THE CERVICAL SYMPATHETIC AND ITS RELATION TO THE THYROID GLAND IN EXOPHTHALMIC GOITRE.

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In this country theories as to the causation of exophthalmic goitre have principally been focused on the thyroid gland, and as a result of such hypothetical basis for the disease operative treatment has been almost entirely directed towards this structure. On the other hand, a very cursory review of the literature of the etiology of this disease, especially from Continental and American sources, demonstrates the fact that in the minds of a very large proportion of investigators an explanation based on a morbid change in the thyroid alone is inadequate to account for the complex phenomena of the disease, and accordingly many theories have been propounded introducing a neurogenic or toxico-neurogenic factor.

Surgery has followed up this reasoning by attempting to effect a cure through extirpation of presumably diseased nervous pathways of the cervical sympathetic system. What, briefly, are the results of surgical intervention directed towards two totally different anatomical structures? Since the commencement of the present century a large series of operations for exophthalmic goitre have been carried out both on the sympathetic and the thyroid; and the outcome of both procedures has been a reasonable proportion of absolute cures or of cases where there has been pronounced amelioration of the symptoms. In order to exemplify briefly this point the following observations may be cited.

Chalier in 1926 reported a series of nineteen cases of cervical sympathectomy for toxic goitre. The end-results will be seen from the following table.

Cured	...	...	...	...	...	3
Greatly improved	...	...	...	...	...	9
Slightly improved	...	...	...	...	...	6
Recurring	...	...	...	...	...	1

During the past few months I selected at random a series of eleven cases of exophthalmic goitre all of which had undergone partial thyroidectomy or ligation of the thyroid vessels, and visited the patients personally in their homes. Their condition as shown in the table below is assessed on such cardinal symptoms as exophthalmos, tremor, pulse rate, nervous irritability, digestion, weight, and general well-being.

Cured (7 years 1; 3 years 1; 2 years 1; 1 year 1*)	...	...	...	...	...	4
Unchanged (5 years 1*; 2 years 1; 1 year 1; 6 months 1*)	...	...	...	...	...	4
Improved (1 year 1; 9 months 1)	...	...	...	...	...	2
Dead (four years later from phthisis)	...	...	...	...	...	1

An asterisk indicates that the patients had undergone ligation. The patient who died showed no improvement before death.

Allowing for spontaneous cures one absolute fact emerges, and that is that the syndrome of exophthalmic goitre can be definitely relieved or absolutely cured by either (a) extirpation of a considerable portion of the thyroid gland, or (b) excision of the right and left superior cervical sympathetic ganglia and as much of the cervical sympathetic cord as will embrace the variably present middle ganglion.

The preliminary results of an investigation of the neuroglandular etiological relations may now be discussed under two headings—clinical and anatomical.

CLINICAL.

Two cases of exophthalmic goitre have been subjected to the operation of cervical sympathectomy, and in each case there was an exhaustive examination before and after operation.

CASE I.

A woman, aged 62½ years, was taken ill in 1921 with asthenia and palpitation. A few months later exophthalmos developed, and enlargement of the thyroid gland was noticed by her friends. It was further observed that the gland varied in size from time to time; when it was especially prominent the neck was painful. Despite medicinal treatment her condition deteriorated, and she was admitted to hospital on June 8th, 1926. On admission she presented a nervous and emaciated appearance; she weighed 99 lb. The thyroid gland showed diffuse hypertrophy of right and left

lobes, with a small adenoma of the isthmus. Exophthalmos was bilateral, and was present to a marked degree; measurement of the globe projection on the micrometer scale was 50 + 2. The pronounced tremor of both hands is indicated in the accompanying illustration. The basal metabolic rate determined by the Douglas bag and Haldane apparatus was + 44 per cent. (The patient had been many weeks in bed, and samples were collected after twelve-

hour fasts.) In the adrenaline tolerance test 5 mm. of 1 in 1,000 solution produced a rise of brachial pressure of 2 mm. of mercury and 43 beats per minute.

Heart.—Severe auricular fibrillation was present; the apex beat was highly irregular. There was no bruit; the pulse rate was 104 per minute.

Electro-cardiograph.—Lead I: Extrasystoles, R.V., 1. Lead II: Rate, A. 480; V. 120. Rhythm irregular.

Bowels frequency:

Day (6 a.m. to 10 p.m.)	...	...	...	1	1	1
Night (10 p.m. to 6 a.m.)	...	...	...	0	0	0

Micturition frequency:

Day	...	...	...	5	6	5
Night	...	...	...	1	1	1

The knee-jerks were very sluggish. Pressure pain over the thetar region was produced by 2.5 kilos.

The patient was treated by x rays and digitalis, but the result was negligible, and there was pronounced increase of the nervous instability. At an operation on August 21st, 1926, the right and left superior cervical sympathetic ganglia and both cervical cords as far as the inferior ganglia were excised. The operation was conducted under gas and oxygen anaesthesia; there was a rise of the radial pulse of 6 per minute; both pupils were contracted, and enophthalmos was easily observed.

During the first few days after operation there was severe auricular fibrillation, which was controlled by digitalis. The exophthalmos steadily returned to the pre-operative condition. The micrometer reading was 50, and after seven days the basal metabolic rate was reduced by 13 per cent. The tremor showed decided diminution in frequency and amplitude of cycles. Neck measurements before and after the operation were as follows:

	August 26th.	September 28th.
Trans-cricoid plane	...	30 cm.
Mid-crico-manubrial plane	...	32 "
Supramanubrial plane	...	34 "

The pressure pain and adrenaline tolerance were unchanged.

Re-examination, August 27th, 1927.—Her condition shows a steady improvement up to this date; she has gained in weight and feels stronger. The exophthalmos has slightly improved, tremor is practically negligible except when overtired or worried. Prior to operation her writing was illegible; it is now clear with no suggestion of vibration. Pulse 80 to 90; she still has attacks of palpitation. The thyroid shows no change in the size of the lateral lobes. The adenoma has now become cystic and slightly larger.

Re-examination, May 25th, 1928.—She has had a recent attack of influenza and much mental worry. Tremor has returned within the past fourteen days; her handwriting is legible though extremely shaky; the weight has considerably decreased; the radial pulse is 90 per minute; heart-beat very irregular; neck measurements show a pronounced diminution in the size of the thyroid; circumferences were as follows: trans-cricoid plane 28 cm.; mid-crico-manubrial plane 30 cm.; supramanubrial plane 33 cm.

Exophthalmos was still very pronounced, and certainly more so than on the last previous visit.

CASE II.

A man, aged 31, with a history of cyclical nervous instability, with early onset of hand tremor, loss of weight, and nervous irritability. Three years after the appearance of the initial symptoms enlargement of the thyroid gland was noted. Eighteen months later exophthalmos developed, and six months after this severe attacks of palpitation occurred. On December 8th, 1927, the right and left superior thyroid vessels were ligatured; iodine was administered and the patient was sent home on December 18th. Following this he lost 23 lb. in six weeks during a severe exacerbation of all the symptoms. He was readmitted to hospital on January 30th, 1928. On examination he weighed 7 st. 4½ lb. (his normal weight was 11 st.). Exophthalmos was present in both eyes, principally due to pronounced spastic retraction of the eyelids, especially the outer part of the superior lid; there was slight oedema of the lower lids. There was diffuse enlargement of the entire thyroid gland; it was pulsatile with audible bruit.

Circumferences of the neck were as follows: cricoid plane 36 cm.; mid-crico-manubrial plane 40 cm.; supramanubrial plane 43 cm.

The tremor was of the rapid fibrillary type with a rhythm of eight cycles per second. There was slight dilatation of the right side of the heart and auricular fibrillation. Pulse 101. The basal metabolic rate, estimated by the Douglas bag and Haldane apparatus, was +75 per cent. Pressure pain was 10.5 kilos over the thenar region. In the adrenaline tolerance test 5 mm. of a 1 in 1,000 dilution produced a rise of 25 mm. of mercury in the blood pressure and an increase of pulse rate to 112. There was a generalized faint pigmentation and alopecia of the face and scalp. His bowels acted twice during the day and not at all in the night, and he passed water two to four times in the daytime.

On February 29th resection of the left cervical sympathetic cord was performed without disturbing the ganglia. Immediately after the operation there was a pronounced increase in tremor and rhythmical motion of the whole arm, with a frequency of three cycles in five seconds. The hand tremor increased ten cycles per second. The exophthalmos was unchanged. There was hyperidrosis of the right side of the face; the left side was dry. Immediately after operation the temperature was 99° F., the pulse 128, and the respirations 24. After five days the corresponding figures were 98.4° F., 118, and 22.

On March 7th, 1928, excision of the right superior sympathetic ganglion and a portion of the cord was performed. Following a transitory febrile period due to tonsillitis the hand tremor subsided markedly, the recording lever remaining stationary for considerable intervals, with an occasional slow rhythm of four or five cycles per five seconds. There was pronounced diminution in the spastic retraction of the eyelids.

On March 20th the basal metabolic rate was +32 per cent., a fall of about 40 per cent. The adrenaline tolerance test showed a rise of blood pressure of 10 mm. of mercury, with no increase in the pulse rate. The pressure pain figure on the right side was 9 kilos; on the left 8 kilos.

Re-examination, May 23rd, 1928.—The patient appeared to be very well and had gained weight; on May 14th he weighed 8 st. 4 lb. Hand tremor was negligible. The exophthalmic appearance was greatly improved. He had no attacks of palpitation; pulse rate 88.

From a study of the data of the foregoing cases the following points may be deduced.

1. That in cases of exophthalmic goitre extirpation of the cervical sympathetic ganglia has a threefold effect on the syndrome of the disease: (a) an immediate phase of increase in all the symptoms, due probably to augmented thyroid activity; (b) followed quickly by the first improvement phase, in which there is a considerable fall in the basal metabolic rate and a diminution of hand tremor; (c) a second improvement phase sets in after a month or more in which there is a general amelioration of all the symptoms. It is the variability of the degree to which this latter improvement progresses that determines the question of ultimate success of the operation.

2. The effect of sympathectomy on the exophthalmic appearance is apparently uncertain. If the appearance is due to spastic retraction of the eyelids as in Case ii, then sympathectomy effects an improvement. On the other hand, where the appearance is due to the projection of the ocular globe as a whole sympathectomy has little or no effect. It is interesting to note here an observation made *post mortem* on an exophthalmic eye. After death there was still decided ocular prominence, and incision of

the conjunctiva and examination of the orbital contents showed the forward displacement to be due entirely to the accumulation of a considerable quantity of clear fluid.

3. The effect of sympathectomy on the thyroid gland in Case i produced post-operative increase in the size of the adenoma and shrinkage and atrophy after some months. In Case ii the size and tension of the thyroid diminished from the onset of the first improvement phase.

Floresco, Missirolli, and Wiener found that section of the cervical sympathetic excited transitory thyroid hyperfunction, followed by rapid atrophy of the thyroid gland, an observation which provides us with an explanation of the post-operative crises and the changes in the size of the thyroid.

4. In weighing the foregoing results it will be remembered that Case i had had prolonged radiation and Case ii ligation of the superior thyroid vessels, and both had undergone a course of iodine treatment, the results of which procedures had been negligible at the time of sympathectomy, at which period they were judged grave operative risks. The inadequate ultimate results in Case i led to a closer investigation of the anatomical connexions between the sympathetic and the thyroid glands.

5. In each case histological examination of the extirpated ganglia revealed the following changes: granular degeneration or atrophy of the nerve cells, increase of connective tissue, and hyperpigmentation comparable to the changes described by Wilson and Durante of the Mayo Clinic.

In conclusion a few words may be added as to the practical aspects of the sympathetic operations for this disease. As far as one can say at present they are not a cure, but nevertheless, if successfully carried out, they produce a very considerable improvement. This amelioration is considerably greater than that obtained by ligaturing the blood vessels, and since the technique is no more difficult, and the risks are not more hazardous, it seems a reasonable proposition to undertake it in cases where the symptoms are of such a degree of severity as would contraindicate a partial lobectomy, thereby obtaining a margin of improvement which would permit this operation to be performed at a later stage.

Again, this operation would appear to be eminently suitable in cases where the cardiac derangement is too serious to allow any thyroid operation to be contemplated, and where the thyro-toxic symptoms are progressive despite medicinal treatment and therefore endanger life, as in Case i.

ANATOMICAL.

According to Berkeley, Crissafulli, and Rhinehart, and further quoted by Wilson and Durante, the superior and middle cervical sympathetic ganglia furnish the entire nerve supply to the thyroid gland.

It is obvious that if this statement is accepted the operation of sympathectomy need only embrace these two ganglia on both sides in order to effect a complete denervation of the gland. Such is the operation usually practised, and such was the technique in the cases investigated personally. The measure of success for this procedure has been fully discussed; that this should be incomplete at once suggests an inadequate denervation, hence a most careful investigation of the nerve supply from the inferior cervical ganglion has been carried out.

In all, six adult bodies and five fetuses have been examined. In every case a communication was found to exist between this ganglion and the thyroid gland on both sides of the neck; it was variable in its position and anatomical course. The following are the chief variations.

1. The communication may arise either as one or two delicate nerves from the inferior cervical ganglion. On the left side, after passing inwards and downwards a short distance, it doubles back along the course of the recurrent laryngeal nerve to be distributed to the postero-inferior aspect of the lower pole of the left lobe of the thyroid. On the right side this filament (or filaments) frequently anastomoses with the right recurrent laryngeal nerve at a distance of about 1 to 2 cm. from the origin of the nerve from the vagus, after which the fibre may be traced as a distinct fasciculus on the lower and inner surface of that nerve, and leaves it as a plexus of delicate filaments

to be distributed to the corresponding aspect of the right lower pole.

2. The communication may arise as a branch from the sympathetic cord between the middle and inferior ganglia, in which case the ultimate distribution is the same as in the previous instance.

3. On the left side there may be several small filaments arising from the inferior and middle cervical ganglia, which pass inwards and downwards closely associated with the vertebral artery and reach the left recurrent nerve, when they are distributed both upwards and downwards in that nerve; those fibres passing towards the head may be partly traced into branches to the thyroid gland.

These communicating fibres to the recurrent laryngeal are indicated in the accompanying illustrations.

Pavlovsky has emphasized the importance of a group of fibres from the inferior cervical ganglion which reach the thyroid along the inferior thyroid arteries. Although in a few instances there were filaments from the middle ganglion accompanying this vessel they were not so constant and definite a feature as that described above.

The practical deduction to be made from the anatomical findings is the importance of extirpation of the middle and inferior cervico-ganglionic section of the sympathetic on at least one side—namely, that on which the thyroid changes are most pronounced. If partial denervation of the gland results in considerable mitigation of the symptoms, then it seems logical to suppose that a similar and still more complete procedure would be correspondingly more effective.

Further, it might be tentatively pointed out that since all the sympathetic supply to the thyroid passes out of the spinal cord at the level of the first and second dorsal segments and traverses the inferior ganglia, it follows that removal of the latter should be equivalent to removal of the entire three ganglia, and would obviate a more extensive operation.

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DELAYED CORNEAL ULCERATION FROM MUSTARD GAS.

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THE two following cases which have come under our notice seem sufficiently important to be placed on record, and this for two reasons: first, because of their intrinsic clinical interest, and secondly, because of their specific importance from the point of view of war pensions. One of us has seen both cases, and so is able to be sure of the essential similarity between them.

We wish to emphasize that these ulcers have features which are so characteristic as to render them almost pathognomonic, and there should be no fear, therefore, of false claims being made for pensions on account of ordinary corneal ulcers.

The history of the two cases is as follows.

CASE I.

A medical man was attacked by mustard gas in 1917, and is in receipt of a pension for defective sight of the left eye from corneal nebulae resulting from ulceration in 1922. The right cornea was unaffected until May 7th, 1928—that is, eleven years after the gassing. It then spontaneously became ulcerated at a point downwards and to the nasal side. The ulcer at first was small, but afterwards enlarged so as to involve more than one-third of the area of the cornea. From the first it was deep and crater-like at its centre, extending down to Descemet's membrane. For many weeks it seemed that it would perforate at this spot; but this did not happen, and it ultimately healed over. In the substance of the cornea were grey lines of infiltration radiating more or less from the borders of the ulcer; a small area only was stained by fluorescein.

On curetting, the surface epithelium of the cornea was found to be sodden and ill nourished for a considerable area around; it easily separated, leaving a large bare surface. The substantia propria was infiltrated in such a way as to produce a sort of cleft in its substance in a plane parallel with the surface. The ocular conjunctiva exhibited the appearance, to be referred to later, which is characteristic of these cases. (Fig. 1, C, Fig. 2, D.)

FIG. 1.

FIG. 2.

Some iritis developed, but it was very mild in degree, and caused no trouble; the left eye remained quiescent throughout. There was never any very acute reaction in the eye, and photophobia was less marked than would have occurred from an ordinary ulcer. The general appearance was that of a slowly spreading, very indolent ulcer, of which a small part only stained; corneal infiltration extended in advance of the ulceration, which gradually spread so as to invade the pupillary area, producing considerable defect of vision, which necessarily is permanent.

At the end of five months it seemed that the extension of the ulcer had stopped. The clear point where Descemet's membrane had been exposed was becoming healed and the excavation gradually filling in. This progress has continued up to date; repair, however, is even now, at the end of seven months, by no means complete.

CASE II.

A healthy man, aged 38, when first seen by one of us gave the following history. He had suffered badly from mustard gas burns in the usual parts of the body, including the eyes, in July, 1917;