



An Oculist Looks at Endocrine Exophthalmos

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Abstract

Based on a talk delivered before the Royal Medical Society on Friday, 12th December 1958.

When it was suggested to me that I should talk around some subject that held interest beyond the strictly ophthalmological one I saw a chance to present the ophthalmologist as someone other than a man confined within the bony boundaries of his orbit, often fighting stern actions to defeat the invasive tactics of his neighbours, the neurosurgeons and the nose and throat doctors. Here was an opportunity to demonstrate the many connections of our subject and the many other branches of medical practice with which we are at times associated, ranging from neurology and rheumatology, through paediatrics, midwifery, and dermatology, to metabolic disease and endocrinology--to mention but a few of the pies in which an ophthalmological finger may be found.

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ISSN: 2051-7580 (Online) ISSN: 0482-3206 (Print)

Res Medica is published by the Royal Medical Society, 5/5 Bristo Square, Edinburgh, EH8 9AL

Res Medica, Autumn 1959, 2(1): 16-20

[doi:10.2218/resmedica.v2i1.327](https://doi.org/10.2218/resmedica.v2i1.327)

AN OCULIST LOOKS AT ENDOCRINE EXOPHTHALMOS

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When it was suggested to me that I should talk around some subject that held interest beyond the strictly ophthalmological one I saw a chance to present the ophthalmologist as someone other than a man confined within the bony boundaries of his orbit, often fighting stern actions to defeat the invasive tactics of his neighbours, the neurosurgeons and the nose and throat doctors. Here was an opportunity to demonstrate the many connections of our subject and the many other branches of medical practice with which we are at times associated, ranging from neurology and rheumatology, through paediatrics, midwifery, and dermatology, to metabolic disease and endocrinology—to mention but a few of the pies in which an ophthalmological finger may be found.

For the purpose of instructing the student and to enable him to compile lists of the 'signs of this' or the 'complications of that' it is necessary to present facts as being either black or white, with little of the many confusing shades of grey which actually lie between. Not only do our classes present this misleading picture but so of course do the books we use.

In the past few years the conception of endocrine influence upon the orbital contents has changed. In the textbook which I used before qualification I find the bare information that the eyes become prominent in Graves' disease and that various clinical signs mainly related to movements of the lids have been described by the gentlemen whose names are perpetuated in this way.

Since that time the emphasis has changed and there are recognised at least two varieties of exophthalmos of an endocrine nature. The first is the classical exophthalmos of Graves' disease, with the staring eyes, tremor, loss of weight and irritability; and the second a far less well-defined condition which may or may not have been preceded by a thyroid upset. This second variety is called exophthalmic ophthalmoplegia and its very name reminds us that one of its features is interference with ocular motility. It is uncertain just how exophthalmic ophthalmoplegia fits into the scheme of things and, in any given case, we may see exophthalmos without much paralysis, gross limitation of movement without exophthalmos, or both together. And again we may see patients showing obvious palsy of ocular muscles and the other features of exophthalmic ophthalmoplegia, together with such thyrotoxic manifestations as lid retraction.

Table 1 represents the general view of the differentiation between what we call 'thyrotoxic' and 'pituitary' exophthalmos. The pituitary appears here as there is little doubt that it has a part to play, and perhaps the major part, in the production of exophthalmos.

If we leave the underlying cause of exophthalmos for the present we can look at the possible forces which might lead to an increased protusion of the eye.

In some animals the globe is surrounded by a sheet of smooth muscle, which could act as a propulsor of the globe, but no such force is available in the human orbit. I am only speaking now of actual exophthalmos, for no

EXOPHTHALMOS

THYROTOXIC

PITUITARY

Female : Male :: 9 : 1 SEX Female : Male
 Early adult AGE Middle life or later
 No OEDEMA Yes
 Present LID RETRACTION Absent
 None DIPLOPIA Often
 Often improves THYROIDECTOMY May be disastrous

TABLE 1

	'THYROID'	PITUITARY	'MIXED'	TOTAL
MALE	3	2	3	8
FEMALE	14	11	6	31
TOTAL	17	13	9	39

TABLE 2

doubt lid retraction, as seen in thyrotoxicosis, occurs as a result of over-activity of the smooth muscle in the upper lid, either in response to thyroxine itself or some related substance.

Vascular congestion has to be ruled out as there is no muscle in the human orbit which might constrict the venous return.

Muscular weakness is another doubtful possibility as the development of generalised muscular weakness in thyroid disease does occur.

The final factor that I want to consider is an increase in the bulk of orbital contents, and this is a factor of recognised importance. It has been shown without doubt that the degree of exophthalmos is quantitatively related to the increased bulk of the orbital contents, and a similar increase in bulk has been demonstrated in experimental exophthalmos.

But what is the ultimate cause of the protrusion?

There is no need for me to remind you that we should regard endocrine disorders as perversions of normal physiology rather than as true diseases,

and it is clear that each of the ductless glands may influence others either by the direct stimulating action of its hormone, or by the way in which variations in the concentration of one circulating hormone influence the production of another. We know that the anterior pituitary, by its thyroid stimulating hormone, controls thyroid activity. The amount of thyroxine produced, in its turn, alters the output of pituitary thyrotrophic hormone.

Thyroxine itself does not cause exophthalmos; though it (or one of its allies) has a sympathetic-like effect on the smooth muscle of the orbit, leading to lid retraction. That this sign is not due to actual sympathetic overactivity is proved by the occurrence of lid retraction in cases where the cervical sympathetic is paralysed.

That some substance other than thyroxine causes protrusion of the eyes is brought home to us most dramatically in those cases in which exophthalmos develops or increases after reduction of thyroid secretion, either surgically or otherwise.

It is more than twenty years since experimental evidence was produced to show that the pituitary could lead to proptosis in rabbits and that this proptosis occurred more readily after thyroidectomy. Soon afterwards, the injection of anterior pituitary extracts was shown to induce proptosis of the eyes in minnows.

In man, however, the circulating levels of pituitary thyroid stimulating hormone have not been linked with the degree of exophthalmos; and the injection of serum from certain exophthalmic patients has been shown to give rise to ocular protrusion in a certain species of goldfish, while serum from other patients produced no such effect.

It is in fact uncertain that there is a single pituitary hormone involved. Methods of assay are so difficult technically and so uncertain in their interpretation that it cannot be said that the exophthalmos producing factor and the thyroid stimulating hormone are one and the same thing.

This brings one to wonder whether there are not perhaps two variables interacting with one another; the first a hormonal stimulus whose nature is certainly linked in some way with the pituitary, and the second the orbital contents acting as the target organ, whose response to the stimulus is so uncertain. That some variation in organ response occurs is indicated by the not infrequent occurrence of unilateral proptosis, or proptosis which is so asymmetrical as to remain unilateral for some time and to lead to the suspicion of the presence of a local orbital lesion.

We cannot leave the question of the causation of exophthalmos without wondering if other endocrines are in some way involved. A suggestion linking the adrenals with Graves' disease was originally based on the occurrence of skin pigmentation in thyrotoxicosis. With the introduction of cortisone and corticotrophin into clinical practice, it was not unexpected that the effect of these substances on exophthalmos should be investigated. In fact the Medical Research Council sponsored two investigations into the problem and the net result was to the effect that no significant benefit occurred after the use of cortisone and ACTH in exophthalmic ophthalmoplegia.

While the use of steroids therapeutically has not found support, we are now seeing some evidence of the influence of cortisone on the development of exophthalmos. In this case experimental exophthalmos induced by cortisone is prevented by removal of the pituitary and lessened by the production of thyrotoxicosis by thyroxine. A similar result has been obtained in rats rendered exophthalmic by thiouracil due to uninhibited activity of the pituitary. The exophthalmos was markedly increased by cortisone. There seems no doubt that cortisone was acting through the pituitary and not by a direct action on the contents of the orbit.

I think we can accept the pituitary as being the prime mover (literally)

in the production of exophthalmos though the mechanism is not clear. Whether this result is simply a secondary effect of uninhibited thyroid stimulating hormone or a specific function of some other fraction of the pituitary secretion is unknown. It seems hardly possible, as someone has previously remarked, that the small amount of fat found in the normal orbit has a function so important that a pituitary hormone is detailed to control its amount.

Whatever may be the actual cause of exophthalmos I think that we would now agree that the two types are not separate entities, but merely represent, as it were, a change of emphasis; an alteration in balance; an infinite gradation of features, from the condition seen in simple toxic goitre where lid retraction predominates, to the grossly oedematous state of the orbit, with diplopia, ocular palsies, and, often, real risk of the loss of an eye.

It is not my intention to discuss differential diagnosis or treatment. This avoidance is not to be taken as indicating any lack of importance, for the choice of appropriate treatment and the time at which to apply it may stretch the combined judgment of the physician, ophthalmologist, neurosurgeon and radiotherapist. Battles may easily rage among the rival claimants of radiotherapy, orbital decompression, tarsorrhaphy, and endocrine replacement therapy, as being the treatment of choice in any given case. It is simply that I regard these problems as too technical to be usefully discussed at this time.

I have said that we speak about two types of exophthalmos; the thyrotoxic variety associated with lid retraction, and generally accepted as being much commoner in women; and the pituitary type, characterised by oedema of the orbital tissues, palsy of ocular muscles and risk of damage to the eye through exposure. In this type the sexes are equally represented and the disease tends to occur at a later age than does the first variety.

We must remember that, working in a specialised field, each of us may be seeing a series of cases not at all representative of the overall picture. This snag is illustrated by my examination of the records of the cases of exophthalmos appearing in the index of the Eye Department for the years 1955, 1956, and 1957. There are thirty-nine cases, which must indicate that only certain cases come into our hands, as exophthalmos must surely be commoner than this.

It has not been possible for me to divide these cases strictly into the 'toxic' and 'pituitary' groups, for there are a number of cases showing features of both kinds, and these we must call the 'mixed' group. (Table 2.)

There are appreciably more women than men, but there is no evidence in these figures that would say that toxic signs are more likely in the early age groups or that exophthalmic ophthalmoplegia is really a disease of later life. In this series I have a girl of seventeen and an old lady of seventy-three, both apparently suffering from thyrotoxicosis; while there are also three women in the middle thirties showing well-marked paralytic signs. Even if you take the average ages you are not getting much help, for the average ages of the women with toxic eye signs is fifty and of those with pituitary eye signs forty-five years; though you do not need me to remind you of the dangers attached to the taking of averages when there are only small numbers involved.

In the past there has been more than one suggestion that these cases of exophthalmos sometimes get worse if the balance between their various glands is interfered with, by a surgical or medical attack on their thyroid activity.

I think we have all seen this happen; though a reported series of 533 operations of thyroidectomy performed elsewhere apparently only produced three such events. I find it difficult to be so sanguine. Of the thirteen cases

I have designated purely 'pituitary' in this small series, nine had had previous treatment directed at reducing thyroid activity. This had taken the form of antithyroid drugs in five cases, surgery in three and radioactive iodine in only one. The other four cases of exophthalmic ophthalmoplegia apparently arose *ab initio* with no previous thyroid disturbance.

There are these various ways, therefore, in which our rather specialised experience in an eye-department seems to show us a different side of the picture from that seen elsewhere.

For my part, I find difficulty in understanding why exophthalmic ophthalmoplegia may arise sometimes several years after the original disturbance of endocrine balance and why this condition so often subsides again, apparently spontaneously, if allowed time to do so. Time is the important factor here. If we can ensure the integrity of the eye and watch the progress of the various orbital changes day by day or month by month, a condition of stability seems often to be restored, and we may find that all is well.

Another feature that is hard to explain is the occurrence of ocular palsy without exophthalmos. It is easy to understand limitation of ocular movement in the grossly oedematous orbit of the severe case, where the whole orbital circulation seems almost strangulated; but why should an isolated ocular palsy occur in the absence of a local lesion to account for it?

There is a great deal more that could be said about exophthalmos; about its treatment; about its effect on the function of the optic nerve with consequent field changes; about corneal ulceration and perforation; and about the severe burden that the condition imposes on its sufferers, for it may be unsightly in the extreme.

Nobody knows the answer to it all, and perhaps some of you may, in the future, be granted the ability to put another brick or two in place and so help to build up the whole.