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TOXIC GOITRE*

BY

CECIL A. JOLL, M.S., F.R.C.S.

Senior Surgeon, Royal Free Hospital and Miller General Hospital

LECTURE I

The term "toxic goitre" is applied to a disease complex dependent on a deranged activity of the thyroid gland with consequent production of one of the following states: (1) an excess of normal secretion; (2) a perverted secretion; (3) a combination of an excessive and a perverted secretion. As to which of these alternatives is the correct interpretation will be discussed later. The above definition, admittedly open to criticism, begs no question, and merely implies that an abnormal thyroid gland is an essential condition, but does not rule out the possibility that the *causa causans* of the disease is of extrathyroid origin.

FIG. 1.

The very fact of the existence of the terms "primary" and "secondary" thyrotoxicosis, not to mention numerous synonyms, would imply that two different types of toxic goitre exist. It is well known that Plummer and Boothby and Plummer and Wilder have consistently maintained that there is an essential distinction between the diffuse toxic goitre, which they believe to combine hyperthyroid and dysthyroid qualities, and the nodular toxic goitre, which they conceive to have a purely hyperthyroid quality. The majority of clinicians, pathologists, and biochemists, however, find no solid grounds for the distinction. It seems logical, therefore, to assume that the *causa causans* is the same in all types of toxic goitre

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and that differences in the state of the thyroid gland itself, the age, sex, and physical and psychical make-up of the individual affected, particularly as to the pre-existence of cardiovascular or general constitutional disease, are together sufficient to explain the observed differences in the syndromes of toxic goitre.

Incidence.—It is at present impossible to give any figures of the actual incidence of toxic goitre in any country. In very few are even the mortality rates available. The Registrar-General publishes annual death rates under the heading of "exophthalmic goitre," though

FIG. 2.

probably it includes the other thyrotoxic syndromes. From the graphs (Figs. 1 and 2) it is clear that there has been a notable rise in mortality in both sexes, especially during the last twenty years, and this in spite of the improvement in therapeutic measures. These facts argue against psychic shock or infections being important factors in the aetiology of toxic goitre, since the steepest parts of the curves of mortality do not coincide with the great war or notably with that of the influenza pandemics. The *sex incidence* has remained in this country at approximately eight females to one male throughout the period covered by the Registrar-General's report, but the sex ratio in Boston is four females to one male, and in Michigan, where "simple" goitre is endemic, the ratio is four to three.

Aetiology and Pathogenesis

It is as well to admit that we do not know the cause of toxic goitre. Warthin falls back on the rather threadbare idea of a "Graves's constitution," and Eason describes the physical make-up of those who have this constitution, but a careful review of my own material reveals such a wide diversity of physical and psychological types among thyrotoxicos that it appears to me impossible to justify such generalizations. The older school of physicians regarded thyrotoxicosis as a disease of the central nervous system, and some of the moderns attribute it to the vegetative nervous system activated possibly by the adrenals. Labbé goes so far as to regard exophthalmic goitre as a combination of hyperthyroidism with a neuro-vegetative syndrome. Whatever the importance of the vegetative nervous system in toxic goitre, there is no evidence worth the name that it originates the disease.

Friedgood and Fortune lay great stress on the almost constant presence of lymph nodes in the thyroid gland in toxic goitre, but in my own material they are far less constant than these observers state. The other ductless glands have nearly all been given prominence in relation to pathogenesis. Partial suppression of the cortex of the adrenals was said by Marine, in 1930, to cause thyrotoxicosis; but Crile, on the other hand, attributes the disease to adrenal overactivity. Marine more recently has laid stress on the aetiological influence of the thyrotrophic hormone of the anterior pituitary, and Drouet, Jeandelize, and Gault ascribe many of the symptoms of toxic goitre to this cause. It is significant, however, that it is impossible to produce *progressive* thyrotoxic symptoms in experimental animals by any preparation of the anterior pituitary hormones. Hertz and Oastler could find no trace of excessive thyrotrophic hormone in the blood of thyrotoxic patients, nor is there any other evidence of excessive activity of the anterior pituitary in these cases. To sum up, it is fair to say that we have no real knowledge of the aetiological significance of the other ductless glands in toxic goitre.

Infectious diseases such as influenza often precede thyrotoxicosis, and a direct aetiological significance has been attached to this fact on the basis of the work of Farrant. There was, however, only a trivial rise in the incidence of toxic goitre during and after the great influenza pandemic of 1917-19. A history of psychic trauma, emotional strain, severe anxiety, shock, etc., is said by Conrad to be obtainable in 94 per cent. of cases, but the graphs in Figs. 1 and 2 show no rise as a result of the enormous increase in psychic trauma during the great war. It seems fair to conclude that the psychic trauma, like the infectious diseases, may activate latent toxic goitre, but that neither can act as a *causa causans*.

We are thrown back on the view of Rehn, of Möbius, and of Murray that the thyroid is itself a source of the disease, though whether merely as a result of an excessive formation of the normal hormone as Rehn and Murray surmise—supported as their views are by Harington's biochemical work—or, on the other hand, a dysthyroidism as Möbius, Plummer, and Boothby postulate (for primary thyrotoxicosis) is still unproven. The outstanding fact is that without an abnormal thyroid gland thyrotoxicosis does not occur.

Chemistry of the Thyroid Gland in Thyrotoxicosis

In the diffuse goitre of primary thyrotoxicosis the percentage iodine content may be reduced to a mere fraction

of the normal, though the total iodine content may be actually raised in certain cases, while in some the iodine content is within normal limits. After iodine therapy the percentage iodine content may rise to well above normal. Waller, in 1914, first ascribed the good effect of iodine therapy to its capacity to induce colloid stasis in the vesicles, and later Marine and Mosser both conceived a similar quasi-mechanical explanation.

Pathological Changes in Other Organs in Thyrotoxicosis

Drouet has described changes in the pituitary in thyrotoxicosis, but Means could find no post-mortem evidence of any such changes. Crile maintains that the adrenals are increased in size and in vascularity, while Marine speaks of their showing a defective cortical structure. Beaver and Pemberton found evidence of fatty changes, subacute necrosis, and simple atrophy in the liver in certain cases. Defective hepatic function may be of significance in relation to morbidity and mortality after operation for thyrotoxicosis.

LECTURE II

The Clinical Features of Toxic Goitre

The Merseburg triad—namely, goitre, exophthalmia, and tachycardia—though usually present at some stage in a majority of the cases of primary thyrotoxicosis, by no means always appear simultaneously. The presence or absence respectively of any one of the common clinical features must not be accepted as proving the existence or absence of thyrotoxicosis. Thus exophthalmia is absent in primary toxic goitre in about one-third of the cases, and may certainly be found irrespective of thyrotoxicosis.

The Goitre

In primary thyrotoxicosis the gland is slightly or moderately enlarged, rarely exceeding five to seven ounces in weight. It is usually smooth, such irregularities as exist being due merely to intensification of the normal surface irregularities. The pyramidal lobe shares in the enlargement, and is sometimes bulky enough to be of importance in relation to post-operative recurrence. The consistence of the gland is significant. It suggests solidity rather as does the pancreas or the parotid gland. Occasionally in early stages it has a soft doughy character; while, on the other hand, in old-standing cases it is tough or even hard. The main arteries of the neck are thrust backwards by the goitre, but even in the hardest gland there is no obscuration of the carotid pulse. The presence of bruits and thrills over the thyroid is significant but not pathognomonic.

In secondary thyrotoxicosis the gland differs in no way clinically from the simple nodular enlargements of endemic or sporadic goitre. In elderly patients particularly, the enlargement may be very slight and the nodules difficult to detect.

● The Ocular Signs

These are numerous, but their significance can easily be exaggerated. The "staring" eye is seen more often and at an earlier stage than is exophthalmia, and it also occurs, though infrequently, in secondary toxic goitre. The retraction of the upper lid, exposing the sclera above the cornea, described by Dalrymple, has some diagnostic importance, though Mulvaney believes that a narrow band of sclera above the lower lid is visible at an even earlier stage. Extreme proptosis may occur in mild thyrotoxicosis, and also in a progressive or "malignant" form in post-operative states associated with evidence of

myxoedema. Naffsiger and Brain, who attribute the proptosis to the thyrotrophic hormone, believe that it may occur independently of thyrotoxicosis. It is difficult on this hypothesis to account for its rapid regression in certain cases after thyroidectomy. The mechanics of the condition are still obscure, but Naffsiger and Jones have shown that in certain cases there is a great increase in the bulk of the extrinsic muscles of the eye, produced by diffuse fibrosis and oedema of the muscle fibres with extensive focal lymphoid infiltration as well as venous congestion and oedema of the whole orbit. Mulvaney describes two types of exophthalmia—one characteristic of thyrotoxicosis, and the result of the overaction of Müller's orbital muscle with stretching of the extrinsic muscles; and the other of pituitary origin associated with changes similar to those described by Naffsiger. Brunton says, however, that Müller's muscle, while capable of producing proptosis in animals, is incapable of doing so in human beings. There are many other ocular signs, most of them secondary to the exophthalmia, and they have therefore little importance individually.

Tachycardia

Tachycardia is not a constant phenomenon. It may be purely paroxysmal for months before it becomes persistent, so that at any given examination a normal pulse rate is not unusual. The extremely high persistent rates are usually of bad omen. Palpitation may be an early symptom, yet it may be denied entirely by patients whose forcible apex beats can be observed at a distance. There is an inveterate tendency for fibrillation to develop sooner or later in all toxic goitres. In men it is more frequent and appears earlier in the course of the disease than in females. In secondary toxic goitre fibrillation is often the first indication of abnormality, though it is obvious from the pathological character of the goitre that the latter is of long standing. It is quite certain that a large proportion of cases of auricular fibrillation is of thyrotoxic origin (Percy puts the figure as high as 90 per cent.). Parkinson and Hoyle have shown the importance of obscure thyrotoxicosis in the development of insidious hyperpiesis, especially in women past middle age. It is a matter of opinion as to whether there is a true myocarditis in toxic goitre, the consensus of opinion being that there is no change in the heart muscle. It is probable that the cardiac lesions are of a functional character and based on the abnormal demands on the heart muscle necessary to maintain the blood-flow increase in toxic goitre. Cardiac hypertrophy is not met with in uncomplicated thyrotoxicosis, but characteristic forms of hypotonia and dilatation do occur (Parkinson and Cookson). Cardiac failure, both congestive and anginal, eventuate in a notable percentage. The possibility of antecedent cardiac and vascular disease is important in this connexion. The greater frequency of cardiac complications in the male may be due to such factors.

Nervous and Muscular Phenomena

(a) Excessive fatigue is complained of by many patients at the onset. It is related to the increased cost of muscular work generally in thyrotoxicosis.

(b) Tremor is extremely common. It is usually fine, and its frequency about 8 to 9 per second. Each finger may have its distinctive rhythm. The tongue may show tremor when the fingers do not. Muscular incoordination is well seen when the patient is asked to step up unaided on to a stool. Muscular weakness is revealed by noting the length of time during which the patient can maintain

the knee extended. The thyrotoxic is seldom able to hold the posture thirty seconds, while the normal person can do so for at least a minute.

(c) Nervousness may be extreme, though many patients deny it even when it is obvious. Perfectly placid individuals do, however, occur among thyrotoxics.

(d) Emotionalism may accompany the preceding, and is exhibited by fits of crying—which the patient is often quick to recognize as abnormal. Some patients, for a time stimulated by the enhanced metabolic status, have a sense of well-being.

(e) Definite psychoses are not uncommon. Toxic goitre patients are occasionally admitted to asylums and the connexion of the abnormal mental state with the thyroid gland recognized only later. There is a special tendency to psychoses among patients being prepared for operation and during the post-operative period.

(f) Myopathies of several orders have been described by Brain. The profound muscular wasting in certain cases is difficult to correlate with the moderate activity of the other physical signs.

Blood Changes

Blood changes described by Kocher as having diagnostic and prognostic value have not proved helpful in my clinic, though Hertz and Lerman report both an absolute and a relative increase of monocytes in primary toxic goitre. The alcohol-insoluble iodine fraction in the blood is greatly increased, the alcohol-soluble fraction little changed. After iodine therapy the latter is greatly increased and the former unaffected. Some importance diagnostically can be attached to the combination of a high soluble-iodine fraction with a raised B.M.R., though there are cases in the secondary group to which this statement does not apply.

Digestive Disorders

There is often enhanced appetite, sometimes amounting to bulimia; yet most patients waste, sometimes as rapidly as in anorexia nervosa. Rarely the patient for a time actually gains weight, even very considerably. Diarrhoea is common, constipation unusual. The liver shows a defective power to store glycogen, but if this be combated the metabolism of carbohydrates is normal. Jaundice, usually of slight to moderate degree, occurs in the severe grades of the disease, and may be related to the tendency to toxic hepatitis in thyrotoxic states.

Metabolism

Metabolism of foodstuffs is unaffected in toxic goitre, with the proviso above mentioned in relation to carbohydrates. Spontaneous creatinuria occurs and there is diminished creatine tolerance, both of these related to increased metabolism in the skeletal muscles.

If one can exclude such diseases as acromegaly, leukaemia, severe anaemia, erythraemia, certain drugs, and some cases of non-thyrotoxic hypertension, etc., and be sure the estimation is truly basal, a constantly raised B.M.R. suggests thyrotoxicosis. There are numerous points to consider before accepting the evidence of this laboratory test. There is no absolute standard by which the B.M.R. can be judged, and although it is customary to accept such ranges as ± 10 per cent. or even ± 15 per cent. as within normal limits, it is certain that some healthy individuals have rates well above or below these ranges. A rise from subnormal up to $+15$ per cent. in one individual is as significant as a rise from a high

normal to +50 per cent. in another. More valuable than the actual figures is the effect of adequate iodine therapy, which, as shown in the graph (Fig. 3) in favourable cases reduces the rate by approximately 3.5 per cent. daily. If the patient has been under iodine for a prolonged period before the B.M.R. is tested omission of iodine will induce a rise in the rate. This provides an alternative diagnostic method. It is probable that the more rapid the fall in the B.M.R. under iodine the better the

FIG. 3.

prognosis. The above statements need qualification in respect to my own clinic, since only about 75 per cent. of the cases conform to them, approximately 25 per cent. being unaffected by iodine therapy. Means, however, reports only 3.4 per cent. of his cases as recalcitrant to iodine.

Clinical Types of Toxic Goitre

1. *The Hyperacute.*—These rare cases progress without remission to a fatal termination, sometimes rapidly. They do not respond to iodine, and succumb in a "crisis" or in delirium or coma. Great restlessness, and diarrhoea and vomiting, are features of this type, signs of cardiac failure except at the end being rare.

2. *The progressive type* is common, the disease tending gradually to destroy life after a period of years usually as a result of cardiac complications.

3. *The relapsing type* is confined to the primary form. The rises and falls in the intensity of the toxæmia may occur regularly, but usually there is no definite periodicity; eventually this type merges into the chronic.

4. In the *chronic type* there is persistence of toxic symptoms at a low ebb. It is said that chronic forms tend to merge into myxoedema, but I have never observed this sequence.

5. An *apathetic type* is described by Lahey.

6. *Masked thyrotoxicosis* is an association of certain thyrotoxic phenomena with little or no obvious thyroid enlargement. This type is poorly defined owing to the difficulty of deciding sometimes whether a goitre is or is not present. In toxic goitre the gland is frequently of the "circular" type, embracing the oesophagus and pharynx, most of it then being out of reach of the palpating fingers. Many cases labelled "masked hyperthyroidism" are either recognizable as having a definite goitre (therefore not truly masked) or they belong to the category of neurocirculatory asthenia, etc., and are therefore not toxic goitres.

The *diagnosis* of toxic goitre rests on the presence of one or other of the syndromes indicated above. If doubt exists after weighing up the clinical features repeated estimation of the B.M.R. with and without iodine therapy will usually resolve it. The worst possible treatment for neurocirculatory asthenia is subtotal thyroidectomy. *When in doubt do not operate* is the golden rule in unproven toxic goitre.

Prognosis

Prognosis is extremely difficult to discuss divorced from particular methods of treatment. There is no reliable evidence as to the likelihood of spontaneous cure. Many cases regarded as examples of natural cure can be shown to be still chronic thyrotoxics, sometimes with auricular fibrillation, etc. The prognosis in untreated cases is bad, and sooner or later cardiac decompensation of a congestive or anginal form eventuates.

Treatment

Toxic goitre cannot be adequately treated by the individualistic clinician; only by pooling all resources is it possible to combine a high percentage of cures with low mortality and recurrence rates. Toxic goitre therefore needs to be treated in special clinics. The consideration of treatment under various headings is purely for convenience and does not imply that these should be regarded as alternative but rather as auxiliary methods. It follows, therefore, that under the first two are included the therapeutic methods antecedent to surgical treatment, which can be safely applied only when every precaution has been adopted to ameliorate cardiac, pancreatic, and hepatic insufficiency.

MEDICAL

(a) *Rest* is the time-honoured method of reducing the activity of the symptoms by relieving all unnecessary strain on the various organs. Under rest the B.M.R. may fall as much as 2.5 per cent. daily for a time.

(b) *Iodine Therapy.*—It is doubtful if it is ever necessary to exceed a dose of 20 minims of Lugol's solution thrice daily. An equivalent amount of iodine given as the tincture or as potassium or sodium iodide acts as well. I have used di-iodo-tyrosine as suggested by Harington in over 600 cases, but found it not more effective, though far more expensive, than simpler preparations. The work of Means suggests that we are inclined to overdose our toxic goitres with iodine in this country. The optimum effect is usually but not invariably obtained in 10–14 days, after which there is a gradual relapse with a rise in the B.M.R. If the iodine be stopped for some weeks a similar but less striking improvement may follow its resumption and so on. Eventually the repetition of iodine therapy fails to produce any effect (Fig. 4). Means

FIG. 4.—The upper continuous line indicates course of disease without iodine therapy. The undulating line indicates effect of iodine therapy. a, a', a'', a''' = points at which iodine therapy starts.

dissents from this view and claims that iodine maintains a certain control of the disease so long as it is continued, though he admits that it does not cure thyrotoxicosis. The danger of prolonged iodine therapy has been stressed by Kocher, but I have seen no case of iod-Basedow in my series.

(c) *Diet.*—There is no justification for modifying the diet appreciably. There is some reason to believe that

vitamin B has a special value, especially in relation to its action in cardiac muscle metabolism.

(d) *Sedatives*.—Means objects to chloral hydrate because of the rather vulnerable liver, but I have found it more effective than are the barbiturates, luminal, etc.

(e) *Serotherapy and Hormone Therapy*.—The various "sera" are without beneficial action whatsoever in thyrotoxicosis. Anti-thyrotrophic hormone is already unfortunately being exploited therapeutically.

(f) *Digitalis* is useless for tachycardia, though indicated in cardiac failure complicating thyrotoxicosis. Post-operatively, digitalis or strophanthin is valuable in auricular fibrillation. Quinidine will restore cardiac rhythm in nearly all cases of arrhythmia, but its real value is post-operatively, when it will usually regularize and maintain cardiac rhythm.

(g) *Blood transfusion* is seldom indicated in toxic goitre. Intravenous therapy by the continuous-drip method with 5 per cent. glucose in *distilled* water is of great value in emaciated cases, especially those with marked diarrhoea and vomiting.

RADIOLOGICAL

X-ray therapy and curietherapy are said to be able to reduce thyroid activity to any degree, even up to myxoedema. Its disadvantages are its unreliability, the high mortality, and the long interval before success is achieved or failure admitted. More than two hundred goitres removed by me after x-ray therapy, examined pathologically, revealed no changes ascribable to the treatment. In a small series, in which we applied curietherapy to one lobe only, no difference could be detected histologically between the irradiated and non-irradiated lobes. X-ray therapy and curietherapy should be reserved, therefore, for cases in which surgical treatment has been refused.

LECTURE III

Surgical Treatment

The advantages established for surgical treatment are the high proportion of cases which can be restored quickly to economic efficiency, the low mortality, and the rarity of relapses and recurrences. The disadvantages are sequels such as myxoedema, tetany, and damage to the vocal apparatus, all except the first being rare with non-surgical treatment.

Phase at which Operation should be Undertaken.—Since all except fulminating cases and those of minor degree come within the scope of surgery, the prime necessity is to decide when the risks are at a minimum. The problem is hardly capable of reduction to any definite formula. Speaking generally, operation is advisable when iodine therapy, etc., have produced their optimum effect. Restlessness and persistent excitability, especially if combined with diarrhoea and vomiting, are the main danger signals.

Choice of Operation.—The objective is to reduce the activity of the gland to a normal level and to prevent subsequent reactivation. This necessitates the removal of about seven-eighths of the gland—the actual proportion depending on the features presented by individual cases. Equally important is the simultaneous control of the arterial blood supply, so that the possibility of recurrence of glandular activity is reduced to vanishing-point: failure to achieve this accounts for numerous relapses.

(i) *Preliminary Arterial Ligation*.—The ligation of both superior arteries in the type of case in which it is most clearly

indicated involves much risk and little real advantage. The variation in the size and position of the inferior arteries makes formal ligation a difficult and sometimes an almost impossible feat.

(ii) *The "Staged" Operation*.—Surgeons for whose views I have a high respect believe that the mortality in "bad risk" cases can be reduced by operating in two or more stages. It is, in my opinion, rather a matter of surgical technique than of fundamental principle, and all the advantages claimed for the "staged" operation can be achieved by one suitably planned operation.

(iii) *Subtotal symmetrical thyroidectomy* is the procedure of choice. If all the arteries are ligated it is sufficient to preserve in diffuse goitres about one-sixth to one-eighth. If the main inferior arteries are not tied a larger fraction of thyroid tissue should be extirpated and a higher percentage of recurrences faced.

Pre-operative Preparation.—This vital phase has already been dealt with. The following additional matters need expansion:

(i) *Is it Desirable to Eliminate "Focal Sepsis" before Operation on the Thyroid Gland?*—In general it is unwise to perform such operations as tonsillectomy as a preliminary to thyroidectomy.

(ii) *Susceptibility to Adrenaline*.—Much misconception exists as to the alleged ill effect of adrenaline in thyrotoxicosis. A sustained rise of pulse rate and pulse pressure is the basis of Goetsch's test. In only a very minor percentage of cases is this reaction obtained. It is sufficient, therefore, to apply the test a few days before the proposed operation, and if the full reaction follows, adrenaline should not be used with the local anaesthetic.

(iii) The *oxygen tent* represents the main advance in the treatment both of thyroid crises and of the cardiac and pulmonary complications of thyrotoxicosis. It is necessary, however, to accustom the "bad risk" cases to the tent before operation.

Anaesthesia.—The indications are for an anaesthetic which is non-toxic, avoids anoxaemia at all stages, and induces tranquillity. Morphine and its derivatives (for example, omnopon) are valuable in moderate doses. Hyoscine may cause uncontrollable excitement in certain patients. Avertin is used extensively in certain clinics, and I find it valuable for the highly excitable patient, but it sometimes induces anoxaemia, which cannot be fully controlled by regulating the percentage of oxygen in gas-oxygen anaesthesia. The peculiar anaesthetic problems of the thyrotoxic patient are best met by a combination of basal, local, and general anaesthesia. The most generally useful series is: morphine or avertin as a basal anaesthetic, local infiltration with 0.5 per cent. novocain and adrenaline, and gas-and-oxygen intratracheally.

Results of Surgical Treatment

The primary mortality should not exceed 1 per cent. in a well-organized clinic; the recurrence rate should be no greater and the incidence of laryngeal paralysis should be considerably less than that figure. The patient should be able to resume his work within three months. In the case of women there is no reason why they should not marry and bear children, though pregnancy is usually better postponed for two years after operative treatment. Patients with auricular fibrillation regain normal rhythm in at least 80 per cent. of cases with or without the aid of digitalis or in certain cases of quinidine. In cardiac failure compensation is restored in most cases, but full compensation is not so likely to follow when rheumatic or syphilitic cardiac lesions complicate the problem.