OBSERVATIONS ON SO-CALLED THYROTROPIC EXOPHTHALMOS

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Exophthalmos is known to be one of the main features of Graves's disease. It was first described by Parry in 1815. Exophthalmos may vary greatly in degree and take very different courses. Whereas in most cases it is stationary and does not endanger the eyeball, in some cases the extreme protrusion of the globe may lead to oedema of the lids, injection of the conjunctivae, chemosis, lagophthalmic keratitis, ulceration of the corneae, and finally even to loss of the eye. These two entirely distinct forms of exophthalmos are therefore basically different, and the latter, owing to its progressive character, is termed "malign" exophthalmos.

Until a few years ago exophthalmos was assumed to occur with Graves's disease only, and thus to be of purely hyperthyroid origin. Of late, however, clinical and experimental investigations have clearly shown that, besides the thyrotoxic form, there must be another—to be attributed to the pituitary body: in particular, the thyrotropic factor of the anterior pituitary lobe was held responsible for its occurrence (thyrotropic exophthalmos).

Loeb and Friedman in 1932 produced exophthalmos in guinea-pigs by injecting an acid extract of anterior pituitary of cattle. This exophthalmos, however, always regressed when the injections were discontinued, and the same occurred under narcosis and after death. Experimentally produced exophthalmos must therefore differ fundamentally from that occurring in man. Marine and Rosen in 1934, and Smelser in 1936, produced exophthalmos in guinea-pigs by injecting thyrotropic hormone of the anterior pituitary lobe; such results were even more readily obtained when thyroidectomy had been performed prior to the injections. Friedgood in 1934 also found that exophthalmos due to the thyrotropic hormone deteriorated on reduction of thyroid function, particularly so when the basal metabolic rate fell.

As to the thyrotoxic form of exophthalmos, two factors must be considered most important from the aetiological point of view. The first is the contraction of Mueller's palpebral muscles owing to increased sympathetic stimulation. These muscles exert a pull on the upper and lower poles of the globe through connexion with expansions from tendons of the upper and lower rectus muscles to lid tissues. Contractions of these muscles tend to produce lid retraction and proptosis. Landstroem's circular muscle, too, exerts a direct concentric pull on the globe. It should be noted, however, that even now evidence that increased sympathetic tonus is responsible for the ophthalmic manifestations in human Graves's disease has not been uniformly established, since sympathectomy has proved entirely ineffective in the treatment of exophthalmos in man. The second factor is the adynamia of the recti which normally retract the eye globe. It is noteworthy that it is not merely of late that adynamia of the recti has been assigned a part in the development of exophthalmos; for Cooper (1849), later Moebius (1886) and Lemke (1894), and more recently Sainton and Hesse in 1931, and Plummer and Wilder (1935), have expressed the same opinion. One of us (H. Zondek) was able to show in 1938 that in one case adynamia of the eye muscles led to a condition resembling complete ophthalmoplegia which could be temporarily relieved by the use of prostigmin. The great significance of the adynamia and muscular metabolism in Graves's disease induced one of us (H. Zondek), in 1935, to classify a certain form of this disease as its "muscular type" (*Diseases of the Endocrine Glands*, 1935, p. 157; 1944, p. 162). A third factor is the occurrence of anatomical changes. Within the orbit they are generally not very marked, and in particular the extrabulbar muscles usually are of normal shape and consistence. In some cases, though, general wasting of muscle fibres, accompanied by loss of striation, fibrillation, and amorphous granulation of sarcoplasm, is found (Burch,

1929; Naffziger, 1933). For details see the exhaustive paper by Mulvany (1944).

With regard to thyrotropic exophthalmos, the phenomenon of proptosis seems to play a far more important part in its development than the widening of the palpebral fissures. There is neither lid spasm nor raised sympathetic tonus. The globe cannot be pushed back into the orbit, and owing to increased retrobulbar pressure such attempts are very painful. With thyrotoxic exophthalmos this is not so. The strong pressure acting on the eyelids from behind results in lid congestion, oedema, and chemosis, which are probably due to compression of the palpebral venous arcades. The lids press on the corneae, and this and the lagophthalmos lead to ulcerations and necrosis in extreme cases. The most important cause of the proptosis must be sought in muscle disorders such as (1) diffuse extense fibrosis, (2) oedema, (3) abundant round-cell infiltration, and (4) a special type of degeneration resulting in fibrosis or disintegration and absorption of muscular fibres (Mulvany). From the subjective point of view it is typical that patients suffering from so-called thyrotropic exophthalmos complain of pains, epiphora, photophobia, diplopia, and difficulty in convergence, whereas patients with thyrotoxic exophthalmos are usually free from such troubles. So-called thyrotropic exophthalmos—which, by the way, mainly occurs in male patients—generally seems to assume far higher degrees of proptosis than the thyrotoxic; the so-called malign exophthalmos (see above) mostly corresponds to the thyrotropic. It remains to be seen, however, whether milder degrees of exophthalmos, and in particular those without any accompanying signs of hyperthyroidism, will also fall into this group.*

Which clinical facts lead us to the conclusion that exophthalmos is not in all circumstances of hyperthyroid origin? (1) It must be remembered that some cases of exophthalmos not only are not improved but are even considerably harmed by thyroidectomy (see Case III). (2) The thyrotropic hormone in the serum is abnormally high with so-called thyrotropic exophthalmos, whereas the opposite is true of the thyrotoxic form. (3) Thyrotoxicosis accompanying so-called thyrotropic exophthalmos is usually comparatively mild and in striking contrast to the degree of ophthalmic manifestations. (4) Exophthalmos may also occur with hypothyroidism. (5) We think that the association of exophthalmos with Hand-Schueller-Christian's disease may possibly shed some light on this problem. Many authors maintain that exophthalmos in these cases is due to mechanical processes only. This assumption, however, is not generally agreed upon. If this mechanical theory be not true of all cases the coincidence with diabetes insipidus that is more or less characteristic of this disease would rather indicate involvement of the pituitary gland or the diencephalic nuclei, since the thyroid gland does not have any part in it.

We have examined three cases of excessive exophthalmos (one post-operative) which, according to the above differentiation, ought to be classified as the so-called thyrotropic type of the disease. How very rare such cases are is demonstrated by the fact that one of us (A. T.) found among 150,000 ophthalmic patients only these three cases.

Case I

A man 47 years old. Family and previous history negative. The patient had always been healthy until about seven years ago, when he contracted influenza. Thereafter he noticed for the first time some swelling of the eyelids and slight protrusion of the eyeballs. This condition remained stationary until about six weeks ago, when the globes grew more and more prominent. Three weeks ago he developed nervousness and profuse perspiration. He had lost 3 kg. during the past three years.

Examination revealed extreme exophthalmos, especially of the left eye (see below); no goitre; pulse rate, 104-110; blood pressure, 130/75 mm. Hg; no adynamia; no tremor; reflexes normal; visceral organs, nothing abnormal. Urinalysis: urobilinogen increased, otherwise nothing abnormal. Blood count: R.B.C., 4,000,000; Hb, 85%; W.B.C., 7,000; differential count, normal. Glucose-tolerance test: 103, 154, 147, 181, 176, 163 mg. per 100 c.cm. Limbus capillaries normal. Heart radiologically normal. Radiograph of the skull:

* Just before this paper went to press we had the opportunity of observing a fourth case, which, although showing typical features of pituitary-diencephalic disorder such as high blood cholesterol level, deformation of the sella turcica, and changes in the osseous skull, lacked all signs of malignancy.

sella turcica enlarged; osseous outlines of the sella badly defined; frontal region of the skull considerably deficient in lime. B.M.R. +60%. Eyes:—Chemosis and corneal ulcerations of the left eye. The degree of proptosis could not be measured on the left, the Hertel ophthalmometer going only as far as 30 mm., but was estimated to be about 35 mm. On the right it amounted to 30 mm.

The patient was given di-iodo-tyrosine (200 mg. a day for 10 days—i.e., a total of 2,000 mg.). When seen again after having finished this course the exophthalmos had become less (L. 30, R. 27 mm.). The limbus capillaries were of normal width and formation. When seen once more after the lapse of another week without any specific treatment, the pulse rate had dropped to 84 and the blood pressure to 115/80 mm. Hg. Exophthalmos—L. 28, R. 26 mm. No chemosis. Good lid closure. The corneal ulcerations were turning into scars. Surgical closure of the palpebral fissure, which had been attempted before the patient came under our observation but had not yielded any results, was now carried out without any difficulty.

Case II

A man aged 57. Family and previous history negative. The patient's left eye had been bad for two years, the right for one year. Otherwise he was all right until eight months ago, when he started complaining of loss of weight, heart palpitations, and nervousness. The basal metabolic rate was said to have been +40% six months ago. For the past three months the patient had been taking 15 drops of Lugol's solution a day.

Condition on examination:—Pronounced exophthalmos (see below); no goitre; pulse rate, 96; blood pressure, 155/70 mm. Hg; tremor of fingers and tongue; slight adynamia; visceral organs, nothing abnormal; reflexes normal. Urinalysis, nothing abnormal. Blood count: R.B.C., 4,600,000; Hb, 105%; W.B.C., 7,000; differential count, normal; blood calcium, 11.4 mg. per 100 c.cm.; phosphorus, 5 mg. per 100 c.cm.; cholesterol (two different readings), 294 and 375 mg. per 100 c.cm. Glucose-tolerance test: 88, 177, 170, 148, 183, 141 mg. per 100 c.cm. Limbus capillaries partly narrow, otherwise without abnormal findings. B.M.R. +19%. Fluoroscopic examination of the heart showed nothing abnormal. Radiograph of the skull: Sella turcica uniformly enlarged; very thin skull bones, especially the base, which was extremely thin and atrophic; vascular congestion, as made evident by widening of the meningeal vessels. Exophthalmos—R. 27, L. more than 30 mm.; congestion of ciliary vessels, insufficient closure of the eyelids; left optic disk pale but well defined.

The patient was given prominal and di-iodo-tyrosine (a total of 2,000 mg.) for 10 days. At the conclusion of this course his exophthalmos was found to have decreased by 1 to 2 mm. He was again given di-iodo-tyrosine, for five days (i.e., 1,000 mg.). After the lapse of another five days he felt much better; pulse rate, 84–90; blood pressure, 130/50 mm. Hg. The left eye could be closed better (on extreme closure there was about 3 mm. of uncovered globe left) and was less inflamed. He was then given 500 mg. of di-iodo-tyrosine a day for five days (i.e., a total of 2,500 mg.). When he was seen again he had lost almost all his general complaints; pulse rate, 76. The left eye could be closed almost completely (about 1 mm. uncovered globe left). Blood cholesterol, 290 mg. per 100 c.cm. Di-iodo-tyrosine was continued in reduced amounts (200 mg. a day for a week). Exophthalmos—R. 27, L. 29 mm. Thereafter the patient was submitted to x-ray irradiation of the pituitary gland. During this treatment the left eye seemed more inflamed and its closure less complete. Unfortunately the patient left Jerusalem directly after the course of irradiation was completed, so that its results could not be adjudged. He wrote after a few months, when he seemed to be rather satisfied with his general condition as well as with the state of his eyes; but he did not give any particulars, and had apparently not been seen by any doctors.

Case III

A man 46 years old. Family and past history irrelevant. For the past two months there had been diarrhoea, loss in weight, profuse perspiration, heart palpitations, trembling of the fingers, and progressive exophthalmos. The B.M.R. was +25% in the beginning and +15% after complete rest some weeks later. While resting the patient had gained in weight, but the remainder of the above symptoms were unchanged. The state of the patient's eyes had even taken a turn for the worse: the globes had steadily protruded, and consequently both eyes had got inflamed, lid closure had become insufficient, and the vision decreased.

Condition on examination:—Exophthalmos (see below); no goitre; pulse rate, 100; blood pressure, 145/65 to 175/90 mm. Hg; tremor of tongue and fingers; no adynamia. Visceral organs, N.A.D. Reflexes normal. Urinalysis, nothing abnormal. Blood count: R.B.C., 4,080,000; Hb, 80%; W.B.C., 5,800; differential count, normal; blood cholesterol, 182 mg. per 100 c.cm.; B.M.R. +40%. Eyes: Stellwag's sign positive; Moebius's and Graefe's signs negative. Exophthalmos—R. 24, L. 21 mm. (two months previously the respective measures had been R. 19, L. 16 mm.). Radiographs of the sella turcica were without pathological findings.

When we saw the patient again about five months later he had undergone thyroidectomy some four months before. He said that only one day after operation his sight had been clear, whereas afterwards he developed keratitis, conjunctivitis, and pronounced lacrimation. The eyes had protruded at a great rate (R. from 24 to 29–30 mm., L. from 21 to 24 mm., within four weeks). Graefe's, Moebius's, and Stellwag's signs positive. Lid closure accordingly became still more insufficient (R. 12, L. 3 mm.). The thyrotoxic symptoms had subsided, though gradually. The basal metabolic rate, which had dropped to +15% after operation, had risen again to +38% at a reading taken two weeks ago. (The patient admitted, however, that he had been very nervous at the time.) Exophthalmos was extreme (see above); pulse rate, 70; blood pressure, 135/80 mm. Hg; no tremor; no adynamia; normal reflexes; visceral organs, nothing abnormal; limbus capillaries on microscopical examination, normal. Radiograph of skull, nothing abnormal; B.M.R., +29.5%.

The patient was given prominal and di-iodo-tyrosine (2,000 mg. within 10 days). When coming back after the lapse of three weeks he stated that for the first two weeks he had felt much better, lid closure having become easier and eye movements less inhibited. He had gained 3 kg. in weight, and made no complaint as to his general condition. Exophthalmos—R. 26, L. 22–23 mm.; B.M.R. +10%. Di-iodo-tyrosine was given again (100 mg. on alternate days for one month). When seen after the end of this course the patient was complaining of some nervousness. His eyes were not controlled on this occasion, but the exophthalmos appeared stationary, or even somewhat improved, and the signs of irritation were less pronounced than before. He was given quinine and prominal, and some time later x-ray irradiation of the pituitary gland. During irradiation the exophthalmos was: R. 25, L. 20 mm. General condition as above. The patient was given another course of di-iodo-tyrosine (a total of 2,000 mg. within 10 days). Thereafter he was able to close the left eye completely, whereas the right remained 4 mm. open on extreme closure. He was given quinine and di-iodo-tyrosine alternately (the latter amounting to another 2,000 mg.). One month later the patient stated that he was working hard and felt quite able to do so. Exophthalmos—R. 24–25, L. 20–21 mm. (See Figs.).

FIG. 1.
Case III before treatment

FIG. 2.
Case III after treatment

Di-iodo-tyrosine and quinine were given at regular intervals, and three months later another irradiation to the pituitary gland was started as the exophthalmos had remained stationary for the last few months. No visible results were seen after irradiation, so that two months later another course of di-iodo-tyrosine was given. When seen again the exophthalmos had scarcely changed (R. 23.5, L. 22 mm.), but the eye movements were free and easy. Lid closure was nearly complete. Blood cholesterol, 228 mg. per 100 c.cm. After one injection of a mercurial diuretic the patient felt much better subjectively, although the objective state had not greatly changed.

Discussion

The two cases of extreme exophthalmos accompanied by comparatively mild hyperthyroidism show more or less extensive changes in the osseous skull (bone atrophy round and above the sella turcica and moderate enlargement of it in Case I, extensive decalcification of the whole skull, and some uniform enlargement of the sella in Case II). Both cases had diabetic glucose-tolerance curves. These findings point to diencephalic or pituitary-diencephalic disorders. In Case II the blood cholesterol was found to be unusually high (in Case I, unfortunately, it was not examined), which suggests that this case cannot be designated as pure hyperthyroidism.* We should like to add that we often found such abnormally high blood cholesterol values in processes localized to the pituitary-diencephalic region. This matter will be reported upon on another occasion. Neither the above metabolic nor the osseous

* Another patient who came under our observation just before this paper went to press also had an abnormally high blood cholesterol level.

changes were met with in Case III (post-operative exacerbation of the exophthalmos).

With regard to the pathogenic part played by the thyrotropic factor in this connexion, the following facts ought to be taken into consideration; the results of the animal experiments as described above seem conclusive. (The most suitable animals for these experiments are guinea-pigs, less so rabbits and rats.) In our opinion, however, it is very doubtful whether the results of experimental work may be applied to human pathology without any reservation. According to knowledge acquired thus far, no influence whatsoever of the thyrotropic factor on volume and water content of the extra-orbital muscles has been established. Another argument against the pathogenic part played by the thyrotropic hormone is the fact that exophthalmos is very rarely encountered in myxoedema, although the production of the thyrotropic hormone in this disease is abnormally increased. This may serve as additional evidence against the unreserved application of animal experiments to human pathology. On the other hand, the posterior lobe is known to produce an antidiuretic factor, and since this is passed straight into the liquor of the third ventricle, the possibility of its contributing to the production of ophthalmic manifestations through water retention might at least be taken into consideration. Marine assumes that in addition to the anterior pituitary the gonads play an important part in the production of exophthalmos. For example, castration of male rabbits caused an existing exophthalmos to regress; the administration of testosterone propionate to the same rabbits caused the exophthalmos to recur (Marine, 1938). As to the relation of androgens and water metabolism, the fact was pointed out by Mulvany that the capon's comb inflates in response to androgens, presumably owing to rise of its water content. The relation of oestrogens to water metabolism is well known and need not be gone into here (see Zondek, *Diseases of the Endocrine Glands*, 1944, p. 53). The fact that in certain cases the exophthalmos rapidly deteriorates after removal of the thyroid, so that finally malign exophthalmos develops, may be at least partly explained by the following hypothesis: thyroïdin is known to have a dehydrating effect; thus after its elimination a factor causing water retention will obtain dominance.

In brief, it may be said that the cause of so-called thyrotropic exophthalmos in man is not yet definitely known. Our cases make it appear probable that this type of exophthalmos is part of a complex disturbance originating in the pituitary-diencephalic centres. It is still open to doubt whether in the individual case one or more diencephalic centres or one or more pituitary hormones respectively ought to be considered as the primary seat of the disorder. We therefore raise the question whether these cases would not be more properly covered by the name of "pituitary-diencephalic" exophthalmos so as not to anticipate any undue conclusion. It is worthy of note that Daniels (1938) also attributed the type of exophthalmos described in this paper to diencephalic disorders.

Therapeutically, all three patients received an average of 200 to 300 mg. of di-iodo-tyrosine a day for two weeks, at three-weeks intervals. Two additionally had irradiation to the pituitary. Di-iodo-tyrosine apparently had a beneficial effect, although it cannot be stated with certainty how great a part of it has to be attributed to the irradiation. Thyroïdin administration, which would appear plausible in light of the above argument, was in fact recommended for post-operative exophthalmos by Gasteiger (1931) and Mulvany (1944). In any event, it is noteworthy that in Case I medicinal treatment alone brought any considerable regress of the exophthalmos. It should also be noted that in Case III dehydration through a mercurial diuretic resulted in at least subjective improvement of the eyes. In the same case relief of the intra-orbital pressure through partial removal of the orbital roof (Naffziger), which for quite a time appeared the only possible way to safeguard the eye, was rendered unnecessary by medicinal treatment and local protective measures.

Summary

Three cases of exophthalmos are recorded which, according to the present classification, would have been designated as thyrotropic exophthalmos. The ophthalmic manifestations were of particularly severe degree in all these cases. Two of them presented marked

decalcification of the skull bones and enlargement of the sella turcica; this finding points to involvement of the pituitary-diencephalic region. Both cases had diabetic glucose-tolerance curves. The abnormally high blood cholesterol level in two cases argues against hyperthyroidism. All three cases favourably responded to di-iodo-tyrosine. In one case (post-operative exacerbation of the exophthalmos) di-iodo-tyrosine, in combination with pituitary irradiation on two occasions, resulted in considerable improvement of the eyes (regress of proptosis, disappearance of chemosis and epiphora, etc.), and thus rendered surgical intervention unnecessary. In view of the fact that the part played by the thyrotropic hormone in the production of this type of exophthalmos is doubtful, while that of the pituitary-diencephalic system seems to be highly probable, the looser definition of "pituitary-diencephalic" exophthalmos is suggested.

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HEPATIC ENLARGEMENT WITH ASCITES IN CHILDREN

BY

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For many years cases of abdominal enlargement in coloured children in Jamaica, due to ascites and an enlarged liver, have attracted attention, but the aetiology of the condition remains uncertain. It closely resembles the disease among Indian children described by Sir Upendranath Brahmachari (1938), and called infantile hepatic cirrhosis. In our experience the fatal outcome is not so common, perhaps because the condition is not entirely the same or the cases seen by us are in an earlier stage. No cases of the acute type described by Sir Upendranath occurred in this series. The descriptions given by other observers known to us vary, but all are agreed that ascites and enlargement of the liver are present in every case. One member of the staff states that he observed five of these cases some years ago, and all were cured by a generous diet and improved living conditions; he followed them up for a period of over two years. Another member states that he has seen many of these cases, and that in his opinion the majority are fatal sooner or later.

Report on a Series of Cases

This paper is based on a series of 18 cases observed by us over a period of about a year; of these 15 have been followed up for six months or longer, and two patients were found to have died, apparently of this disease. There were 11 males and 7 females, but this series was too small to warrant conclusions as to the sex incidence. The illness is a chronic one, beginning between 1 and 10 years of age, usually in children who until then had been well. It lasts for months or years, and in our experience has ended in recovery in the majority of cases, though other observers have had contrary results. The history given is that the illness begins usually with fever, which may be intermittent, lasting for days or weeks, and is accompanied or followed by painless abdominal enlargement, of slight or moderate extent, which may progress slowly or rapidly, finally being greatly increased in size. Loss of appetite, nausea or vomiting, and irregularity of the bowels have been common, and in some cases paracentesis had been performed on one or more occasions, with temporary relief, but with reaccumulation of the fluid in a short time. Slight jaundice is not uncommon, and the skin is dry and scaly, sometimes shiny, but never wrinkled; there is no tendency to other skin diseases. Umbilical hernia