Recommendation 31: D.E.S. Research Councils not to have the right to reject Contracts from Departments without Good Reason agreed with the Sponsoring Department.—This proposal is acceptable only in relation to any transitional period when the departments concerned are obliged to spend a particular sum through the Medical Research Council and some safeguard would be required even during the transitional period.

Recommendations 32-33: Right of Departments to contract Work to Organizations other than the D.E.S. Research Councils.—The Council agree.

Recommendation 35: Financial Transfers, amounting to £27.7 million from the D.E.S. to the M.A.F.F., D.H.S.S., D.O.E., S.H.H.D., and S.D.D.—The Council are unable to agree with the figures in Table 4, which appear to be calculated on no logical basis. The Council recommend that no transfer should be made until a full review has been carried out—see Memorandum, paragraph 12.

Recommendations 39-40: Representatives of the appropriate Departments to the M.R.C., A.R.C., and N.E.R.C. Members.—The Council do not agree with the assertion in paragraph 35 of the report that the Department of Health and Social Security and the Scottish Home and Health Department participation in the M.R.C.'s affairs has been small. In addition to the welcome presence of the chief medical officers of the two departments as assessors on the Council and as assessors on the Clinical Research Board there is currently participation by health department assessors or members in the work of the majority of the Council's committees and working parties, and there is an extremely close day-to-day relationship between the staffs of the departments and the Council at all levels. Nevertheless, while the Council believe that the health department assessors have had every opportunity to represent the views of their departments they have no objection to the representation of Government departments on the Council, provided that the number of representatives is not so large as to cast doubt on the independence of the Council. This independence is, in the Council's view, an important asset to all the users of medical research—the Government, the medical profession, and the public. It helps the Council to secure collaboration in research programmes with many people, and it facilitates access to confidential information needed for research purposes. Codes of conduct in research matters which touch on the ethics of the medical

profession are formulated by the Council in a way which generally secures acceptance by the profession.

Recommendations 41-42: Functions and Composition of the Council for Scientific Policy.—The Council would welcome the appointment of their Secretary as a member of the C.S.P. The President of the Royal Society should also be a member of this body. The Royal Society has an important contribution to make in many of the problems coming before the Council for Scientific Policy.

Recommendation 43: the useful Lifespan of D.E.S. Research Council Units needs Special Attention.—The following is the record of closures for M.R.C. units in recent years (out of a total of about 70 units):

1966-67 ...	3	1968-69 ...	1	1970-71 ...	3
1967-68 ...	6	1969-70 ...	3	1971-72 ...	4

In addition, in 1969 the Council approved a reduction in the scale of one of its major units to about half its former size. When closing units, however, the Council are always mindful of the interests of their staff and seek to minimize any hardship or dislocation of careers that might result. The stringency of the Council's current policy is illustrated by the fact that in the past year they have decided to close two units before the completion of the proposed period of tenure.

DAINTON REPORT

The Council endorse the analysis of the situation presented in parts II to VI of the report and the conclusion that the advantages of the research council system should be retained while providing stronger links with the needs and policies of Government departments. A board on the general lines proposed in the Dainton report, including members from the research councils and departments, is desirable. This would provide opportunities to strengthen the partnership between departments and the research councils. However, the Council think that the board should be advisory rather than executive and that there is no need for it to be a chartered body. There would be some advantage in retaining flexibility over its composition—at least in the early years.

Clinical Endocrinology

Endocrine Exophthalmos

C. W. H. HAVARD

British Medical Journal, 1972, 1, 360-363

Exophthalmos or proptosis refers to forward displacement of the eyeball and must be distinguished from retraction of the eyelids, which causes an illusion of exophthalmos. This is especially so when lid retraction is unilateral, in which case the eye showing lid retraction will appear to have a much higher degree of exophthalmos. In a study of 100 patients with thyrotoxicosis treated with antithyroid drugs Barr and Shorr¹ noted an apparent reduction in exophthalmos in all patients. Nevertheless, when the degree of exophthalmos was measured in no case was there any reduction and in some patients it had increased from 2 to 4 mm. Lid retraction is attributed to activation of the autonomic nervous system. Exophthalmos is a

more serious disorder of unknown aetiology and inflammatory or infiltrative in character. Lid retraction occurs in half the patients with Graves's disease, whereas exophthalmos is only present in a quarter.² True protrusion of the eyeball results in the white of the sclera becoming visible between the iris and both the lower and upper lids. Readings with an exophthalmometer usually show a forward protrusion of 18 to 20 mm, but lower readings may be found with distressing symptoms.

Though exophthalmos may occur in Cushing's syndrome,³ it is essentially a feature of thyroid disease. Exophthalmos commonly starts shortly after the development of thyrotoxicosis, but it may arise months or even years after this has been treated successfully. The worst examples of exophthalmos occur in the euthyroid state and may appear in patients who have never had thyrotoxicosis. Exophthalmos has also been described in chronic thyroiditis.⁴ In some instances the only evidence of thyroid dysfunction is a failure of administered tri-iodothyronine to suppress the ¹³¹I uptake. The course of the exophthalmos is

Royal Free Hospital and Royal Northern Hospital

C. W. H. HAVARD, D.M., F.R.C.P., Physician in Charge, Endocrine Unit, Royal Free Hospital. Physician, Royal Northern Hospital.

unpredictable. When associated with thyrotoxicosis it may improve when the hyperthyroidism is controlled or it may get worse, but it commonly shows little change. Of 50 patients reported by Brain⁵ with severe exophthalmos, 23 were toxic, 24 euthyroid, and 3 hypothyroid—and, more importantly, 9 had never been thyrotoxic.

Endocrine exophthalmos has several synonyms. Some, such as ophthalmic Graves's disease, describe the ocular manifestation of Graves's disease in patients who are euthyroid and have no past history suggesting hyperthyroidism. Others, such as endocrine exophthalmos, are equally applicable to patients with or without thyrotoxicosis. Progressive exophthalmos, infiltrative ophthalmopathy, dysthyroid eye disease, thyrotrophic exophthalmos, malignant exophthalmos, and exophthalmic ophthalmoplegia have also been used to describe the same disorder. There is no fundamental difference between the endocrine exophthalmos of thyrotoxicosis and that associated with normal thyroid function, apart from the greater tendency to asymmetry in ophthalmic Graves's disease.

Clinical Features

Clinically endocrine exophthalmos may present with nothing more than an increased prominence of one or both of the eyes. It is commonly asymmetrical and frequently unilateral.⁶ The retro-orbital infiltration or ophthalmopathy is, however, always bilateral.⁷ The patients may complain of grittiness and a feeling of pressure together with photophobia. Forward protrusion of the eyes separates the lids, and this may be accentuated by lid retraction when hyperthyroidism coexists. Conjunctival oedema may become extreme and lead to eversion of the lower eyelid, with interference of lacrimal drainage. Inability to close the eyes (lagophthalmos) and consequent exposure of the globe may lead to ulceration and perforation of the cornea with loss of vision.

Extreme degrees of ocular dislocation result in stretching of the optic nerves, papilloedema, and visual impairment. Diplopia may develop due to infiltration and weakness of the external ocular muscles. Convergence and elevation of the eyes are restricted initially and the upward and outward movements of the eye are particularly affected. In rare instances paralysis may become complete with central fixation of the globes. The severity of the ophthalmoplegia is not directly related to the magnitude of ocular protrusion and it appears to bear an inverse relation to the degree of thyrotoxicosis. Vision may be lost as a result of optic neuritis, retinal haemorrhage, or corneal ulceration. Exophthalmos may have a sudden onset and progress rapidly over a few weeks. On the other hand, more commonly it develops insidiously and progresses slowly. The more rapid the protrusion develops the greater the risk to the eyes.

Progression may cease spontaneously; occasionally the exophthalmos may subside as rapidly as it develops. Though progression ceases spontaneously in most patients, some degree of protrusion remains and regression is rarely complete. The longer the exophthalmos has been present the less likely is regression to occur. Total return of exophthalmos to normal after persistence for over six months is unusual. Endocrine exophthalmos may be associated with pretibial myxoedema and clubbing of the fingers, a triad known as thyroid acropathy.

Pathology

The conspicuous finding in exophthalmic subjects at operations to decompress the orbit is the increased bulk of the orbital contents due to fat, mucopolysaccharide, and oedema.^{8,9} The extraocular muscles are enlarged to three to eight times their normal size and they vary in colour from a deep red to a pale, half-cooked appearance and appear hypertrophied and oedema-

tous.¹⁰ Retro-orbital fat has a peculiar characteristic in its tendency to oedema, which is not shared by renal or axillary fat.¹¹ The histological changes are well recorded.

Oedema fluid separates the muscle fibres and fatty and mucopolysaccharide infiltration into retro-orbital tissue occurs. Invasion by lymphocytes and plasma cells is prominent and fibroblasts proliferate and lead to the formation of fibrous tissue, which in long-standing cases may virtually replace the muscles. The increase in diameter of the muscle fibres is accompanied by a loss of striation and an increase in granularity. These changes are also present to lesser degree in patients with thyrotoxicosis who do not have eye signs.¹² Histological changes are not restricted to the retro-orbital space and may occur in other peripheral tissues—pretibial myxoedema and finger clubbing are two familiar examples.

Infiltration ophthalmopathy is a regular finding in Graves's disease, but it is not synonymous with exophthalmos. Not all patients with orbital infiltration develop exophthalmos, presumably because the orbital cavity is sufficiently large to accommodate the increased retro-orbital contents. About 6% of patients with orbital infiltration develop chronic dysthyroid infiltration without exophthalmos, and this is characterized by orbital pain with chemosis and conjunctival injection together with an increase in orbital tension without exophthalmos.¹³

The immediate cause of exophthalmos is the increase in volume of the retro-orbital tissues and a consequent rise in intraorbital pressure. The critical factor in exophthalmos is the ratio between the bulk of the orbital tissue and the volume of the orbit. The capacity of the orbit varies widely and a minor degree of retro-orbital enlargement may cause exophthalmos in some people.

Investigation

Exophthalmos may occur with any space-occupying lesion within the orbit. The fact that endocrine exophthalmos is frequently unilateral, especially in the euthyroid patient, makes it important to be able to exclude other causes of exophthalmos. The association of exophthalmos with lid retraction, even if unilateral, makes the diagnosis of endocrine exophthalmos almost certain. Similarly, if the patient is or has been thyrotoxic the likelihood of a diagnosis of endocrine exophthalmos is great. Asymmetry of exophthalmos rarely exceeds 6 mm in endocrine exophthalmos, but this figure is exceeded in four out of five patients with orbital tumours.¹⁴ The normal globe sinks back in the recumbent position and the exophthalmometer reading is correspondingly reduced by 1 to 3 mm. This postural difference is absent in both eyes in endocrine exophthalmos.⁷ In unilateral exophthalmos due to an orbital tumour the physiological postural difference is preserved in the opposite eye.

The presence of thyroid antibodies in high titre is also a useful diagnostic aid.⁶ Nevertheless, if unilateral exophthalmos is not associated with lid retraction in a euthyroid person, causes other than endocrine are likely to account for nearly 80% of cases.¹⁵ While pulsating exophthalmos or the presence of bruits makes a vascular pathology certain, these diagnostic features are unusual and hence it is important to have some scheme of investigation to ensure that retro-orbital tumours and intracranial lesions are not overlooked. Plain x-ray films and carotid angiography will detect the intracranial lesions causing exophthalmos as well as those originating in the nasopharynx or paranasal sinuses. Intraorbital lesions are, however, more difficult to demonstrate by these procedures and only two-thirds will be detected. Even with orbital pneumography and orbital venography no abnormality will be observed in one-quarter of those patients with non-endocrine retro-orbital lesions causing unilateral proptosis.¹⁵ Symptoms such as progressive loss of vision and signs such as papilloedema or optic atrophy should suggest the diagnosis of a primary orbital tumour.

Aetiology

The association of exophthalmos with the general symptoms of thyrotoxicosis has been known for nearly 120 years¹⁶ but the aetiology is still obscure. In at least half the euthyroid patients with endocrine exophthalmos, the ¹³¹I uptake by the thyroid cannot be fully suppressed by tri-iodothyronine (see Table).

Tri-iodothyronine (T3) Suppression Test in Patients with Ophthalmic Graves's Disease

Series	Uptake	Daily dose T3	No. of Patients	Failure of Suppression with T3
Werner ¹⁸	24-hr ¹³¹ I	75µg, 8 days	10	10
Guinet & Descour ⁴⁵	24-hr ¹³¹ I	200µg, 8 days	13	9
Burke ⁴⁶	24-hr ¹³¹ I	75µg, 8 days	8	4
Bayliss ⁴⁷	4-hr ¹³¹ I	120µg, 6 days	12	11
Wyse <i>et al.</i> ⁴	24-hr ¹³¹ I	75µg, 5 days	6	5
Bowden & Rose ⁴⁸	4-hr ¹³¹ I	120µg, 3 days	23	15
Hall <i>et al.</i> ⁴	6-hr ¹³¹ I	100µg, 7 days	26	13

It is known that in Grave's disease the suppressibility of iodine uptake tends to return with remission in most patients, possibly owing to reduction in the level of the long-acting thyroid stimulating hormone (L.A.T.S.).

It was therefore natural that L.A.T.S. should be considered as a cause of endocrine exophthalmos. Nevertheless, a frequent finding of normal suppression along with the low frequency of detectable L.A.T.S. in the blood of patients with ophthalmic Graves's disease is evidence against L.A.T.S. playing a major part in the pathogenesis of the eye signs of Grave's disease.⁶ Pituitary thyrotrophic hormone (T.S.H.) is unlikely to be a major aetiological factor, as its level is usually decreased and often undetectable in patients with thyrotoxicosis.¹⁸

Though some authors have reported a correlation between the L.A.T.S. response and the severity or progress of exophthalmos,¹⁹ others have not found this.²⁰ It has been suggested that L.A.T.S. may have an aetiological role in producing exophthalmos but because it is important only during the acute stage of the development of proptosis it may not be detected in established exophthalmos.¹⁹ The clinician is acutely aware that deterioration of eye signs is not associated with increasing thyroid activity, so that if L.A.T.S. is the cause of thyrotoxicosis it is unlikely to be responsible for exophthalmos. Correlation of the presence of L.A.T.S. is closer and more uniform with the presence of pretibial myxoedema than with any other aspect of clinical correlation.²¹ Furthermore, whereas thyroid tissue neutralizes the biological activity of L.A.T.S., retro-orbital adipose tissue and muscle tissue do not, even when obtained from hyperthyroid patients with exophthalmos.²²

Another factor which plays an undefined part is the exophthalmos-producing substance (E.P.S.)—a factor in serum which can be shown to produce exophthalmos in animals. Nevertheless, it is unlikely that L.A.T.S. and E.P.S. are identical substances since measurements of both activities in the same subject have shown a lack of correlation, one frequently being strongly positive and the other negative.²³ Moreover, L.A.T.S. has not been found in pituitary extracts containing E.P.S.²⁴ The best interpretation of this data is that the occasional coincidence of high L.A.T.S. concentration and severe exophthalmos is that they both reflect autoimmune phenomena with the precise role of autoimmunity in the causation of ophthalmopathy still to be defined.²⁰ This is supported by the fact that hyperthyroid patients with exophthalmos have higher titres of thyroglobulin antibodies than those without proptosis.^{25, 26} The incidence of high titres of thyroglobulin antibodies is significantly greater in patients with ophthalmic Graves's disease than in those with thyrotoxicosis.⁶

It has been suggested that patients with ophthalmic Graves's disease do not become hyperthyroid because their thyroid reserve is limited and hence the gland is unable to respond to thyroid-stimulating agents.²⁷ This is not so because many of these patients can increase their iodine uptake and protein-bound iodine concentration in response to stimulation by T.S.H.^{6, 28}

Exophthalmos can be produced in animals by the injection of pituitary extracts. This exophthalmos is due to an increase in bulk of the retro-orbital tissues, especially orbital fat.²⁹ The exophthalmos-producing substance of the anterior pituitary is distinct from thyrotrophic hormone.³⁰ The serum of patients with endo-

crine exophthalmos also contains a substance capable of producing exophthalmos in animals.^{31, 32} It has never been proved that exophthalmos-producing substances in the serum are the same as those studied in pituitary extracts, and clinically exophthalmos may occur in patients who have had their pituitary glands removed.³³ Experimental exophthalmos has recently been produced in the guinea pig by sensitization to homologous Harderian gland.³⁴ All immunized animals developed exophthalmos at about 25 to 35 days; control animals given Freund's adjuvant alone did not. The exophthalmos was of the same magnitude as that produced by pituitary extracts and was associated with cellular infiltration and circulating antibody. This suggests that exophthalmos may develop as a result of inflammation of retrobulbar tissues. There is recent evidence that the blood of some exophthalmic patients contains an immunoglobulin which unlike L.A.T.S. increases the weight of the Harderian gland in the guinea pig.³⁵

Management

Since the cause of endocrine exophthalmos is unknown treatment has remained empirical. Most of the published therapeutic trials have been uncontrolled and the results are difficult to interpret as the disorder is subject to spontaneous remissions and relapses. The aim of treatment is to prevent corneal ulceration and panophthalmitis. If papilloedema is present treatment is directed to preventing optic atrophy and preserving sight by an operation of decompression.

Time is on the patient's side as endocrine exophthalmos is a self-limiting disease. Since ocular symptoms are usually worse in the morning the patient should be advised to sleep with the head propped up on pillows—for with diminution of venous engorgement the nocturnal increase in oedema is lessened. Eye-drops such as methylcellulose may be helpful in soothing the gritty sensation in the eyes. Spectacles with dark lenses relieve photophobia and also protect the eye from irritating winds with some relief of excessive lachrymation. If ophthalmoplegia is present the affected eye may be covered by spectacles containing a frosted lens. Side-shields fitted to the spectacles reduce the risk of abrasion of the cornea by dust particles, and eye-pads worn at night effect approximation or closure of the lids.

Diuretics may afford some relief; guanethidine eye-drops improve lid retraction but have little effect on exophthalmos.^{36, 37} They may, however, improve the gritty sensation and the peri-orbital oedema. The only effective medical treatment of severe exophthalmos is corticosteroid therapy.^{38, 39} Large doses are necessary—usually 60 mg prednisolone daily or more—but this regimen is successful in more than half the cases. The doses of steroid may be reduced by combining it with an immunosuppressive agent such as azathioprine. Corticosteroids are of greatest application in rapidly progressive exophthalmos.

LOCAL TREATMENT

Local treatment of the eyes is directed towards preventing corneal ulceration and subsequent infection. More severe proptosis preventing adequate opposition of the eyelids warrants a lateral tarsorrhaphy or requires that the lids be sewn together completely. Good initial results have been reported from the intraorbital injection of corticosteroids,¹⁸ but this form of treatment has not received widespread acceptance. Irradiation of the orbit is effective in reducing ocular proptosis in some patients,⁴⁰ while there are reports of improvement in endocrine exophthalmos after pituitary ablation.⁴¹ Often, however, the improvement has only been subjective and the degree of ablation achieved undocumented. Moreover, exophthalmos may appear in the other eye after hypophysectomy for the same condition in the first eye.³⁸ A beneficial effect from total thyroidectomy whether by surgery or by ¹³¹I has not been confirmed.¹⁸ Diplopia may be due to contractures of the extraocular muscles. In the healed fibrotic phase of the disease and when the condition is stable, surgical relief of contractures can be undertaken.

MALIGNANT EXOPHTHALMOS

The most effective treatment of malignant exophthalmos is orbital decompression. It should be considered if vision is threatened as a result of raised intraorbital pressure or from severe exposure keratitis. Corneal ulceration, papilloedema, or serious limitation of eye movements may also be indications for operation. There are various operations: in some the floor of the orbit is removed, in others the lateral wall, and in the Naffziger operation the roof. Operative interference is considered only in patients whose vision is threatened by extreme proptosis. In this condition, when retinal vein distension and papilloedema may be evident, lateral or even supraorbital decompression offers a predictable means of relief and a chance to preserve the eye. This is a major operation requiring an expert surgeon, but the results are often striking.⁴² The transantral approach to the floor and medial wall of the orbit by means of a Caldwell-Luc exposure has recently become favoured. It is simple, safe, and effective, and it has the additional advantage of not being an intracranial procedure.⁴³

Much debate has centred on the effect of different methods of treatment for thyrotoxicosis on the patient's exophthalmos. Exacerbation of exophthalmos may occur after any form of treatment of thyrotoxicosis—whether it is antithyroid drugs, subtotal thyroidectomy, or radioactive iodine therapy—though the incidence of deterioration is small, usually about 10%.^{19 44} It is important to avoid hypothyroidism, but there is no rationale for giving thyroxine to euthyroid patients. Even so, there may be an argument for controlling the hyperthyroid state cautiously. There is clinical evidence that in thyrotoxic patients treated by drug, surgery, or radiation there is a greater fall in the serum protein-bound iodine level and a greater rise in L.A.T.S. in those developing an exacerbation of exophthalmos than in those who do not develop this complication.⁴⁴

In conclusion, endocrine exophthalmos can usually be recognized clinically even in euthyroid patients. In a majority the diagnosis can be confirmed either by a failure of tri-iodothyronine to suppress the ¹³¹I uptake or by the presence of thyroid antibodies. As far as treatment is concerned it should always be remembered that time is on the patient's side and a conservative course should be pursued unless exposure keratitis or papilloedema constitute a threat to vision, when a more radical approach to decompress the orbit is indicated.

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Scientific Basis of Clinical Practice

The Haemoglobinopathies

G. W. G. BIRD

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Haemoglobinopathies are inherited disorders of haemoglobin synthesis. They comprise, firstly, the thalassaemias, in which the synthesis of haemoglobin is impaired, and, secondly, the abnormal haemoglobin syndromes, in which normal haemoglobin is replaced by a structural variant.

Blood Transfusion Service, Birmingham B15 2SG

G. W. G. BIRD, PH.D., F.R.C.PATH.

The Haemoglobin Molecule

The haemoglobin molecule consists of a protein, globin, to which is bound a prosthetic group, haem, an iron-porphyrin compound. The iron in haem is in the divalent (ferrous) state and is able to combine reversibly with oxygen to form oxy-haemoglobin without change in the valency of iron.

Much precise information has been obtained about the structure of haemoglobin.

It has a primary structure of two pairs of amino-acid chains; a secondary structure, which is a regular α -helical coiling of the