Occasional Review

Progress in endocrine exophthalmos

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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. Lid retraction usually results from activation of the autonomic nervous system. Exophthalmos is a more serious disorder caused by inflammatory and infiltrative changes in the retro-orbital tissues, and is essentially a feature of Graves's disease, though it has been described in chronic thyroiditis¹ and may occur in Cushing's syndrome.² Exophthalmos commonly starts shortly after the development of thyrotoxicosis but may arise months or even years after hyperthyroidism has been successfully treated.³ Only 2-3% of patients with Graves's disease develop severe exophthalmos.⁴ The degree of exophthalmos is not correlated with the severity of hyperthyroidism, even when their onset is simultaneous. Some of the worst examples of endocrine exophthalmos occur in the euthyroid state and may appear in patients who have never had thyrotoxicosis—a disorder named ophthalmic Graves's disease.

Clinical features

Increased prominence of one or both eyes may be the only clinical sign of endocrine exophthalmos. It is commonly asymmetrical and often unilateral,⁵ though retro-orbital infiltration or ophthalmopathy is always bilateral.⁶ 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. 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 nerve, papilloedema, and visual impairment. Raised orbital pressure also causes loss of vision through reduced blood supply to the optic nerve. Diplopia may develop because of infiltration and weakness of the external ocular muscles. Convergence and elevation of the eyes are restricted initially, the upward and outer movements being particularly affected. Severity of ophthalmoplegia is not directly related to the magnitude of ocular protrusion, and severe ophthalmoplegia may exist with minimal exophthalmos. Vision may be lost as a result of optic-nerve stretching, retinal haemorrhage, or corneal ulceration. Exophthalmos may have a sudden onset and progress rapidly over a few weeks, though it more often develops insidiously and progresses slowly. Rapid protrusion increases the risk to the eyes. Though progression stops spontaneously in most patients, some degree of protrusion remains and regression is rarely complete. Endocrine exophthalmos may be associated with pretibial myxoedema and clubbing of fingers, a triad known as thyroid acropachy.

Pathology

The pathological changes in the orbit include inflammation and oedema of the connective tissue, fat, and extraocular muscles. The extraocular muscles are enlarged three to eight times their normal size.⁷⁻⁹ Oedema fluid separates the muscle fibres and glycosaminoglycans (mucopolysaccharide) infiltration into retro-orbital tissue occurs. Invasion by lymphocytes and plasma cells is prominent, and fibroblasts proliferate, leading to the formation of fibrous tissue that may eventually replace the muscle. These changes also occur in patients with Graves's disease who do not have exophthalmos, and ultrasonography has confirmed an increase in size of the extraocular muscles in most cases of Graves's disease.¹⁰ In such patients the orbital cavity may be large enough to accommodate the increase in retro-orbital contents.

The two probable pathological processes are: firstly, myositis of the extraocular muscles with oedema, fat, and lymphocytic infiltration and muscle necrosis; and secondly, proliferation of retro-orbital fat and connective tissue.¹¹

Pathogenesis

Hyperthyroidism of Graves's disease is due to immunological stimulation of the thyroid-stimulating hormone (TSH) receptor on the thyroid cell membrane. Thyroid-stimulating (TS) antibodies are antibodies to the TSH receptor and are found in 70-90% of patients with Graves's disease.¹²⁻¹⁴ Some of these antibodies mimic all the effects of TSH, while others fit the receptor incompletely and can provoke the effects of TSH only partially. The long-acting thyroid stimulator (LATS) does not stimulate the human thyroid but increases thyroid activity in many mammals.¹⁵ The human thyroid-stimulating IgG or LATS-protector is specific for the human thyroid.¹² These antibodies are called thyroid-stimulating antibodies to distinguish them from the more familiar destructive antibodies that are directed against thyroglobulin and intracellular thyroid microsomes and are responsible for Hashimoto's disease and primary myxoedema. Human TS antibodies activate adenyl cyclase in plasma membrane preparations of human thyroid gland.¹⁶ Cytochemical assays, the basis of which is that the selected hormone will appreciably alter some chemical activity of its target cell, have been used to show the ability of TS antibodies to activate endocytosis of colloid droplets by thyroid follicle cells in vitro.¹⁷ The intracellular colloid droplet count is a sensitive indicator of thyroid function. TS antibodies also accelerate secretion of thyroid hormone in human volunteers,¹⁸ inhibit the binding of TSH to its receptor on the thyroid cell membrane,¹² and protect LATS from neutralisation by thyroid extract by competing with LATS for a receptor in thyroid tissue—hence acquiring the name of LATS protector.¹⁹ Another group of antibodies bind to the TSH receptor but neither stimulate nor destroy,¹¹ presumably because they fit the receptor so incompletely that they cannot mimic any of the effects of TSH.

Immunoglobulins from patients with endocrine exophthalmos induce proptosis in animals by stimulating retro-ocular tissues.²⁰ Experimental exophthalmos has also been produced in guinea-pigs by sensitisation to homologous Harderian gland.²¹ All immunised animals developed exophthalmos after about 25-35 days; controlled animals given Freund's adjuvant alone did not. The exophthalmos was as extensive 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 retro-orbital tissue.

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Relation of TSH to orbital fat

TS antibodies are relevant to exophthalmos because TSH receptors are found on retro-orbital fat cells.²²⁻²³ The reason for this is uncertain, though it may be teleologically related to the need for rapid heat production in the neonatal period by activation of TSH receptors on the cell membranes of brown fat.¹¹ TSH has a lipolytic effect on adipocytes *in vitro*.²⁴⁻²⁵ More recently, TSH and TS antibodies have been shown to have similar effects on guinea-pig adipose tissue,²² and thyrotrophin-receptor sites have been shown on purified plasma membranes from human adipocytes.²⁶⁻²⁷ Furthermore, TSH can be fragmented by partial pepsin digestion to yield a derivative with exophthalmogenic activity, but no thyroid-stimulating ability.²⁸ This derivative, which is called the exophthalmos-producing substance, induces exophthalmos in guinea-pigs.²⁹ This is interesting, since many years ago pituitary extracts were known to induce exophthalmos in animals, and even then the thyroid-stimulating factor could be separated from that which caused exophthalmos.³⁰ An exophthalmos-producing immunoglobulin is also found in the sera of patients with endocrine exophthalmos,²⁰ and this IgG increased *in-vitro* binding of TSH and the TSH-derived exophthalmos-producing substance to plasma membranes of guinea-pig retro-orbital tissues but not to thyroid plasma membranes.³¹ It enhances the binding of the exophthalmos-producing substance to retro-orbital tissue plasma membranes by increasing the number of TSH receptors and shifting the association constants of receptors to much lower levels.²²

This evidence may show that human exophthalmos is caused by the synergistic effects of an exophthalmos-producing immunoglobulin and a derivative of TSH molecule with no thyroid-stimulating properties. The exophthalmos-producing substance may be able to compete with TSH for the receptor sites in retro-orbital tissues, and if ophthalmogenic immunoglobulins are also present the binding propensities of the exophthalmos-producing substance are enhanced. This theory suffers from two drawbacks. Firstly, TSH and TSH subunits are suppressed in Graves's disease³² and secondly endocrine exophthalmos may occur after hypophysectomy.³³

Extraocular myositis

Extraocular myositis may have a different pathogenesis, for retro-orbital muscle has no TSH receptors. An immunological basis for this has been suspected for some time. A pronounced rise in circulating thyroid antibody concentrations occurs in patients with Graves's disease one to six months after receiving treatment with iodine-131,³⁴ and the onset of exophthalmos or the deterioration of pre-existing exophthalmos³⁵ may also occur at this time. An anatomical communication between the thyroid and the orbit has been shown using radioactive colloidal solutions to show a shared lymphatic drainage system.³⁶ Thyroglobulin discharged from the thyroid gland could thus penetrate the orbit and there provoke an immunological reaction. In untreated thyrotoxicosis serum thyroglobulin concentrations are one hundred times greater than normal and after surgery or iodine-131 treatment the values rise even further.³⁷ Increased quantities of thyroglobulin may therefore be present in the lymphatic drainage of the thyroid. Thyroglobulin-antithyroglobulin complexes have been found in the orbit, and when the affinity of these complexes and of thyroglobulin itself for various tissues was studied the extraocular muscles showed eight times the affinity of heart muscle or liver or kidney tissue. Furthermore, extraocular muscle membrane showed no affinity for human antithyroglobulin, normal IgG, human TSH, human growth hormone, or immune complexes of TSH and growth hormone.³⁸ Thyroglobulin has been detected by direct immunofluorescence on the surface of eye-muscle specimens obtained at necropsy, and this extracted thyroglobulin is the antigen to which sensitised lymphocytes from exophthalmic patients produce the lymphokine that is called migration inhibiting factor (MIF).³⁹

As a result of retrograde flow into the orbit thyroglobulin may attach itself to extraocular muscles.³⁶⁻³⁸ This binding is augmented by complex formation due to the arrival of locally synthesised anti-thyroglobulin antibodies from the thyroid by the same retrograde flow. A series of immunological events then take place, including muscle injury, histamine release, leucocyte attraction, and increased vascular permeability, which are manifestations of the inflammatory events of an immune-complex disease. Sensitisation of lymphocytes to muscle antigens might occur, since antigen-antibody complexes stimulate non-sensitised lymphocytes.⁴⁰ Lymphocytes from normal individuals and patients with Graves's disease stimulate glycosaminoglycans production by cultured fibroblasts obtained from retro-orbital connective tissue and it has been suggested that the accumulation

of lymphocytes would be sufficient to explain the histochemical changes in the orbit.⁴¹ This hypothesis, however, fails to explain the lack of temporal relation between exophthalmos and thyrotoxicosis, and to account for the existence of ophthalmic Graves's disease. Furthermore, plasma exchange induced regression of endocrine exophthalmos and pretibial myxoedema associated with a fall in TS antibody concentration in a patient without immune complexes in the serum.⁴² This suggests that an antibody rather than immune complexes caused exophthalmos in this patient. The hypothesis, however, does account for the familiar clinical picture of severe ophthalmoplegia with minimal exophthalmos.

Nevertheless, the association between exophthalmos and the presence of TS antibodies is imperfect. Human TS antibodies are present in most patients with Graves's disease but only in just over half the patients with ophthalmic Graves's disease.⁴³ Furthermore, thyroglobulin-antithyroglobulin complexes could not be detected in the sera of 21 patients with endocrine exophthalmos, eight of whom had concomitant thyrotoxicosis.⁴⁴ Humoral immunity alone cannot entirely explain the pathogenesis of endocrine exophthalmos.

Cellular immune mechanisms

Both cellular and humoral components are concerned in most autoimmune disorders. This co-operation has been reported in the exophthalmos of Graves's disease.⁴⁵ Cellular immune reactions against retrobulbar tissues occur in patients with endocrine exophthalmos⁴⁶ and lymphocytes become sensitised to extraocular muscle antigen.⁴⁷ Purification of the retro-orbital antigen suggests that it may be thyroglobulin or an antigenic component of the thyroglobulin molecule.³⁹ The MIF test is generally regarded as the best indicator of a cellular immune response. The test shows that lymphocytes will produce MIF when in contact with a specific antigen to which they have been sensitised. Leucocytes are harvested, packed into capillary tubes, and allowed to migrate into a planchet that contains medium. If an antigen is added to the medium to which the lymphocytes have been previously sensitised, migration is inhibited and the degree of inhibition can be readily measured. This test has shown that patients with exophthalmos and thyrotoxicosis have the cellular immune response to both retro-orbital muscle antigen and thyroid antigens, but in those without exophthalmos MIF can usually be shown only against the thyroid antigen.⁴⁷ Conversely, in some patients with exophthalmos who have no evidence of thyroid disease MIF is produced only against retro-orbital muscle antigen.⁴⁷

Some authors maintain that it is possible to predict which patients with Graves's disease will develop exophthalmos by showing a cellular immune reaction to retro-orbital antigen and that exophthalmos can be prevented in these patients by treatment with an immunosuppressive drug such as azathioprine.⁴⁸ The proponents of the cell-mediated hypothesis for Graves's disease and exophthalmos believe that the two disorders are due to separate, though closely related, inherited defects in immune surveillance. Each of these defects would permit the mutating, self-reactive clone of T lymphocytes to survive and interact with its complementary antigen in thyroid or retro-orbital tissue and induce a cellular immune response. Co-operation with the appropriate B lymphocytes allows the specific immunoglobulins to be produced that seem to be necessary for the full expression of these disorders.⁴⁹ Humoral immunoglobulins certainly co-operate in the development of exophthalmos, since immunoglobulins from the sera of exophthalmic patients can induce exophthalmos in animals.²⁰ Hence Graves's disease and endocrine exophthalmos seem to be two closely related, but nevertheless separate, organ-specific autoimmune diseases. Although they usually coexist, either occurs alone.

Ophthalmic Graves's disease

Ophthalmic Graves's disease describes the ocular changes of Graves's disease that occur in the absence of past or present hyperthyroidism. As endocrine exophthalmos may occur in Hashimoto's thyroiditis, some authorities now include in ophthalmic Graves's disease patients with evidence of hypothyroidism.⁵⁰ Euthyroid patients with ophthalmic Graves's disease often show abnormalities of thyroid function such as lack of suppression of radioactive iodine uptake after administration of oral triiodothyronine,⁵¹ impaired response of TSH to thyrotrophin-releasing hormone,⁵⁰ and an increased prevalence and raised titre of thyroid autoantibodies.⁵² The incidence of a high titre of thyroglobulin antibodies is significantly greater in these patients than in those with Graves's disease who have hyperthyroidism.⁵¹ Few of these patients ever develop frank hyperthyroidism, though overt hypothyroidism occurs in a quarter of them.⁵²

Perhaps some patients with ophthalmic Graves's disease do not become hyperthyroid because the thyroid reserve is limited, and hence cannot respond to thyroid-stimulating agents.⁵³ Nevertheless, an appreciable rise in circulating thyroid hormone concentration or radioactive iodine uptake after exogenous TSH administration⁵¹ is seen in many patients, and it seems probable that in these patients the TS antibodies fit the TSH receptor poorly and cannot provoke hyperthyroidism. In a few patients thyroid function appears to be controlled by TS antibodies, but hyperthyroidism is prevented by autoimmune destruction of the thyroid.⁵⁴

Further evidence that ophthalmic Graves's disease is not a single entity comes from the United States.⁴³ One group of patients had TS antibodies, thyroid activity was not suppressed by exogenous triiodothyronine, and the serum contained high titres of thyroid antibodies. These patients were assumed to have three autoimmune diseases: Hashimoto's thyroiditis, Graves's disease, and Graves's ophthalmopathy. Another group of patients in whom TS antibodies were not shown, thyroid antibodies were not present, and thyroid activity was suppressed by exogenous triiodothyronine were assumed to have isolated Graves's ophthalmopathy without autoimmune thyroid disease.

Exophthalmos thus may not always be associated with clinical or immunological thyroid disease and exophthalmos should perhaps be considered a separate, but closely related, autoimmune disorder.

Management

Exophthalmos may occur when any sizable lesion is present in the orbit. Since endocrine exophthalmos is often unilateral, especially in euthyroid patients, other causes of exophthalmos must be excluded. The association of exophthalmos with lid retraction, even if unilateral, makes the diagnosis of endocrine exophthalmos almost certain. Similarly, if the patient has or has had thyrotoxicosis the likelihood of a diagnosis of endocrine exophthalmos is great. Asymmetry in endocrine exophthalmos rarely exceeds 6 mm, but this figure is exceeded in four out of five patients with orbital tumours.⁵⁵ Nevertheless, if unilateral exophthalmos in a euthyroid patient is not associated with lid retraction non-endocrine causes account for nearly 80% of cases.⁵⁶ 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, since the disorder is subject to spontaneous remissions and relapses. Treatment is aimed at preventing corneal ulceration and panophthalmitis. If papilloedema is present treatment is directed at preventing optic atrophy and preserving sight by an operation of decompression.

Time is on the patient's side, since endocrine exophthalmos is a self-limiting disease. Ocular symptoms are usually worse in the morning, and the patient should be advised to sleep with the head of the bed raised, for as venous engorgement diminishes, the nocturnal increase in oedema is lessened. Eye-drops, such as methylcellulose, may help to soothe the gritty sensation in the eyes. Spectacles with dark lenses relieve photophobia and 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,^{57 58} though they may relieve the gritty sensation and the periorbital oedema. The only effective medical treatment of severe exophthalmos is high-dose corticosteroid treatment (usually 80 mg prednisolone/day or more).^{59 60} This regimen is successful, at least temporarily, in just over half the cases. The steroid dosage may be reduced by combining it with an immunosuppressive agent such as azathioprine. Corticosteroid treatment is most suitable in rapidly progressive exophthalmos. The results of combined corticosteroid and immunosuppressive treatment are disappointing in established exophthalmos.^{61 62}

Local treatment

Local treatment is directed towards preventing corneal ulceration and subsequent infection. More severe proptosis preventing adequate opposition of the eyelids warrants a lateral or total tarsorrhaphy. Good initial results have been reported from the intraorbital injection of corticosteroids,⁶³ but this form of treatment has not been widely accepted. Irradiation of the orbit is effective in reducing ocular

proptosis in some patients.^{64 65} 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 may 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 intervention 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.⁶⁶ The transantral approach to the floor and medial wall of the orbit by means of a Caldwell-Luc exposure is now favoured. It is simple, safe, and effective, and has the additional advantage of not being an intracranial procedure.⁶⁷

Plasmapheresis is effective in conditions such as Goodpasture's syndrome⁶⁸ and myasthenia gravis,^{69 70} in which specific circulating IgGs mediate the basic injury. Since patients with endocrine exophthalmos have circulating immunoglobulins that are exophthalmogenic, we have used plasmapheresis in acute and rapidly progressive exophthalmos with encouraging results.⁴² Patients must be chosen carefully for this form of treatment, since improvement occurs only in acute and rapidly progressive disease. Furthermore, sudden withdrawal of antibody from the circulation stimulates a brisk compensatory increase in its synthesis, so that subsequent antibody concentrations may exceed or even double those before plasmapheresis.^{71 72} Plasmapheresis must therefore be combined with an immunosuppressive drug, such as azathioprine, and steroids to suppress this response.

Much debate has centred on the effect of different methods of treatment for thyrotoxicosis on exophthalmos. Exophthalmos may be exacerbated after any form of treatment for thyrotoxicosis—whether it is antithyroid drugs, subtotal thyroidectomy, or radioactive iodine treatment—though the incidence of deterioration is slight, usually about 3-10%.^{35 61} At the Mayo Clinic clinically important ophthalmopathy developed in 3.4% of 177 patients treated by subtotal thyroidectomy and in 5.1% of 98 patients treated with iodine-131—a difference that was not statistically significant.⁴ Improvement in exophthalmos in the five years after treatment of thyrotoxicosis is limited to 3-5% of patients,^{73 74} and the measured exophthalmos commonly remains unchanged. Nevertheless, the appearance of the eyes usually improves in most patients, owing to the disappearance of lid retraction. Hypothyroidism must be avoided, since exophthalmos develops more often in hypothyroid patients.⁴ Hyperthyroidism should perhaps be controlled cautiously because clinical evidence shows that in patients with thyrotoxicosis treated by drugs, surgery, or radiation the fall in the serum protein-bound iodine concentration and the rise in TS antibody titre are greater in those who develop an exacerbation of exophthalmos than in those who do not.⁶¹

Conclusion

Endocrine exophthalmos can usually be recognised clinically even in euthyroid patients. In most the diagnosis can be confirmed either by failure of triiodothyronine to suppress uptake of iodine-131, a flat TRH test, or by the presence of thyroid antibodies. Time is on the patient's side, so a conservative course of treatment 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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Should antibiotic cover be given to patients with underlying heart valve abnormalities before skin biopsy or other dermatological surgery? If so, what is the recommended schedule for (a) an uncomplicated case, (b) a patient already taking penicillin, and (c) a patient allergic to penicillin?

The practice of giving antibiotic cover only for dental procedures is no longer adequate. Skin biopsy should be a minor procedure. The degree of risk of bacteraemia arising as a result of it will depend on the suspected nature of the lesion and whether it and the surrounding skin are infected at the time of the biopsy. The extent to which the heart lesion is at risk of infection will also vary according to its nature. The ostium secundum type of atrial septal defect rarely if ever becomes infected, unless there is associated mitral valve disease. Small ventricular septal defects, minor mitral regurgitant lesions, bicuspid aortic valves, and co-arcuation of the aorta are lesions that are prone to infection. In a given patient these points may be imponderable, and it is better to cover even this minor procedure with a single dose of antibiotic given immediately before starting the biopsy. No continuation treatment is required.

The organisms likely to cause transient bacteraemia in these circumstances are *Staphylococcus epidermidis* and skin diphtheroids, and these organisms are capable of causing non-operative, medical endocarditis. The single best antibiotic would be vancomycin, 500 mg, by slow intravenous infusion over 20 min, and as the biopsy would be done at or in hospital this need not present undue difficulties. It would certainly be necessary in a patient with known penicillin allergy. If this regimen was thought to be impractical for routine use amoxycillin, 1 g, with gentamicin, 80 mg, intravenously or intramuscularly would be the alternative and would be appropriate whether or not the patient had been taking penicillin. Gentamicin is the only antibiotic other than vancomycin to which *Staph epidermidis* remains

predictably sensitive at present. The combination of amoxycillin and an aminoglycoside would cover even penicillin-resistant diphtheroids and also faecal streptococci, a possible problem with perianal lesions and infected lesions elsewhere.

I read in an American paediatric textbook that amphetamines can help children and adults with brain damage. What are your expert's views on this?

I never use the term "brain damage" unless a child has suffered known postnatal injury in an accident. No psychological or neurological test proves that brain damage has occurred at birth. The term causes great distress to parents, and it implies totally unjustifiable blame on the doctor or midwife who delivered the child: furthermore, it is harmful for the child, for it puts a label on him that is unjustified. The terms "brain damage," "minimal brain dysfunction," and "minimal brain damage" are extremely popular in the USA, and up to 40% of all American children have been said to suffer from it. It is a mythical ragbag of a diagnosis, to which over 100 symptoms have been ascribed, notably "overactivity,"¹ and in the USA scores of thousands of children are given regular pills of amphetamines or methylphenidate, despite their harmful effect on growth² and other side effects, and the lack of indications for drug treatment. In Britain the use of amphetamines is frowned on, because of the risk of addiction: and few doctors prescribe methylphenidate for symptoms that are nearly always normal though annoying manifestations of children's development.

¹ Schmitt, B D, *American Journal of Diseases of Children*, 1975, **129**, 1313.
² Safer, F, et al, *New England Journal of Medicine*, 1972, **287**, 217.