granulation tissue with giant cells¹⁶, an epidermal tumour¹¹, serous cysts of the iris², pearl cysts of the iris¹⁶, and in two cases^{6,7} sympathetic ophthalmitis. The second case⁷ was rather doubtful. A subconjunctival granuloma has recently been reported¹³ from an embedded cilium.

I wish to thank Messrs. A. D. Griffith, R. H. Rushton, and A. Sorsby for their kind and helpful advice and assistance with this case.

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A CASE OF "EXOPHTHALMIC OPHTHALMOPLEGIA WITH THYROTOXICOSIS"

BY

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LONDON

At the International Congress of Neurology, 1935, Russell Brain reported 22 cases of ophthalmoplegia occurring in patients suffering from exophthalmos with signs of thyrotoxicosis. He suggested that the clinical features of these cases constituted a distinct syndrome.

This disorder may develop spontaneously or occur after partial thyroidectomy for hyperthyroidism. Its onset may be acute or insidious and it appears to affect females to males in the proportion of 7 to 4 (exophthalmic goitre 10 to 1). Russell Brain states that it occurs in middle life, 18 of his 22 patients being over 40 and 9 over 50 years of age. The case described below which came under my care at the Moorfields Eye Hospital was a male aged 31 years.

The thyroid is seldom visibly or palpably enlarged and the exophthalmos is generally of a moderate degree and seldom severe. Tachycardia, digital tremor, increased basal metabolic rate and loss of weight are usually slight as compared with these clinical signs in exophthalmic goitre. The exophthalmos and ophthalmoplegia correspond with each other in being either unilateral or bilateral.

Russell Brain suggests that the ophthalmoplegia is probably due to a combination of the mechanical stress of exophthalmos and a toxic factor affecting the extra-ocular muscles. An opportunity of making a pathological examination of the extra-ocular muscles occurred in the case reported below and the findings agreed with those of other recent observers. The extra-ocular muscles are enlarged about 5 or 6 times their normal size (the levator palpebrae superioris excepted), the muscle bellies are fusiform in shape, pale and oedematous. Histological examination reveals interfascicular oedema and collagen, and small round cells resembling lymphocytes, considered by some authorities to be undifferentiated mesenchyme cells which later form fibrous tissue. Granular and hyaline degenerative changes have been noted in some of the muscle fibres. Perivascular lymphocytic infiltration is present in some cases.

Recent experimental work on the aetiology of exophthalmos with thyrotoxicosis suggests that the thyrotropic hormone produced by the anterior lobe of the pituitary acts either on the sympathetic nerve endings or directly on the fibres of the unstriated muscle in Tenon's capsule, the band 1 cm. in length which extends from the levator palpebrae superioris to the upper margin of the tarsal plate and that in the floor of the orbit attached to the periosteum near the inferior orbital fissure. It is improbable that the contraction of this unstriated muscle alone would be sufficient to cause an appreciable degree of exophthalmos if the extra-ocular muscles are healthy.

Russell Brain has suggested that exophthalmic ophthalmoplegia with thyrotoxicosis is due to the excessive production of an X-factor, which he believes to be the thyrotropic hormone of the pituitary and that hyperthyroidism plays a subordinate part. His conception infers that in exophthalmic goitre both this X-factor and the thyroid secretion are in excess and in toxic adenoma of the thyroid there is pure hyperthyroidism, the X-factor taking little or no part and thus probably accounting for the absence of exophthalmos.

In 5 of Russell Brain's 22 cases the thyroid was examined histologically, one of these presented the hyperplasia typical of exophthalmic goitre and the other 4 showed atypical changes with signs of colloid retention more than colloid secretion. These

features are probably correlated with the mild general symptoms and signs of thyrotoxicosis. Improvement may be spontaneous, but complete recovery is exceptional, some degree of exophthalmos and ophthalmoplegia persisting. Rest, iodine administration and sedatives do not accelerate improvement and partial thyroidectomy has little or no effect upon either the exophthalmos or the ophthalmoplegia. Exophthalmos and ophthalmoplegia may even develop after partial thyroidectomy in a patient whose basal metabolic rate is actually subnormal. The case recorded below had a subnormal basal metabolic rate.

Case Report

W. G. a male, aged 31 years, attended my clinic at the Moorfields Eye Hospital in August, 1934, on account of diplopia. In June, 1934, both eyes were noticed to be prominent and about this time he experienced diplopia on looking up and after having the eyes closed for 2 or 3 minutes. Since June, these symptoms had become progressively worse and he had experienced lassitude and a tired feeling in the eyes.

He was nervous and easily worried. Bilateral exophthalmos was evident, the left side being more marked than the right, and the movements of the left inferior rectus and inferior oblique were defective.

The thyroid was slightly enlarged, soft, and of uniform consistence. His pulse rate varied 64—90. The reflexes were brisk. The basal metabolic rate was -4 per cent., radiographs of the skull and the blood count showed no abnormality. The Wassermann reaction was negative. The nose and throat department reported inflammation in pharyngeal lymphoid tissue.

The patient was transferred to the Medical Professorial Unit at St. Bartholomew's Hospital and I am indebted to Professor Witts and Drs. Spence and Scowen for permission to publish the following notes:—

At 12 noon on September 14, 1934, and at 11 a.m. on September 15 and 16, 1934, 600 organon units of thyrotropic hormone (1,200 Schoeller units) were injected subcutaneously. The basal metabolic rate, temperature, pulse and respiration rate, are charted below.

There was a rise of the basal metabolic rate from 3 to 21 per cent. within 24 hours of the first injection, followed by a further rise to 30 per cent. after the second and third and thence to 41 per cent. (the peak of the curve) three days after the third and last injection.

A rise of temperature occurred during the 12 hours after injection and there was a corresponding slight increase in the pulse and respiration rates. The patient had a frontal headache

10 hours after the first injection (at 10 p.m. on September 14, 1934), and 11 hours after the second and third injections (at 10 p.m. on September 15 and 16, 1934), this was relieved by sleep, was slight on the following morning and was not felt after September 17. On September 16, the patient's appetite lessened and did not improve till September 19.

Redness and swelling were noticed at the sites of subcutaneous injection for 2 to 3 days, after which time these signs subsided.

CHART I.

Graph to show the rise in basal metabolic rate after the three injections of thyrotropic hormone.

The degree of exophthalmos remained the same until September 19, when it was a little increased on the day the basal metabolic rate reached its peak at + 41 per cent; the exophthalmos became less again on September 20, when the basal metabolic rate was + 38 per cent. and on the right side it showed further diminution on September 28, but the left eye remained the same.

On the day following the third injection, September 17, the patient became more nervous, the skin "clammy," the digital tremor more marked, but there was no visible increase in the size of the thyroid gland. On September 28, the digital tremor was slight and the thyroid isthmus was just palpable. On this date the basal metabolic rate had fallen to 15 per cent. On October 4, the basal metabolic rate was 6 per cent. and on October 7, the left

eye became painful and injected owing to corneal ulceration which spread in the next 5 days until it occupied a horizontal transverse band about 4 mm. broad across the centre of the cornea. On

CHART II.

October 10, the basal metabolic rate had risen to 16 per cent. after a sleepless night from pain in the left eye. The conjunctiva became increasingly chemosed and oedematous, exophthalmos of the left eye was more marked and on October 13, a central tarsorrhaphy was performed. Some temporary improvement followed this operation but on October 29 the exophthalmos and chemosis increased, the lids were under considerable tension and on account of severe pain from pressure of the sutured lids on the cornea the tarsorrhaphy was temporarily divided on November 2nd. The pain was relieved, but during the next 4 days the corneal ulceration and chemosis became more extensive and a hypopyon developed. On November 6, under a general anaesthetic, the corneal ulcer was carbolyzed and a paracentesis performed, evacuating the hypopyon, and was followed by resuturing of the tarsorrhaphy.

On November 8, the exophthalmos had increased and by November 10, the tarsorrhaphy gave way and the corneal ulcer perforated. The globe was removed on account of extensive destruction and at the same time a portion of the inferior rectus muscle was excised for histological examination. The extra-ocular muscles were considerably enlarged being 5 or 6 times their normal size, and were pale and fusiform in shape. Histological examination of the piece of the inferior rectus muscle showed an interstitial fibrosis and chronic inflammatory round cell infiltration. The muscle fibres exhibited no definite degenerative changes.

Commentary

Recent experimental and clinical work has suggested that a substance from the anterior lobe of the pituitary gland to which the name of thyrotropic hormone has been applied is an aetiological factor in the production of exophthalmos, and that this substance operates through a nervous mechanism. Some authorities state that the thyrotropic hormone fails to cause exophthalmos if the cervical sympathetic is divided whilst others maintain that it acts directly on the sympathetic nerve endings or on the unstriated muscle fibres in the orbit. Marine and his co-workers Friedgood, Scowen and Spence, have shown that the injection of thyrotropic hormone into an experimental animal increases thyroid activity causing hyperplasia of the gland, an increase of iodine, accelerated pulse rate, raised basal metabolic rate, loss of weight and exophthalmos. The exophthalmos is more readily developed in a thyroidectomized animal.

There is also some clinical evidence to lend support to this view. In some cases of acromegaly due to an adenoma of the anterior lobe of the pituitary the basal metabolic rate is raised. Falta has

noted thyroid hyperplasia and Worster Drought has recorded a case of exophthalmic goitre in association with this disease.

The conclusions to be drawn from a survey of the experimental work are as follows :—

The thyrotropic hormone of the anterior lobe of the pituitary is capable of producing exophthalmos in intact animals and more readily in those which have had the thyroid removed or are suffering from hypothyroidism. After partial thyroidectomy in man even with a subnormal basal metabolic rate progressive exophthalmos may develop or be precipitated by the administration of thyroid extract. In the literature there are reported some 21 cases including that of Russell Brain's in which exophthalmos developed during the administration of thyroid extract for myxoedema, obesity or for some other purpose.

It is probable that certain individuals respond to thyroid extract by producing a substance which operates on the unstriated muscle of the orbit. There is some experimental evidence to suggest that this substance is the thyrotropic hormone of the pituitary.

If this conception be correct it would seem that the course of the orbital changes are first contraction of the unstriated muscle causing upper lid retraction, then exophthalmos which is augmented by the increase of pressure inside the cone formed by the recti muscles with compression of veins and their peripheral engorgement and subsequent oedema. The effective action of the unstriated muscle is enhanced by the myopathy of the extra-ocular muscles the enlargement of which may also contribute in a passive manner towards the exophthalmos.

The clinical features of the case reported above conform with those described by Russell Brain under the diagnostic label of "exophthalmic ophthalmoplegia with thyrotoxicosis;"—the relatively small degree of exophthalmos, moderately increased pulse rate (64—90), slight enlargement of the thyroid and the markedly defective action of two of the extra-ocular muscles of the left eye on the same side as the greater degree of exophthalmos. These features together with the low basal metabolic rate (— 4 per cent.) and the relatively slight general symptoms suggest that possibly some factor other than the products of hyperactivity of the thyroid gland was responsible for the exophthalmos and the changes in the extra-ocular muscles. The injection of thyrotropic hormone of the pituitary was in the nature of a clinical test and it produced such interesting events as a temporarily raised basal metabolic rate, increased temperature, pulse and respiration rate, increased exophthalmos, digital tremor and a perspiring, clammy skin. It may be that the degree of exophthalmos which developed after these injections of thyrotropic hormone would have been less in the case of a normal control.

The features of this case which are worthy of remark are the age of the patient, 31 years; the subnormal basal metabolic rate - 4 per cent.; and the result of a histological examination of a portion excised from the inferior rectus muscle.

Summary

A case of exophthalmos with unilateral partial ophthalmoplegia affecting the inferior rectus and inferior oblique muscles associated with a basal metabolic rate of - 4 per cent. and mild general symptoms of thyrotoxicosis in a male aged 31 years is described. The effects and significance of 3 injections on successive days of 600 organon units (1,200 Schoeller units) of the thyrotropic hormone of the anterior lobe are discussed.

I express my thanks to Dr. Powell, Southend Eye Hospital, for her kindness in referring this case to me at the Moorfields Eye Hospital.

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PERNICIOUS ANAEMIA WITH RETRO-BULBAR NEURITIS

BY

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THE following case seems worth recording as an interesting example of pernicious anaemia with progressively diminishing visual acuity.

Case.—T. M. aged 55 years. Occupation.—Post Office sorter.

In December, 1929, this patient was first seen with a history of nine months' anaemia. He was found to have pernicious anaemia with a red blood count of 1,100,000. He was treated with liver and his blood count steadily rose. In February, 1933, he complained