture site would squirt for a few seconds after removal of the needle. We all felt that the structure was a distended venous channel, but were nonplussed as to its significance. Consequently the operation was completed without decompressing the left side. Immediately after operation the skull was auscultated but no bruit was heard. Little recession of the eyeball was noted on the decompressed side.

The convalescence was smooth, and to our amazement within a day or so of operation, both eyeballs began to subside, and the swollen conjunctival folds to disappear, even on the left side which had not been decompressed. During the second week bilateral percutaneous carotid arteriograms were made, and good definition obtained of the internal carotid arterial tree on either side, including the ophtalmic arteries, but no abnormality was seen. When the patient was discharged on the 20th post-operative day, all conjunctival oedema had disappeared, each eyeball had receded about 2 mm. and had regained about 20 to 30 degrees of lateral and vertical movement, and the papilloedema had disappeared. The visual acuity had improved to right eye 6/18, left eye 6/18. When she was seen again 6 weeks after the operation both eyeballs seemed virtually normal as regards position and movements (Fig. 7b), and the visual acuity had recovered to right eye 6/12, left eye 6/9. Six months later the improvement had been maintained, and the pituitary thyrotropin in the blood was no longer raised.

**PATHOLOGICAL FINDINGS**

Material for histological study was obtained from the orbital contents at operation in six cases and at post mortem in one of these. The thyroid glands of three patients were also available. The histological findings in individual cases are as follows.

(1) **AFTER THYROIDECTOMY**

Case 1.—*Thyroid tissue* removed at operation, weight 34 g. Cut surface uniform and fleshy. Microscopically there is extensive epithelial hyperplasia; some acini have

![Fig. 8.—Case 2. Biopsy of right levator palpebrae superioris showing a diffuse and focal infiltration of lymphocytes; also oedema of the connective tissue separating the muscle fibres. Haematoxylin and eosin (x 144).](http://bjo.bmj.com/content/35/5/253.plot)
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high columnar epithelium, but in others there is some reversion to the resting state shown by low epithelium and colloid accumulation. The appearances are those of a diffuse hyperplastic goitre with reversion due to administration of Lugol's solution.

No biopsy of the orbital contents was made in this case.

Case 2.—Right levator palpebrae superioris muscle. Sections show separation of muscle fibres by oedema. Towards the periphery the muscle sheath is thickened and there is an increase of fibrous tissue separating the muscle fibres. Here there is some swelling and proliferation of fibroblasts. There is also a diffuse lymphocytic infiltration throughout the muscle, and a number of focal aggregations of lymphocytes (Fig. 8f).

Orbital fat biopsy shows no abnormality.

Conjunctiva shows inflammatory changes, both acute and chronic.

Case 3.—Superior rectus muscle. Sections from each orbit show similar features: oedema, more marked on the left side, and diffuse fibrosis, more marked on the right side. Many muscle fibres show degenerative changes, with some swollen giant fibres, sarcolemmal nuclear proliferation, and a replacement fibrosis containing a sparse diffuse infiltration with lymphocytes (Fig. 9).

Orbital fat biopsy shows a perivascular lymphocytic infiltration in some of the connective tissue septa.

Conjunctiva shows acute and chronic inflammatory changes.

Thyroid tissue removed at operation 2 years earlier, weight 50 g. Cut surface has a diffusely fleshy appearance. Sections show extensive epithelial hyperplasia with tall columnar epithelium which in some areas is thrown up into papillary formations. There are extensive areas of reversion to the resting colloid state.

Case 4.—Right superior rectus muscle. Sections show little oedema. There is an extensive fibrosis separating individual muscle fibres; in places this fibrous tissue is of loose texture, in others it is quite dense. The appearances indicate that some muscle fibres are being replaced by fibrous tissue. There is little inflammatory infiltration.
Fig. 10.—Case 4. Biopsy of left superior rectus muscle showing a focal aggregation of lymphocytes and a diffuse infiltration extending between the muscle fibres. Haematoxylin and eosin (x 160).

Left superior rectus muscle. Fibrotic process is also well marked, but there is some oedema. There are numerous focal aggregations of lymphocytes, some in the septa, others within the muscle fasciculi themselves (Fig. 10). The sheath of the muscle is thickened.

Orbital fat normal, although some of the vessels running through it have a perivascular collection of lymphocytes.

Right temporal muscle histologically normal.

(2) Without Thyroidectomy

Case 6.—Right superior rectus muscle. Biopsy specimen obtained at orbital decompression shows separation of muscle fibres by oedematous connective tissue, and a moderate diffuse infiltration of this tissue by plasma cells and lymphocytes. The muscle fibres cut in cross-section are normal and no proliferation of sarcolemmal nuclei is seen (Fig. 11).
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Fig. 12.—Case 6. Low-power view of section through whole orbital muscle cone with the optic nerve in the centre and the four rectus muscles. The distribution of lymphorrhages is shown. Haematoxylin and eosin (x 2).

Fig. 13.—Case 6. Orbital muscles obtained at post mortem shows several large focal aggregations of lymphocytes and an increase in density of the connective tissue septa. Van Gieson (x 91).

*Levator palpebrae superioris* muscle shows similar mild features.

*Orbital contents* on both sides removed in toto post mortem. The orbital muscles are greatly swollen (Fig. 12). In the sections there is an extensive diffuse fibrosis separating the muscle bundles and the individual fibres within the bundles. Some atrophy of muscle fibres with replacement by connective tissue is seen, as well as numbers of giant cells composed of multi-nucleated masses of sarcoplasm which are evidence of muscle regeneration. The muscle sheaths are thickened. Furthermore, throughout the orbital muscles on the right side, are scattered well-defined and closely-packed aggregations of lymphocytes as well as a more diffuse infiltration by these cells (Fig. 13). In the centre of most of these nodules is a thin-walled vessel of capillary or venule size. The arteries and veins do not enter into the formation of these nodules. In the left orbit where the fibrosis of the muscles is much further advanced, the lymphoid collections are less prominent.
Orbital fat normal.

Lacrimal gland shows a slight diffuse periacinar fibrosis with some focal lymphocytic collections.

Thyroid gland (weight 122 g.) symmetrically enlarged. Cut surface firm and pale. Microscopically there is intense epithelial hyperplasia with little colloid storage and widespread nodule formation. This is a hyperplastic nodular goitre (Fig. 14).

Case 8.—Extra-ocular muscles. Sections show individual muscle fibres separated by oedematous loose connective tissue. No lymphocytic infiltration is seen. Many of the muscle fibres are swollen, and in some areas proliferation of the sarcolemmal nuclei is seen.

Left temporal muscle, sectioned for comparison, shows no abnormality.

Case 11.—Levator palpebrae superioris muscle. Sections of each side show some oedema and increased fibrosis of the septa. There is a diffuse lymphocytic infiltration. Some of the muscle fibres are swollen, and there is proliferation of the sarcolemmal nuclei.

Orbital fat normal.

Temporal muscle biopsy shows no abnormality.

Comment.—This series is valuable from the pathological aspect in that histological material was available from a wide variety of clinical cases, with and without thyroidectomy. Our experience in Case 6 demonstrates that a biopsy fragment obtained at operation may not give a true picture of the extent of pathological changes in the muscle, a point emphasized by Offret (1939).

All our biopsy specimens from the orbital muscles conform to a more or less uniform histological pattern. The muscle fibres are separated by oedematous connective tissue producing fasciculi with greater bulk than normal. Some muscle fibres show degenerative changes, seen as swelling of the fibre and alteration in its staining reactions. Regeneration of muscle fibres is seen in the form of large multinucleated masses of sarcoplasma. There is frequently evidence of replacement of muscle fibres by fibrous tissue. The fibrous sheaths of the muscles and the septa
separating the fasciculi tend to be of increased density and thickness. In some cases they too are oedematous. Scattered throughout the muscle fasciculi is an infiltration with chronic inflammatory cells, which are often found as round or oval focal aggregations either in the connective tissue between adjacent fasciculi or actually extending between individual muscle fibres. In addition, there may be a scattered diffuse infiltration with these chronic inflammatory cells. The larger foci contain vessels of small calibre, but the arteries and veins, although often close to the focal collections, are not in intimate relation with them. The diffuse infiltrations are frequently more prominent along the course of a large vessel. The cells forming these collections, both focal and diffuse, are predominantly small, round cells with compact nuclei of lymphocytic type. Some cells have larger nuclei with the chromatin pattern of plasma cells, and there are a few large mononuclear cells with pale oval indented nuclei. The lymphoid nodules contain no germinal centres. The intramuscular nerve twigs show no abnormality in routine stains.

CONCLUSIONS.—If we accept oedema, fibrosis, and inflammatory cell collections as the principal changes, then we find that these changes are present in all cases examined. The extent and intensity of the changes vary from case to case, but these variations do not allow any basis for distinguishing different types of the disease. The pathological changes found throughout this series correspond with those described by Mulvany (1944) under the heading "thyrotropic exophthalmos". The changes he describes for "thyrotropic exophthalmos" (in which "oedema, diffuse or extensive round-celled infiltration, or marked fibrosis is absent") were not recognized in this series. Mulvany's photomicrographs of the pathological histology of thyrotropic exophthalmos are unconvincing, especially his references to degeneration of the intramuscular nerve bundles, for the staining methods used are not indicated.

Offret's view is that these cases of subacute and chronic orbital myositis are in reality cases of subacute and chronic phlebitis of the intramuscular veins. While vessels of capillary or venule size are regularly found in the centre of the lymphoid nodules, our observations do not support the view that the underlying process is a phlebitis.

To summarize, the pathological findings, irrespective of the clinical history, are essentially the same. There is oedema of the interstitial tissue of the muscle, often associated with degenerative changes in the muscle fibres, and this is accompanied by lymphocytic infiltration, either of focal or diffuse or both. Later there is an increase in fibrous tissue, replacing the degenerated muscle fibres and also thickening the fibrous septa and sheaths. Minor variations in this histological picture do not warrant any subdivision of types of the disease.

DISCUSSION

This series of twelve cases illustrates the wide variations that may occur in this condition, both as regards its natural course and also the response apparent to orbital decompression, thyroid therapy, and other treatments. In the main our observations are paralleled by those of previous authors, but in some respects our conclusions...
run counter to views at present current regarding the nature of the condition. Certain points arise for consideration:

(1) *Is malignant exophthalmos a single entity or not?*

First of all, our findings rather refute Mulvany's view that there are two distinct types of malignant exophthalmos, and instead favour the view that the condition is a single entity.

The wide variations in the symptomatology and clinical course of the disease, and in the apparent responses to orbital decompression and thyroid therapy, led Mulvany (1944), and to a lesser extent Mann (1946), to regard malignant exophthalmos as caused by more than one distinctive pathological process. Our patients illustrate well the differing clinical types. First of all we have a subgroup of five patients (Cases 1 to 5) in whom exophthalmos began within a few days or weeks of thyroidectomy for toxic goitre, and progressed with varying degrees of rapidity, which led to the patient’s being referred to us at periods from a month to three years after the operation. A significant feature in this subgroup is that while removal of the goitre apparently promptly relieved the thyrotoxic symptoms, the ophthalmic features then progressed instead. The clinical features of all five cases would fit them into Mulvany's group of “thyrotropic exophthalmos”, and into Mann's Group II designated “primary excess thyroxine as initial symptom, replaced by excess thyrotropic hormone”. All our five patients were demonstrated as having an excess of pituitary thyrotropic hormone circulating in the blood, but so of course do most patients after thyroidectomy or thiouracil therapy for toxic goitre (Purves and Griesbach, 1949).

Next comes a subgroup of three patients (Cases 6, 8, and 11) in whom malignant exophthalmos was associated with a palpable goitre and with features of thyrotoxicosis. (In Case 6 the clinical manifestations of thyrotoxicosis were late in presenting themselves.) From their clinical criteria these cases would fit into Mulvany's group of “thyrotropic exophthalmos”, and into Mann's Group III designated “excess thyroxine and excess thyrotropic hormone arising simultaneously”. Of our three patients, only one (Case 8) was found to have an increase of thyrotropin in the blood when the ocular condition was active.

Finally, we have a subgroup of four patients (Cases 7, 9, possibly 10, and 12), in whom malignant exophthalmos occurred without thyrotoxicosis and without a palpable goitre. These cases conform to Mulvany's group of “thyrotropic exophthalmos”, as do the post-thyroidectomy cases, and also to Mann's Group I, designated “primary deficiency of thyroxine with compensatory excess of thyrotropic hormone”. Two of our four patients exhibited an excess of pituitary thyrotropin in the blood and two did not.

Now the chief difficulty in regarding these three sub-groups as distinctive pathological types is that in all those in whom orbital decompression was performed, from whichever subgroup they came, we found pale, swollen muscles which, when biopsied, showed the same type of chronic inflammatory change. * We have been unable to confirm in our pathological material

* Certain in one case (Case 6), the operative findings and biopsy examinations were inconclusive, and at the time we deemed the muscles to be virtually normal. But, at post mortem less than 3 weeks later, this impression was speedily corrected, and the case shows how difficult it may be to obtain a true assessment of the orbital contents merely from an operative exposure. Further, in Case 12 we were nonplussed by the finding of a dilated venous channel, and consequently did not explore the orbital muscles.
the histological distinctions between Mulvany's "thyrotropic" and "thyrotoxic" groups which that author described. On the contrary, our findings suggest one histological process common to all cases, with variations in the intensity and degree of the process between individual patients. Instead of being compounded of two or more distinctive types of case, malignant exophthalmos is a single pathological entity which can occur either in association with, or independently of, enlargement of its thyroid and thyrotoxicosis.

(2) What is the relationship of the condition to the pituitary thyrotropic hormone and to thyroxin metabolism?

Our cases indicate that, although malignant exophthalmos can occur without a demonstrable increase of pituitary thyrotropin in the blood and without a palpable goitre and thyrotoxicosis, these three features occur together sufficiently often to indicate that there must be some relationship between them, although the connection is probably an indirect one.

Thus the concentration of pituitary thyrotropin in the blood was estimated in eleven of our twelve cases, and found to be raised in eight and not increased in three. Five of the eight cases in which it was raised however, had a thyroidectomy, and the raised levels in these cases may in part at least, be the sequel of this operation. Of the six cases which had not undergone a thyroidectomy, three showed a slight to moderate increase in the blood and three showed no increase at a time when the ocular protrusion was reaching its zenith. It is perhaps of significance that in many cases, where repeated estimations were made, the levels of pituitary thyrotropin in the blood were observed to fall as the ophthalmic signs receded. In Case 9, however, delayed increase of pituitary thyrotropin was noted some months after the eyeballs had started to recede.

Again, in only three of the twelve cases was malignant exophthalmos associated with thyrotoxicosis, and therefore presumably with an excess of thyroxin secretion. On the other hand, the frequency with which the ophthalmic signs sometimes advance after a thyroidectomy is too great to be a mere coincidence. It seems, therefore, that in some way malignant exophthalmos is related to thyroxin secretion as well as to pituitary thyrotropin, but that the connecting linkages are unknown.

In one patient, in whom exophthalmos was associated with thyrotoxicosis (Case 8), we noted an extraordinary lability in the B.M.R. determinations, which did not seem to be reflected in the clinical state. These are referred to in the case report, and their significance likewise is not known.

(3) Is the condition self-limiting?

It would seem that the condition is often self-limiting, although the degree of recession may be incomplete. One must beware of ascribing a spontaneous improvement to the effects of the particular therapy which happens to have been tried at the time. Dunnington and Berke (1943), in describing their cases of "chronic orbital myositis" draw attention to the self-limiting nature of the condition.

Spontaneous improvement and even recovery were noted in several
patients, especially in Cases 9 and 10, who were not treated surgically but recovered completely. In Case 10 even medicinal therapy was withheld, and in Case 9 a short course of thyroid therapy, given after spontaneous improvement had started and before it was complete, did not seem to influence the result. Similarly, the complete recovery which occurred in Case 12 must have been spontaneous, because it could scarcely have been due to the unilateral orbital operation, and no medicinal therapy had been given. Again, some improvement was noted in Cases 5 and 11 over a period when no medicinal or other active therapy was employed.

For reasons to be considered in the next section, it would seem that spontaneous recovery occurred in the remaining cases also.

(4) *What is the effect of thyroid therapy?*

In contrast to those who have extolled thyroid therapy are the remarks of Means (1948):

The administration of thyroid is based, of course, on the theory that excess thyrotropic activity is a major factor, and that thyroid may suppress such action. We have given thyroid to tolerance in a large number of cases and cannot say that it is productive of very immediate or dramatic improvement.

Thomas and Wood (1936) had earlier reported failure of thyroid administration in five patients with progressive exophthalmos following thyroidectomy. We would go further and say that in our experience thyroid therapy has neither prevented the development of the condition nor noticeably influenced its progress.

Case 8 actually developed malignant exophthalmos after she had been taking thyroid regularly for more than two years to keep her weight down. Also in this case and in four others (Cases 2, 4, 5, and 11), the administration of thyroid in what are generally conceded to be adequate doses did not check the advance of the condition. Furthermore, in none of the remaining cases in which thyroid therapy was employed, as for instance after orbital decompression, was any beneficial result observed that could not equally well be ascribed to the self-limiting nature of the disease.

Usually the administration of 2 to 3 grains thyroid daily produced slight but definite toxic signs, and raised the basal metabolic rate by about 20 per cent. (e.g., Cases 4, 9, and possibly 8), but in other instances (e.g., Cases 2, 3, and 5) there was no definite effect. Indeed, in Cases 2 and 3, an extraordinary tolerance was observed to massive doses of thyroid, even as much as twenty times that which may be expected to produce marked symptoms. Even massive doses of thyroxin given intravenously were without obvious effect in one case. We do not know the significance of these observations, neither have we seen them described previously. Salter and Soley (1944) described a case of malignant exophthalmos treated with intravenous injections of thyroxin with the production of thyrotoxic manifestations and with apparent benefit to the eyes. The amount of thyroxin administered was only a fraction of that used in our case.

(5) *What is the effect of orbital decompression?*

The theoretical principle underlying orbital decompression is the enlargement of the orbit the better to accommodate the swollen orbital
contents, so enabling the eyeball to recede. The operation is purely palliative, and does nothing to correct the unknown aetiological basis of the condition. In some cases it apparently produces striking beneficial results, in some the eyeball does not recede, and in some, after a period of temporary recession, the eyeball protrudes once more as the pathological process within the orbit advances. We have been unable to foretell in individual cases the exact effect of the operation.

Orbital decompression was performed in nine cases. Excluding Case 12, in which a unilateral operation could scarcely have accounted for the improvement that occurred in both orbits, three (Cases 1, 2, and 4) appear to have shown prompt and definite recession of the eyeballs, but in the remainder spontaneous recession of the globes was slight or doubtful. In Case 2 the beneficial effect of the operation appears to have been controlled, for the operation was only performed on one side and only that side improved. Where orbital decompression was promptly followed by recession of the globes, we usually observed at operation that, when the periorbita was incised, the orbital fat bulged upwards as if the orbital contents were under pressure; whereas in those cases where little, if any, bulging of the orbital contents was seen, little or no benefit followed the decompression. There were exceptions to these correlations, yet in both groups the operative findings were otherwise identical: there were the same swollen muscles and the same chronic inflammatory histological changes. We cannot explain, therefore, why the orbital contents seemed to be under increased pressure in some cases, and in others not.

Although little, if any, spontaneous recession of the eyeballs was apparent at the conclusion of the operation in many cases, the swollen orbital tissues could usually be pressed back into the orbit, so that the eyelids could be approximated and stitched together more readily than before. This degree of benefit, although slight and of a passive rather than an active character (e.g., Cases 3, 7, 8, and 11), lasted for several weeks or months while the intra-orbital lesions were at their height, and so helped to preserve the eyeballs until the tide ebbed.

In at least two patients (Cases 1 and 11) the eyeballs, after a slight immediate recession, began to protrude again a few days later, so that fresh corneal ulceration developed, and the globes remained protruded for some time before subsiding again. Evidently this period of protrusion corresponded with the flood tide of the pathological process, and the decompression which had been performed while the tide was rising had apparently had some diminishing effect upon its height.

We feel, therefore, that in certain circumstances, as when the ocular protrusion has reached such a pitch that corneal ulceration has appeared, the operation of orbital decompression has proved a useful adjunct in treatment in spite of its limitations, but that it is not the panacea which some authorities have claimed.

(6) What are the effects of other forms of treatment?

Irradiation of the pituitary to control its thyrotropic activity, irradiation of the orbit, excision of the stellate sympathetic ganglion, and the administration of sex hormones, are other therapies that have been recommended, but all are apparently disappointing in their results.
Malignant exophthalmos is a self-limiting condition, and although it is connected with the secretion of pituitary thyrotropin and of thyroxin, the relationship is an indirect one, and the linkages are unknown. We have no fresh hypotheses to offer to explain the nature of the underlying process.

As regards treatment, thyroid administration is of very doubtful value and is probably ineffective. The effect of any therapy must not be confused with the spontaneous improvement that occurs in the later stages of the condition.

Undoubtedly in one sub-group of cases the ophthalmic signs become aggravated after a thyroidectomy. Therefore, in patients with toxic goitre presenting definite ocular protrusion, as opposed to mere lid-retraction, it is wise to avoid thyroidectomy altogether. If the thyrotoxicosis is slight, thyroidectomy is unnecessary; if the thyrotoxicosis is severe, it is probably safer to treat it by bed rest or by one of the slow non-operative methods. Means (1948), in discussing this point, recommends irradiation of the thyroid or the use of radio-active iodine, rather than thiouracil, which he regards as productive of a "medicinal thyroidectomy", and hence to be avoided for the same reasons as the surgical procedure. We have not been called upon to treat such cases.

In cases of mild or moderate exophthalmos, where the eyeball is not in danger from exposure, active treatment should be withheld in the hope that a spontaneous remission may occur.*

Surgical treatment is indicated if the exophthalmos becomes pronounced. At this juncture, a lateral tarsorrhaphy may be useful as in the cases described by Mann, but in the severest cases, as when chemosis of the conjunctiva and corneal ulceration are present,
orbital decompression should be considered. This operation of itself may greatly benefit some patients, but in others the only benefit apparent may be that the eyeballs can be pressed backwards into the orbit, so enabling the eyelids to be more readily approximated.

The elucidation of the cause and pathology of malignant exophthalmos is one of the most pressing problems confronting thyroid surgery today.

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REFERENCES