COMMUNICATIONS

PITUITARY EXOPHTHALMOS*

AN ASSESSMENT OF METHODS OF TREATMENT

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EXOPHTHALMIC ophthalmoplegia, progressive or malignant exophthalmos, and thyrotropic exophthalmos are synonyms for the same clinical conditions.

The various terms imply that this bilateral exophthalmos is associated with ophthalmoplegia, that the condition is progressive, leading, if untreated, to grave damage and eventual loss of the eyes, and that it is believed to be due to excess of pituitary thyrotropic hormone.

Sound experimental evidence, such as to make this belief acceptable, has accumulated. Among others, Collip and Anderson (1935), Paulson (1939), Aird (1941), and Dobyns (1946), have been able to produce bilateral exophthalmos experimentally in the guinea-pig by administration of pituitary thyrotropic hormone. The exophthalmos so produced is characterized by its persistence during anaesthesia and after death. It is associated with myopathy of the extra-ocular muscles. It appears more rapidly and is of greater severity in the thyroidectomized animal. It is progressive even after administration of thyrotropic hormone has ceased. In the first three of these characteristics it resembles the spontaneous disease observed in human beings. The clinical features and the pathology of the condition have been fully described by Brain (1936), Naffziger (1931, 1933, 1938, 1948), Mann (1946), and Dobyns (1950). Clinically this condition is distinct from the more common type of exophthalmos associated with Graves' disease. The first symptom is usually a burning sensation and watering of the eye, but not infrequently diplopia is experienced before the patient has become aware of protrusion of the eyeball. More often than not the condition presents as an asymmetrical one, and occasionally it is unilateral in the early stages so that distinction from orbital tumour may cause difficulty. It seems appropriate here to stress that in this variety of exophthalmos, more aptly called proptosis, there is rarely lid retraction. From the onset, the lid space is narrow, rather than enlarged, owing to swelling of the lids. There are heavy bags of oedema below the eyes and there is oedema of the conjunctiva of lids and of globe. The orbital contents, including fat and

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muscles, are oedematous and oedema of the optic disks may be present. The eyeballs protrude progressively, so that lid closure becomes impossible and eventually the eyes protrude beyond the orbit. Corneal ulceration and perforation result. In many cases the condition has made its first appearance shortly after thyroidectomy. The experimental evidence justifies the conclusion that progressive proptosis, localized oedema, and myopathy are due to excess of pituitary thyrotropic hormone, and that their development is favoured by thyroid deficiency, whether due to thyroidectomy or depressed thyroid function from the use of antithyroid drugs (Dobyns and Haines, 1946; Purves and Griesbach, 1949).

These considerations lead to three different lines of therapeutic attack—apart from local surgical measures directed to save the eye when it is endangered by exposure or by papilloedema:

- (1) To depress the output of pituitary thyrotropic hormone by administration of thyroid.
- (2) To depress the output of thyrotropic hormone by modifying the metabolism of the hormone-producing pituitary cells directly by *x*-radiation without causing lethal damage to the gland*.
- (3) To remove surgically a portion of pituitary tissue or destroy it *in situ*[†]. This therapeutic method would appear unnecessary if it can be shown that less drastic measures hold reasonable certainty of success.

Mann (1946), who reported on eighteen cases, chose the first method of therapy. She recognized the importance of time relationship between different phases of thyroid dysfunction and of excess thyrotropic hormone secretion. The analysis of the clinical histories of her patients led her to distinguish three groups of cases.

(a) "Cases of primary thyroid deficiency with compensatory excess thyrotropic hormone secretion". All four patients in this group were treated with small amounts of thyroid. The result was satisfactory, but only two of the patients showed sufficiently severe ocular signs to convince the reader of the efficacy of thyroid treatment.

(b) Ten patients whose histories suggest "initial hyperthyroidism followed by thyroid failure or thyroidectomy with subsequent excess thyrotropic hormone". Six patients who exhibited progressive proptosis, oedema, and ophthalmoplegia responded well to thyroid medication combined when necessary with local surgical measures such as tarsorrhaphy; one patient recovered spontaneously without ever presenting a severe oedematous syndrome, and two recovered with tarsorrhaphy only, no specific antipituitary treatment being applied.

(c) Four cases "in which excess thyroxine and excess thyrotropic hormone

* Analogous attempts to treat acromegaly by a moderate dose of *x*-radiation have been made for many years with excellent results. We have observed several young women suffering from acromegaly whose general health improved after pituitary *x*-radiation; acromegalic features regressed, and visual field defects recovered. Two patients who had been amenorrhoeic for several months returned to a normal menstrual cycle and became pregnant; both were delivered of a healthy baby after a normal pregnancy.

[†] Dobyns (1950) quotes four cases from the literature where electrocauterization of the pituitary was undertaken simultaneously with unilateral orbital decompression. In all four cases there was retrogression of proptosis and oedema in the eye which had not been decompressed.

arise simultaneously". One of these patients was in a severe thyrotropic state on admission, showing severe oedematous proptosis, papilloedema, and ophthalmoplegia. Bilateral tarsorrhaphy was carried out. His thyrotoxic condition apparently increased and eventually, after a period of rest, he was subjected to x-radiation of the pituitary. Several months later eye movements had partly recovered, proptosis, and oedema of lids and optic disk had subsided, visual acuity had returned to normal, and the thyrotoxic state was much improved.

It is this last group of patients which presents the most difficult problem. Thyrotropic hormone is known to be low in blood and urine in acute Graves' disease; it is believed that the hyperactive thyroid depresses pituitary thyrotropic activity. One would have to assume, in cases of simultaneous hyperthyroidism and progressive oedematous exophthalmos with ophthalmoplegia, a thyroid dysfunction different from the hyperthyroidism of Graves' disease; in these cases the hyperactive thyroid fails to exert a depressing effect on the pituitary. Obviously these cases will present the most difficult therapeutic problems. Thyroidectomy and the use of antithyroid substances are contraindicated; such measures might further stimulate the pituitary and increase danger to the eyes. Radiation of the pituitary would appear to be the treatment of choice in these cases combined, when necessary, with local surgical measures to protect the eyes immediately.

In the Edinburgh Department of Surgical Neurology this line of therapeutic approach has been in practice, occasioned by a case that came under observation in 1938.

Case Reports

Case 1. Mrs. P., aged 48, first seen October 25, 1938.—Simultaneous bilateral thyrotropic exophthalmos with mild hyperthyroidism. X-radiation of pituitary.

History.—Has been stout since puberty. Six normal pregnancies, now in the menopause. Has shown much fluctuation in weight in the last 3 years but lost altogether 2 st.; still rather plump. Received small doses of thyroid for the last 3 months. Has been jumpy and nervous over the past 2 years. Definite polyuria and polydipsia in the last 3 years, average output 80 oz. in 24 hours. This was not influenced by administration of 1 ml. pituitrin over 7 days. Five months ago patient developed streaming rhinorrhoea with much sneezing; this stopped spontaneously after 3 to 4 weeks and gave way to puffiness of the eyelids. This remained to date. Soon afterwards she developed a corneal ulcer of the right eye which healed after 3 weeks under local treatment, but recurred a few weeks later. Three months ago when oedema of the lids was already marked, patient noticed protrusion of the eyeballs, no diplopia.

Examination.—Patient was found to be overweight. Height 4 ft. 8½ in., weight 10 st. ½ lb. Mild hyperthyroidism, temperature normal, pulse rate between 80 and 96 in bed, average basal metabolic rate after thyroid had been withdrawn for some time +24 per cent.

Blood pressure 140/86. Blood sugar curve 91, 106, 135, 124, 149; one week later 107, 135, 149, 169, last specimen clotted. No glycosuria.

Ophthalmological Findings.—Moderate bilateral proptosis with puffiness of upper and lower lids, chemosis injection of right sclera, small ulcer on right cornea. Right pupil dilated (atropine treatment); left pupil reacts normally. Slight restriction of all external eye movements. Normal visual acuity, fields, and fundi.

X-Rays of Skull.—Definite enlargement of sella turcica with elongation and thinning of dorsum sellae (Fig. 1). Findings indicative of intrasellar expanding lesion.

FIG. 1.—X-ray of skull of Case 1. Note globular sella turcica and elongated dorsum sellae.

Treatment.—Preliminary treatment of hyperthyroidism with Lugol's iodine solution, starting 12 days after admission to hospital, when all investigations had been completed. After 8 days' treatment, basal metabolic rate had dropped to -3 per cent. and continued to remain at an average of -5 per cent. in all subsequent examinations. Under this treatment there was slight improvement of lid oedema, and the corneal ulcer healed. X-ray therapy of the pituitary was given from December 1, 1938, to January 30, 1939, a total dose of 5000r. After initial deterioration of the eye condition—a minute ulcer appeared on the left cornea and the right-sided ulcer recurred on the third day of x-radiation—slow and steady improvement was observed during the period of radiation. At the conclusion of treatment the ulcers were healed, oedema of lids and proptosis greatly improved and the condition continued to improve over subsequent months.

Follow-up.—This improvement was maintained, the patient's general condition remained satisfactory, her blood sugar curve became normal, as did the fluid intake and output, and nervousness and all signs of hyperthyroidism remained absent.

This case is so far unique. We were unable to find another case of thyrotropic exophthalmos with radiological evidence of pituitary enlargement in the literature. Professor Dott, who had experience of the beneficial effect of x-radiation of the pituitary in a considerable number of patients suffering from acromegaly, suggested this treatment for thyrotropic exophthalmos. The result which was achieved without any surgical measures, proved fortunate, so that we adhered to direct attack on the pituitary in all subsequent cases.

Case 2. Mrs. D. E., aged 48, shop assistant, admitted August 9, 1947.—Simultaneous bilateral thyrotropic exophthalmos following thyroidectomy. Bilateral orbital decompression, x-radiation of pituitary.

History.—Has never been pregnant; menopause for 2 years. Twelve years ago swelling of throat, palpitations, nervousness, slight exophthalmos; treated with iodine for a short time; improved and remained well and very active at war work. Fifteen months ago symptoms and signs of recurring hyperthyroidism without increase of exophthalmos. Ten months ago thyroidectomy; good recovery, improvement in general health, increase in weight. Six months ago ($3\frac{1}{2}$ months after thyroidectomy) eyes began to become more prominent, the left one more so. Since then increase of protrusion, gradual development of puffiness of lids and congestion of the eyes. Up to 6 weeks ago, when lids were sutured, no diplopia, no deterioration of vision. When the lids were opened again, the patient noticed that vision had deteriorated and continued to do so rapidly. No diplopia experienced.

Ophthalmological Findings.—Gross bilateral proptosis, more advanced left side, marked swelling of lids, bilateral chemosis, corneal swelling, and opacity, with moderate degree of conjunctival and corneal injection. Left pupil irregular, larger than right; neither reacts to light. Patient unable to converge; abduction of right eye almost completely absent. All other external eye movements only moderately restricted—not more than may be accounted for by the severe protrusion (Fig. 2).

Vision: right eye, hand movements at $\frac{1}{2}$ m. distance with ease, but vision absent in lower nasal quadrant (?due to partial retinal detachment caused by raised intra-ocular pressure); left eye, hand movements at $\frac{1}{2}$ m. distance with difficulty, field of vision full.

Examination of fundi not possible; no other abnormality found except persistently raised blood pressure between 180 and 190 systolic and 118 and 130 diastolic, with pulse rate of 78 at rest.

Treatment.—Immediate bilateral orbital decompression; in addition left cervical sympathectomy was carried out to help improve the nutrition of the seriously damaged left cornea. Biopsy taken from the external rectus muscle on the left side showed the muscle fibres separated, sometimes by oedema, sometimes individually or in groups by

FIG. 2.—Case 2, on admission.

FIG. 3.—Case 2, on completion of x-ray therapy.

FIG. 4.—Case 2, two years after completion of treatment.

young fibrous tissue. Some muscle fibres showed sarcolemmal nuclear increase and oedema. There was marked focal and slight general lymphocytic infiltration. At the conclusion of each decompression the lids were sutured with retaining sutures. On the third day after operation the left tarsorrhaphy appeared to be under tension, and resuturing was required the next day.

Ten days after decompression, x-radiation of the pituitary was started; from August 28, 1947, to September 9, 1947, a total dose of 3,500r was given. Three days later the lids could be opened, tension being much less.

Three weeks after decompression, when the course of x-radiation was almost at an end, all chemosis had subsided. Visual acuity in the right eye was J1 partly. There was still corneal opacity in the left eye. Eyes closed well, but still showed marked puffiness of the lids.

Follow-up.—Seven weeks after operation, and 4 weeks after completion of x-radiation, visual acuity in the right eye was 6/6, left eye 6/36. There was no longer any field defect; no pathological change of the fundi was present. Further progress can be judged from Fig. 3. One year after treatment some puffiness of the lower lids was still present. After another year this too had disappeared (Fig. 4).

Visual acuity in the right eye is now 6/6, left 6/12.

Case 3. Miss N. N., aged 31, midwife (hospital staff), admitted March 16, 1949.—Simultaneous bilateral thyrotropic exophthalmos following thyroidectomy. Bilateral orbital decompression, x-radiation of the pituitary.

History.—This previously healthy woman developed irritability, fatigue, and loss of

weight 10 months before admission, and mild exophthalmos 3 months later. She had 4 weeks hospital treatment with 0.2 g. thiouracil daily, and was discharged on 0.1 g. maintenance dose. Four months ago, although feeling better in herself, she noticed that the eyes had become bloodshot and sore; exophthalmos increased, lid closure became impossible. Two months ago, thiouracil was replaced by iodine, and on February 2, 1949, she underwent partial thyroidectomy. After this the eyes deteriorated and the patient noticed blurring of vision; she did not admit diplopia but could read better with one eye closed. On admission general condition was satisfactory, pulse rate 78, systolic murmur at apex. Blood pressure 150/100. Urine normal, x-ray of skull normal.

Ophthalmological Findings.—Marked bilateral proptosis, epiphora, moderate chemosis, corneal injection but no ulceration, no opacities. All external eye movements somewhat restricted. Visual acuity in the right eye J6, left J10. Engorgement of retinal veins, nasal disk margins blurred, absence of physiological cup. This early congestion of the disk more marked on the right. Before admission the patient had been given stilboestrol without benefit (Fig. 5).

FIG. 5.—Case 3, on completion of x-ray therapy.

FIG. 6.—Case 3, 20 months after completion of treatment.

Treatment.—Immediate bilateral orbital decompression without tarsorrhaphy was carried out. Biopsy of intra-orbital fatty tissue showed focal aggregation of lymphocytes; there were only a few striped muscle fibres in the specimen; 23 days after decompression there was still some chemosis, though owing to decompression the proptosis had much retrogressed. X-radiation of the pituitary was started 9 weeks after operation and over 3 weeks a minimum tumour dose of 3,000r was given. During this period condition improved dramatically. Patient was discharged with mild exophthalmos, slight oedema of lower lids, no lid retraction, no impairment of external eye movements. The plica semilunaris remained somewhat red and swollen on both sides.

Follow-up.—Six months later the eyes appeared satisfactory; left caruncle still looked a little red and prominent. No proptosis, no chemosis. Visual acuity J1 in each eye. Blood pressure 146/102. One year after operation further cosmetic improvement. Blood pressure varied from 134/92 to 158/104. Patient's general condition excellent, worked full time as midwife. After 20 months general condition satisfactory; no symptoms apart from some increase in menstrual flow (Fig. 6).

Case 4. Mr. W. W., aged 58, civil servant, admitted August 21, 1947.—Bilateral asymmetrical thyrotropic exophthalmos without definite thyroid dysfunction. Bilateral tarsorrhaphy and x-radiation of pituitary.

History.—No history of thyroid derangement; 8 months before admission the patient noticed redness and slight protrusion of left eye, preceded by a few twinges of pain in it. This condition remained stationary, until 5 months ago after an illness diagnosed as

influenza redness and protrusion of the right eye suddenly developed, and slowly progressed. The patient developed oedema of conjunctiva, but noticed blurring of vision which advanced rapidly only 2 weeks before admission.

Examination.—Good general condition. Soft swelling of thyroid gland but no other clinical signs of thyroid disturbance. Basal metabolic rate, however, was +46 per cent. Blood pressure 130/90, pulse 76. X-rays of skull negative.

Ophthalmological Findings.—Left eye, slight protrusion, slight injection of conjunctiva, slight restriction of outward movement, other external eye movements normal. Pupillary reactions normal, also visual acuity, field, and fundus.

Right eye, severe proptosis, massive oedema of lids and conjunctiva, eye cannot be closed. Profuse watery-purulent discharge. Slight opacity of cornea. Apart from moderately good inward movement all external eye movements absent. Pupil reacted to light. Vision J8. Field and fundus normal.

Treatment.—August 24, 1947, tarsorrhaphy right eye. August 27, 1947, some chemosis appeared on left eye. August 28, 1947, x-radiation of pituitary started (Fig. 7). Some stitches of right tarsorrhaphy gave way. September 1, 1947, tarsorrhaphy left eye. September 10,

FIG. 7.—Case 4, at beginning of x-ray therapy. Note right-sided partial tarsorrhaphy.

FIG. 8.—Case 4, 2 years after treatment.

1947, both eyes moved fairly well, proptosis subsiding. Some stitches of left tarsorrhaphy cut out to give patient an opening through which he could see; underlying conjunctiva and cornea looked healthy. Lids still puffy. September 18, 1947, x-radiation completed, minimal tumour dose 3,500r. September 27, 1947, lids still puffy, proptosis subsided. Patient could read a little with left eye, as tarsorrhaphy was now only partial. October 26, 1947, oedema of lids subsiding.

Follow-up.—July 2, 1948, proptosis and lid oedema very slight but not completely gone; lids to be opened. October 31, 1948, no diplopia, all external and internal eye movements normal; little if any proptosis; still some bagginess of lower lids. December 13, 1949, apart from some bagginess of lower lids and some loss of eyelashes, no ocular abnormality; blood pressure 163/114. April 15, 1951, has remained free from symptoms; blood pressure 170/115 (Fig. 8).

Case 5. Mrs. E. A., aged 50, housewife, admitted August 20, 1947.—Bilateral thyrotoxic exophthalmos after thyroidectomy. Evisceration right eye, tarsorrhaphy left eye, x-radiation of pituitary.

History.—One sister suffers from exophthalmic goitre. Patient had a soft swelling of the thyroid without symptoms at age 6. Menarche at age 14, periods regular. Four normal pregnancies. Menopause established 4 months ago. Four years ago developed mild symptoms of hyperthyroidism. One year ago these symptoms rapidly increased, with severe dyspnoea and loss of weight. Admitted to hospital on December 13, 1946, in acute state of thyrotoxicosis. Basal metabolic rate +114 per cent. There was then

mild exophthalmos with lid retraction, but no lid oedema. Treated with rest and thiouracil for one month without benefit. During this period 28 blood pressure readings, all taken during strict rest in bed, varied between 140/80 and 188/114, pulse rate between 86 and 104. On January 31, 1947, thyroidectomy was performed; she was discharged barely 3 weeks later in good condition. Basal metabolic rate +14 per cent. She began to put on weight. No noticeable change in the appearance of the eyes.

When she was admitted to the Eye Department on August 20, 1947, she stated that in the first 2 months after thyroidectomy she had gained 2 st. in weight; 3 months after thyroidectomy her eyes became slightly "inflamed", and this progressed over the subsequent 3 months, and marked protrusion and swelling of the lids developed, so that she became unable to close the eyes. A few weeks before admission to the Eye Department vision in the right eye became dim, no diplopia.

Ophthalmological Findings.—Right eye, severe proptosis, chemosis, exposure keratitis with corneal abscess; left eye, proptosis with lid oedema, chemosis, cornea clear but exposed in sleep.

Treatment.—August 23, 1947, evisceration right eye. August 29, 1947 tarsorrhaphy, left eye, leaving medial third of lid space open. September 7, 1947, oedema of lids and right conjunctiva tarsi increasing. September 11, 1947, x-radiation of pituitary started; in 3 weeks minimum tumour dose of 3,000r delivered. Three weeks after completion of this treatment redundant conjunctival tissue from the right orbit was excised and a tarsorrhaphy carried out. A month later the orbital oedema was much less but there was still some left-sided proptosis.

Follow-up.—General condition subjectively excellent 13 months later. Patient had worked hard in house and on the farm; she looked well, but exhibited a blood pressure of 190/120, pulse rate 96. The artificial eye fitted well. No oedema of lids. When the left tarsorrhaphy was undone normal conjunctiva and cornea presented. No proptosis, outward movement moderately restricted, all other movements, fundus and vision normal.

Case 6. Mr. A. A., aged 36, motor-bus wheel fitter, first reported September 12, 1946.—Mild bilateral thyrotropic exophthalmos without thyroid dysfunction. X-radiation of pituitary.

History.—No symptoms of thyroid dysfunction. Two months ago noticed drooping of left upper lid, 1 month ago developed vertical diplopia, 6 weeks ago noticed puffiness of left eye.

Examination.—General condition satisfactory, pulse rate 84. Blood pressure 136/94.

Ophthalmological Findings.—Moderate proptosis, lid oedema, and chemosis left eye, slight proptosis without oedema right eye. Moderate restriction of upward and downward movement, severe defect of inward movement left eye. Slight drooping of upper lid. Normal external eye movements right eye. Pupillary reactions, vision, and fundi normal both eyes. X-rays skull normal. Diagnosis of early thyrotropic exophthalmos.

Treatment.—X-radiation of pituitary started on December 4, 1946; total minimum tumour dose of 3,000r delivered.

Follow-up.—Both eyes appeared normal 6 months later; no puffiness of lids; no impairment of external eye movements. Subjectively no diplopia. General condition very satisfactory. Blood pressure 140/95.

Case 7. Mr. R. W., aged 53, shale miner, first reported May 21, 1946.—Early bilateral asymmetrical thyrotropic exophthalmos with doubtful hyperthyroidism. X-radiation of pituitary.

History.—Ten weeks ago struck across left eye by piece of shale. No discomfort at the time, but 7 weeks ago noticed slight prominence of left eye. This has fluctuated in severity since. Vertical diplopia for a few days.

Examination.—General condition satisfactory. Pulse rate 76. Blood pressure 158/90.

Ophthalmological Findings.—Moderate proptosis left eye, very slight proptosis right eye. Slight puffiness of upper lid and chemosis at outer canthus left eye. Deficient upward movement left eye. Vision, fundi, fields normal. X-ray of skull normal.

One month later the patient reported back and stated that the degree of proptosis was very variable. Sometimes the right, sometimes the left eye was the more prominent. Now upward movement of left eye was almost absent and outward movement deficient. Complained of constant diplopia, but otherwise no change. July 11, 1946, admitted for full investigation and treatment. Eye condition unchanged. Mild clinical signs of hyperthyroidism. Basal metabolic rate +49 per cent.; 3 days later, after 3 gr. nembutal, +20 per cent.

Treatment.—X-ray therapy of pituitary from July 22, 1946, to August 8, 1946, total minimum tumour dose 3,500r. Four months later he still showed great variability in the size of the left lid space, amounting sometimes to a definite droop of the upper lid, sometimes to active lid retraction. No other abnormalities found.

Follow-up.—The patient has been followed-up for over 4 years; he has lost all symptoms and signs of hyperthyroidism, and works steadily in the mines. There has been no change in the eye condition; he has adjusted to the diplopia which can still be elicited, but which he apparently spontaneously suppresses.

Case 8. Miss M. B., aged 48, home duties, admitted October 15, 1943.—Mild bilateral thyrotropic exophthalmos twelve years after thyroidectomy. X-radiation of pituitary and thyroid medication.

History.—Brother and sister suffered from hyperthyroidism. She was a healthy woman, normal periods throughout reproductive life. Menopause established 6 months ago. Developed tachycardia, exophthalmos, and all usual symptoms of hyperthyroidism 13 years ago. Twelve years ago, after partial thyroidectomy, all symptoms disappeared, but right eye always remained a little prominent. Five weeks ago she noticed vertical diplopia with upward gaze and to the right; 2 weeks ago developed puffiness of lower lids.

Examination.—Satisfactory general condition. Blood pressure 120/74. Basal metabolic rate -25 per cent. Fluid intake and output within normal limits.

Ophthalmological Findings.—Slight bilateral proptosis, right 19 mm., left 16 mm. Marked puffiness of eyelids, more on the right. No chemosis. Vertical diplopia in all directions of gaze. Slight restriction of outward movement of right eye, all other external eye movements full. Vision, fields, and fundi normal.

Treatment.—X-radiation of pituitary; minimal tumour dose of 3,000r given in 2 weeks. Thyroid 3 gr. daily; after three weeks, when basal metabolic rate was -10 per cent., reduced to 2 gr. daily. Diplopia subsided within a few weeks of beginning of treatment. Exophthalmometer readings never changed and puffiness of lower lids never quite subsided.

Follow-up.—Condition unchanged after 4½ years.

Case 9. Mrs. J. W., aged 48, housewife, first reported May 7, 1946.—Mild asymmetrical thyrotropic exophthalmos with slight hyperthyroidism. X-radiation of pituitary.

History.—No previous history of thyroid dysfunction. Periods still fairly regular. For 18 months mild insomnia, for a few months nervousness and rapid fatigue. Two months ago noticed diplopia on looking up.

Examination.—No signs of thyroid dysfunction. X-rays of skull negative.

Ophthalmological Findings.—Right eye normal. Left eye shows trace of protrusion and ptosis. Upper lid lags behind in voluntary and automatic elevation and in lid closure. Defect of upward movement. All other movements normal. Pupil, vision, fundus normal. One week later definite puffiness of lids of both eyes, with slight chemosis of left conjunctiva. Upward and outward movements of left eye now deficient. No

increase of proptosis. Defect of movement disproportionate to forward displacement of eyeball and suggests muscular defect.

Admitted July 10, 1946, for further investigation. Apart from persistently raised basal metabolic rate (+42 per cent., +12 per cent., and +47 per cent.), slight tremor of extended fingers and general nervousness, no signs of hyperthyroidism. Diagnosis of thyrotropic ophthalmoplegia with little exophthalmos.

Treatment.—X-radiation of pituitary given from July 18, 1946, to August 7, 1946, minimum tumour dose of 3,500r.

Follow-up.—After 6 months general condition good. Patient sleeps better, is less nervous. No trace of lid oedema or chemosis. No proptosis. No improvement in upward and outward movements of left eyeball. After 3 years diplopia remained unchanged. Patient reports that one to two days before menstruation she always exhibits some puffiness of the lids; on one occasion when she reported during menstruation no puffiness of lids and no chemosis could be detected.

Case 10. Mr. E. K., aged 51, watchmaker, first reported February 7, 1951.—Bilateral thyrotropic exophthalmos without thyroid dysfunction. X-radiation of pituitary.

History.—No symptoms suggestive of thyroid trouble. He noticed slight protrusion of right eye without widening of the lid space but with some puffiness of the lids 8 months ago. A month or two ago noticed some swelling below left eye. Three months ago first noticed double vision, which has been variable in type, sometimes vertical, sometimes oblique. He does not connect the type of diplopia with the direction of gaze; while first intermittent, diplopia is now constantly present. He has noticed slight deterioration of vision in the right eye.

Examination.—The patient showed no signs of hyperthyroidism. There is an extra-pyramidal type of tremor of the head. No other abnormalities. Blood pressure 160/74.

Ophthalmological Findings.—Proptosis right eye, doubtful proptosis left eye (right 27 mm., left 24½ mm.). Oedema of upper and lower lids of right eye, oedema of lower lid of left eye, upper lid being somewhat retracted. Oedema below both eyes. Outward movement of right eye slightly restricted, all other external eye movements full. Deficient downward movement of right upper lid on downward gaze (Stellwag's sign). Pupillary reactions normal. Cornea clear both eyes, conspicuous watering of both eyes. Visual acuity in right eye 6/6 partly, J4; in left eye 6/5, J1. Fields and fundi normal. X-rays of skull normal.

Patient admitted March 13, 1951. During a week of investigations in the ward, no raised temperature, pulse rate averages 76.

Laboratory Findings.—Blood chlorides 530 mg. per cent.; basal metabolic rate +2 per cent.; blood cholesterol 260 mg. per cent.; blood sugar curve 90–140–120–60–60–90.

On March 16, 1950, patient developed oedema of both upper lids, and conjunctival injection, right more than left; slight restriction of outward and down-outward movement right eye.

Treatment.—X-radiation of pituitary started on April 13, 1951; 3,000r delivered in 3 weeks.

Exophthalmometer Readings.—

Date	Right Eye	Left Eye
April 13, 1951	31 mm.	27 mm.
April 18, 1951	27 mm.	24 mm.
April 24, 1951	26 mm.	24 mm.
May 5, 1951	26 mm.	24 mm.

When he was discharged on May 4, 1951, conjunctival injection and oedema of the lids had almost completely subsided. No change in diplopia and external eye movements; vision in the right eye 6/6, J2; left eye 6/6, J1.

Follow-up.—On May 24, 1951, he reported some improvement in diplopia. The findings were unchanged.

Case 11. Mr. J. S., aged 63, machine operator, admitted February 1, 1945.—Asymmetrical thyrotropic exophthalmos without thyroid dysfunction. Unilateral orbital decompression, x-radiation of pituitary.

History.—No symptoms suggestive of thyroid dysfunction; 3 months ago complained of watering of both eyes, this has continued to date; 2 months ago started to see double, and also noticed protrusion of the left eye and that it would not move. Patient has experienced brief attacks of headache behind both eyes.

Examination.—No impairment of general physical condition. Blood pressure 156/90.

Ophthalmological Findings.—Proptosis of left eyeball with downward and inward displacement. Chemosis of left eye. Upward and outward movements practically absent, inward movement slightly defective. Appearance and all movements of right eye normal. No pupillary changes. Vision normal in each eye. Some blurring of nasal disk margin without other signs of congestion in the left eye. X rays of skull, sinuses, and optic foramina negative.

In this case the strictly unilateral proptosis without oedema of the lids suggested the presence of an orbital tumour, though the unusual degree of ophthalmoplegia in the presence of only moderate proptosis raised the possibility of exophthalmic ophthalmoplegia, which had so far remained unilateral.

Treatment.—On February 7, 1945, orbital decompression was carried out. Exploration of orbit disclosed no tumour; orbital fat found to be unusually firm and tense, and muscles appeared unduly bulky. Biopsy specimen of muscle showed several areas of lymphocytic infiltration with surrounding granular degeneration of muscle fibres. At the end of the operation tarsorrhaphy was carried out. The patient was discharged 2½ weeks after operation still showing diplopia and defective upward movement of the left eye, but no proptosis, no lid oedema, and no chemosis.

Further Developments.—Three months later patient still complained of diplopia. Right eye normal in appearance and movements satisfactory.

Fifteen months after the orbital decompression he stated that about 4 months after operation the right eye started to protrude and that the degree of protrusion fluctuated (Fig. 9). In spite of troublesome diplopia he had returned to work, doing 12 hours a day. In the past year he had been under the care of an ophthalmic surgeon in his home town, who had arranged for x-radiation of the pituitary. He had received a total of 500r in 10 weeks, and now showed proptosis of right eye with puffiness of the upper lid, deficient outward and absent upward movement. No chemosis, no papilloedema. No change in appearance of left eye, which was protected by the decompression and still showed some defect of upward movement. Vision in each eye 6/6.

Exophthalmometer Reading.—Right eye 23 mm., left eye 15 mm.

Further Treatment.—In consultation with the radiologist it was decided that the x-ray treatment so far delivered could not be regarded as an effective dosage. The patient was given a further course of x-radiation of the pituitary, a minimal tumour dose of 3,000r was delivered. Halfway through the treatment exophthalmometer readings were unchanged; 2 weeks after completion of treatment exophthalmos had practically disappeared. There was still slight defect of upward movement and diplopia. The left-sided tarsorrhaphy was opened. No further examination was possible, as he was anxious not to lose any time at work and refused to make the journey to Edinburgh.

FIG. 9.—Case 11, 15 months after left orbital decompression and partial tarsorrhaphy, when x-ray therapy was started.

Follow-up.—Four years later his doctor kindly informed us that the patient (now aged 67) was well, and still regularly at work, and that the condition of the eyes was satisfactory.

Case 12. Mr. P. D., aged 46, warehouseman, admitted June 8, 1943.—Bilateral thyrotoxic exophthalmos 8 years after thyroidectomy. Unilateral orbital decompression, x-radiation of pituitary.

History.—Symptoms of hyperthyroidism appeared 12 years ago; 8 years ago partial thyroidectomy for primary thyrotoxic goitre. At that time he exhibited bilateral exophthalmos, but this and all other symptoms disappeared soon after operation, and he returned to full work. At routine follow-up 3 years ago no exophthalmos present. Vertical diplopia started 8 months ago; since then the distance between the two images had gradually increased. For the last 3 months he had been aware of increasing protrusion of the right eye. Lately diplopia has no longer worried him, since one image is "so high up, that he does not bother about it". For years he has had some nocturnal polyuria.

Examination.—General physical condition satisfactory except for blood pressure of 164/102; heart not enlarged; urine normal.

Ophthalmological Findings.—Moderate degree of puffiness of upper and lower lids, more so on the right side. Purplish discoloration of upper lids with small telangiectases. Slight chemosis of lateral portion of right conjunctiva with slight injection. Very gross proptosis of right eyeball, which seems two-thirds outside the orbit, displaced forwards and downwards, and slightly rotated inwards. Slight proptosis left eye (Fig. 10). Right pupil fails to dilate in dim light; pupil is irregular, reacts sluggishly and inextensively to direct and indirect light and convergence. Left pupil normal. Movements of right eye except for inward movement all severely restricted, left eye moves normally. Vision in the right eye 6/60 with central scotoma; left 6/6, normal field. Fundi normal. X-rays of skull and optic foramina normal.

FIG. 10.—Case 12, on admission.

FIG. 11.—Case 12, 15 months after completion of treatment.

It was felt that this was a case of rather asymmetrical bilateral exophthalmic ophthalmoplegia due to excess thyrotropic hormone, exerting its influence in the absence of an efficient thyroid. The central scotoma in the right eye was thought to be due to severe stretch on the retrobulbar portion of the optic nerve.

Treatment.—In order to preserve and restore vision, decompression of the right orbit was carried out on June 14, 1943. At the end of the operation the right eye protruded only a little more than the left. Severe oedema was present for the first five post-operative days. Subsequently retraction of the right upper lid was marked, giving the eye a more exophthalmic appearance than the actual proptosis accounted for. On the 11th day

all external eye movements were free, but the upper lid remained retracted. Vision unchanged, with central scotoma. *X*-radiation of the pituitary started on the 20th post-operative day, completed in 10 days; a minimum tumour dose of 3,000r was delivered.

Follow-up.—Fifteen months after completion of treatment, both eyes still somewhat proptosed, the left, which had not been decompressed, distinctly more so. No puffiness of lids, no oedema of conjunctiva. Both eyes showed deficient outward movement, and the right some defect in upward movement, being still somewhat displaced downwards. Pupillary reactions normal. Vision in both eyes 6/6 with normal fields (Fig. 11).

Fundi showed the appearances of first degree hypertensive retinopathy. He reported symptoms suggestive of hypertensive encephalopathy. These gradually increased. He died from malignant hypertension 3 years after he had first been seen.

Discussion

In all twelve cases the final result was wholly or reasonably satisfactory; no patient showed further progression of the malady after radiation treatment.

For critical assessment of the efficacy of *x*-radiation of the pituitary, those cases are obviously of most value where no local surgical measures were required and where the history suggests steady progress of the malady up to the time that *x*-radiation was started.

Dobyns (1946, 1950) found in the literature 37 cases where *x*-radiation of the pituitary was given; in thirteen the result was satisfactory. He advises that this method should be further considered.

In our Cases 1, 6, 7, 8, 9, and 10, *x*-radiation was applied without local surgical measures; in Cases 11 and 12 it was preceded by unilateral orbital decompression.

Unequivocal evidence based on personal observation that the malady was progressive until treatment was begun, is available in Cases 1 and 10. In both, oedema, congestion, and proptosis improved dramatically during *x*-radiation; ophthalmoplegia, which was less prominent in these cases, also improved.

In Cases 6, 8, and 9, the history strongly suggests progression of the malady until treatment was started. Case 8 is unsuitable for the evaluation of radiotherapy, which was combined with thyroid administration. The final result in case 6 was excellent; oedema, proptosis, and ophthalmoplegia subsided completely. In case 9, oedema and proptosis subsided, while ophthalmoplegia, which had preceded the onset of proptosis, remained unaltered. It is noteworthy that in this case hyperthyroidism also derived benefit from radiation of the pituitary. With the most rigid standard of assessment it can be stated that four patients out of seven were dramatically improved by radiation and that the remaining three were also improved; though it cannot be said with certainty that *x*-radiation was solely responsible for the improvement in the last three.

The record of Case 11 is the most instructive one in our series. Here we have unequivocal evidence that the malady continued to progress after

unilateral orbital decompression, causing the other eye to proptose considerably during subsequent months. There is no reason to believe that spontaneous arrest of the disease process happened to occur just at the time when the patient underwent *x*-radiation.

In Case 12, *x*-radiation was applied within a month of decompression of the more proptosed right eye. The left eye did not require decompression thereafter and remained in a satisfactory condition until the patient died from malignant hypertension. Though spontaneous arrest at various stages of the disease is known to have occurred (Naffziger; Dobyns), one feels that in this case where steady progression of signs had been observed until radiation was applied, it is most probable that the arrest of the malady was due to radiation, while the dramatic improvement in appearance and function of the right eye was effected by local surgical measures.

Proptosis is directly caused by oedema of the orbital contents; it is part of the oedematous complex of the syndrome. Swelling of the lids, and infra-orbital tissues, and especially chemosis and papilloedema are also initially the direct result of orbital oedema; as intra-orbital pressure rises, venous drainage becomes difficult and congestion is superimposed on the oedema and can often be seen at the conjunctival and retinal veins.

Visual defect as met with in this syndrome may be due to a variety of lesions: to swelling or ulceration of the cornea, to partial detachment of the retina (Case 2), to severe stretch of the optic nerve (Case 12), or to long-standing papilloedema with subsequent optic atrophy. This last possibility is rather theoretical; if orbital oedema which is sufficiently severe to cause papilloedema remains unrelieved, the eye will be lost before optic atrophy has developed. Visual defect may, of course, be due to more than one such lesion, all of which are ultimately due to severe oedema in the orbit.

Interference with eye movements may also depend on various mechanisms. If the eye is pushed forwards by a firm mass behind it, its movements may become restricted from purely mechanical causes, though the muscles are still capable of normal contraction. On the other hand, muscle function may be impaired by oedema between the muscle fibres and by lymphocytic infiltration and granular degeneration of muscle fibres. This myopathy is characteristic of thyrotropic exophthalmos, and is not dependent on the orbital oedema. Muscular defect may arise with a comparatively mild oedematous complex, and may persist, after treatment, in the absence of oedema, once the muscle fibres have been replaced by fibrotic strands.

Table I shows the effect of treatment on oedema and ophthalmoplegia in all cases, irrespective of methods employed. Table II shows in greater detail the effect of *x*-radiation on the individual eye signs in the five cases where *x*-radiation only was given. Whatever oedematous signs were present before *x*-radiation, these had subsided after it in all five cases. On the

TABLE I
METHODS OF TREATMENT AND FINAL RESULT

Case No.	Sex	Age (yrs)	Local Surgical Treatment	X-Radiation	Result
1	F	48	—	+	Full recovery
2	F	48	Bilateral orbital decompression Tarsorrhaphy Sympathectomy	+	Full recovery
3	F	31	Bilateral orbital decompression	+	Full recovery
4	M	58	Bilateral tarsorrhaphy	+	Full recovery
5	F	50	Evisceration right eye Tarsorrhaphy left eye	+	Oedema left eye subsided Some ophthalmoplegia remained
6	M	36	—	+	Full recovery
7	M	53	—	+	Full recovery
8	F	78	—	+ Thyroid	Some oedema remained Ophthalmoplegia recovered
9	F	48	—	+	Ophthalmoplegia remained Oedema and proptosis recovered
10	M	51	—	+	Proptosis and oedema subsided Ophthalmoplegia improved
11	M	63	Unilateral orbital decompression	+	Proptosis and oedema recovered Ophthalmoplegia remained
12	M	46	Unilateral orbital decompression	+	Practically full recovery

TABLE II
RESPONSE OF INDIVIDUAL OCULAR SIGNS TO X-RADIATION

Case No.	Proptosis	Chemosis	Lid Oedema	Infra-orbital Oedema	Papill-oedema	Visual Defect	Ophthalmoplegia
1 { Before treatment After treatment	+ —	+ —	+ —	+ —	— —	slight —	— —
6 { Before treatment After treatment	+ —	+ —	+ —	+ —	— —	— —	+ —
7 { Before treatment After treatment	+ —	slight —	— —	— —	— —	— —	+ +
9 { Before treatment After treatment	+ —	+ —	+ —	+ —	— —	— —	+ +
10 { Before treatment After treatment	+ —	+ —	+ —	+ slight	— —	slight —	+ slight

other hand, ophthalmoplegia disappeared in one case only, and improved in another case, but persisted in three cases. We have not included Case 8 in this analysis; this patient received thyroid in addition to *x*-radiation, and is the only one in our series who showed persistence of oedematous features when ophthalmoplegia subsided.

The aim of orbital decompression is to relieve oedema and congestion in the orbit and thereby to restore adequate drainage of the extra-orbital tissues as well.

Table III shows the response of the individual ocular signs to orbital decompression and *x*-radiation; special attention is paid to a change of signs in the interval between decompression and *x*-radiation. This interval was long enough in only two cases to justify the statement that improvement was accelerated by *x*-radiation.

The analysis shows that ophthalmoplegia will persist in certain cases whatever method of treatment be adopted. As the defective movements

TABLE III
RESPONSE OF OCULAR SIGNS TO ORBITAL DECOMPRESSION AND X-RADIATION

Case No.	Ocular Signs before Decompression		Decompression		Ocular Signs after Decompression		Interval between Decompression and X-radiation	Ocular Signs after X-radiation	
	Left	Right	Left	Right	Left	Right		Left	Right
2	Gross proptosis Chemosis Corneal opacity Severe visual loss Ophthalmoplegia	Proptosis Chemosis Corneal opacity Severe visual loss Ophthalmoplegia	-	+	Initial increase of oedema	Little change	10 days	Oedema and proptosis subsiding Corneal opacity slowly subsiding Vision improving No ophthalmoplegia	All signs subsiding rapidly Vision normal
3	Proptosis Chemosis Papilloedema Visual loss slight Ophthalmoplegia	Proptosis Chemosis Slight papilloedema Visual loss slight Ophthalmoplegia	+	+	Still some chemosis		63 days	No abnormality	
11	Proptosis Chemosis Slight congestion of disk Severe ophthalmoplegia	No abnormality	+	-	Severe ophthalmoplegia	Proptosis Slight oedema of lids Severe ophthalmoplegia	16 months	Ophthalmoplegia	Some ophthalmoplegia
12	Slight proptosis	Gross proptosis Chemosis Visual loss Ophthalmoplegia	-	+	Slight proptosis	Visual loss unchanged All other signs subsided	20 days	Slight proptosis Slight ophthalmoplegia	Doubtful proptosis Slight ophthalmoplegia

result from irreversible changes in the muscles, the duration of diplopia and the severity of muscular defect before treatment will be of prognostic significance.

Table IV shows the relationship between the duration and severity of ophthalmoplegia and the recovery of ocular movements.

TABLE IV
RELATIONSHIP BETWEEN DURATION AND SEVERITY OF OPHTHALMOPLÉGIA
AND RECOVERY OF OCULAR MOVEMENTS

Case No.	Predominant Feature of Syndrome	Duration of Illness	Duration of Diplopia	Degree of Ophthalmoplegia	Recovery of Eye Movements
1	Oedema	4 months	None experienced	Slight	Full
2	Oedema	6 months	None experienced	Severe	Full
3	Oedema	4 weeks	None experienced	Slight	Full
4	Oedema	8 months	None experienced	Slight	Full
5	Oedema	4 months	None experienced	Slight	Almost full
6	None	2 months	1 month	Severe	Full
7	Ophthalmoplegia	10 weeks	5 to 6 weeks	Severe	Little, if any
8	Ophthalmoplegia	5 weeks	5 weeks	Slight	Full
9	Ophthalmoplegia	2 months	2 months	Severe	None
10	None	8 months	3 months	Moderate	Little
11	None	3 months	2 months	Severe	Little
12	None	8 months	8 months	Severe	Little, if any

Seven of the twelve patients showed absence of ophthalmoplegia after treatment; in five, oedematous features dominated the clinical picture, and the fact that they did not experience diplopia before loss of vision makes it certain that ophthalmoplegia, though in several instances severe at the time of admission, must have been a recent development.

It would appear that this malady may take either a very acute course, when congestive features dominate, or a subacute course, when congestive features and ophthalmoplegia are of equal severity or ophthalmoplegia dominates. In these cases, we find weakness of individual eye movements rather than fixation of the eyeball from purely mechanical causes. Early myopathy with irreversible muscular changes appears to be characteristic of the subacute form.

Orbital decompression will not, as a rule, be applied in the less acute cases. This operation is reserved for patients who show rapidly increasing

congestive changes with oedema of the optic disk, or visual defect from stretch of the optic nerve or from retinal detachment.

Damage to the eye from corneal exposure in the severely proptosed eye is avoided by tarsorrhaphy. Tarsorrhaphy alone, however, cannot be expected to remedy rapidly rising intra-orbital pressure. Whenever the eye cannot be adequately closed and there is evidence of further progression of the malady, a combination of orbital decompression with tarsorrhaphy should be employed. In all instances where corneal opacity or ulceration has already occurred, cervical sympathectomy should be carried out, as it will accelerate the healing of corneal lesions.

If immediate danger to the eye has been averted by these surgical measures, it is permissible—and indeed desirable—to observe the patient for a reasonable period without further treatment. Such observation should answer the question how often this malady remains stationary or regresses once the severe congestive phase has been reached. An expectant attitude after local surgical measures will provide an opportunity to study these cases fully and to obtain important biochemical data. If improvement is unduly slow or individual signs (tension under the tarsorrhaphy, ophthalmoplegia after decompression) increase, *x*-radiation of the pituitary should be initiated and biochemical tests should be repeated after a reasonable interval.

In the less acute cases where no local surgical measures are required but where there is evidence of progression of the malady, we believe that *x*-radiation of the pituitary should be applied as soon as full clinical and biochemical data have been obtained.

In this series, the number of patients showing hyperthyroidism associated with pituitary exophthalmos is small. Of the four patients who exhibited a significantly raised basal metabolic rate, only two had clinical symptoms of hyperthyroidism. These two patients improved in their general health after *x*-radiation of the pituitary. The patient who exhibited a severe thyrotoxic state arising simultaneously with pituitary exophthalmos (Mann, 1946), showed dramatic improvement both in general health and in the local condition following pituitary *x*-radiation. Further observations are needed in cases of hyperthyroidism complicated by the oedematous type of exophthalmos. Thyroidectomy as the first therapeutic measure is obviously contraindicated, as is also the administration of antithyroid substances. Both measures must be expected to stimulate the pituitary to increased output of thyrotropic hormone. It is likely that these cases would respond well to pituitary *x*-radiation which should benefit general thyrotoxic symptoms as well as the ocular changes.

Six of our patients (50 per cent.) were females; of these, three developed the malady with the menopause, and two others were approaching the menopause. One of our patients, and several whose records are quoted in the literature (Dobyns, Mann), received oestrogenic substances without benefit to the exophthalmos. The relationship between this pituitary

dysfunction and gonadotrophic pituitary function is a subject for further study.

Summary

The clinical records of twelve patients suffering from exophthalmos of pituitary origin are presented. The effect of pituitary x-radiation on this malady is assessed. The indications for x-ray therapy and local surgical measures are discussed.

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REFERENCES

- AIRD, R. B. (1940). *Arch. Ophthalm., Chicago*, **24**, 1167.
 — (1941). *Ann. intern. Med.*, **15**, 564.
 BRAIN, W. R. (1936). *London Hosp. Gaz.*, **39**, Clin. Suppl., No. 6, p. 1.
 — (1939). *Lancet*, **2**, 1217.
 — and TURNBULL, H. M. (1938). *Quart. J. Med.*, **7**, 293.
 COLLIP, J. B., and ANDERSON, E. M. (1935). *J. Amer. med. Ass.*, **104**, 965.
 DOBYNS, B. M. (1946). *Surg. Gynec. Obstet.*, **82**, 290, 609, 717.
 — (1950). *J. clin. Endocrinol.*, **10**, 1202.
 KLOTZ, H. P. (1948). *Ann. Endocrinol., Paris*, **9**, 184.
 MANN, I. (1946). *Amer. J. Ophthalm.*, **29**, 654.
 NAFFZIGER, H. C. (1931). *Ann. Surg.*, **94**, 582.
 — (1933). *Arch. Ophthalm., Chicago*, **9**, 1.
 — (1938). *Ann. Surg.*, **108**, 529.
 — (1948). *Amer. J. Surg.*, **75**, 25.
 PAULSON, D. L. (1939). *Proc. Mayo Clin.*, **14**, 828.
 PURVES, H. D., and GRIESBACH, W. E. (1949). *Brit. J. exp. Path.*, **30**, 23.
 RUNDLE, F. F. (1941). *Lancet*, **2**, 149.
 — and WILSON, C. W. (1944a). *Clin. Sci.*, **5**, 17.
 — (1944b). *Ibid.*, **5**, 31.