for unity. We need every worker, whether at the bedside or in the laboratory, who is sincerely seeking the truth as Harvey understood it, for in the house of Science there are many mansions. Let us not say I am of Paul, and I of Apollos, and I of Cephas; let the experimentalist not despise the clinical observer as superficial, nor the clinician the laboratory worker as narrow; nor let both condemn the thinker as visionary and unpractical. Let me rather exhort all, as I am bidden this day in Harvey's name to exhort the Fellows of this College, that they continue in love and affection among themselves.

TOXIC GOITRE: THE COURSE OF THE DISEASE, AND ITS TREATMENT*

BY

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During the last ten years, much study has been devoted to the problems of exophthalmic goitre, and much has been written on the subject. There are three lines along which developments have occurred that seem, especially, to have affected our conceptions of this disease and the treatment of the patients. These three lines are:—(1) the correlation of the morbid anatomy of the thyroid gland with the clinical conditions of the patients, (2) the therapeutic use of iodine, (3) the development of surgical treatment. The changes in the thyroid gland that accompany the clinical conditions are very varied, and the numerous histological studies of material removed at operation, and obtained by experiments on animals, have proved of value. Following the work of Marine^{1,2} on animals, Rienhoff and Lewis,³ working on patients, have been able to clarify this subject and to present a conception of the structural changes in the gland that can be correlated with the clinical pictures seen in patients. The relation of iodine to the pathology of toxic goitres is still unsolved, but the empirical employment of this substance in the management of cases has been a valuable step forward in treatment; and the development of surgical skill and judgement now offers possibilities of successful treatment that are among the most dramatic in medicine.

MORBID ANATOMY AND SYMPTOMATOLOGY

The suggestion, made by Plummer,⁴ that the cases could be divided into those of true exophthalmic goitre and those of adenoma with hyperthyroidism or toxic adenoma, was of value in the development of our knowledge, but it now appears that this separation is arbitrary and artificial, and that the changes which the thyroid gland has previously undergone are the essential factor in deciding the clinical picture and the gland structure in a case of goitre with symptoms of intoxication or toxic goitre. Marine showed that increased activity of the gland is accompanied by hypertrophy and hyperplasia, and that involution to the normal resting condition occurs when the activity diminishes. Rienhoff⁵ removed portions of the thyroid gland from patients who were suffering from typical exophthalmic goitre, who had had no previous thyroid disturbance, and who had not received iodine; iodine was then administered, and at a suitable time partial thyroidectomy was performed, and the material removed compared with that removed previous to the iodine treatment. In this way he showed that the clinical improvement that resulted from the iodine, the

so-called iodine remission, is accompanied by an involution of the gland, a change in its structure that brought it nearer to a normal gland, but he demonstrated also that, while the gland in general showed this involutionary change, portions of it, usually lobules, might show hyper-involution, with the formation of areas of acini distended with colloid and resembling colloid goitre, or of colloid cysts, or of areas of degeneration with loss of acinar arrangement and with colloid diffused throughout the area. On the other hand, there were areas where involution failed to take place, where islands of gland remained in the stage of hypertrophy and hyperplasia typical of the condition before the remission occurred, while the surrounding gland showed the general involutionary changes and approach to the normal structure. To these islands remaining in the stage of hyperplasia he applied the term hypo-involution. Around the areas of hyper-involution the gland structures are compressed, and there is fibrous tissue giving the appearance of a capsule, formed possibly by interlobular and intralobular septums, and possibly by replacement fibrosis. These areas of hyper-involution may be single or multiple, and the gland then resembles the nodular gland, commonly found in patients of middle age with toxic goitre. These structural appearances, found by Rienhoff in the iodine remissions, are identical with those found in patients following spontaneous remissions.

There are patients, usually young women, who, with no evidence of previous thyroid trouble, develop the typical picture of exophthalmic goitre, and in the course of a few months, or longer, recover apparently completely. There are others, with a similar onset and initial recovery, who relapse, perhaps repeatedly. There are others who never quite recover, but in whom the condition subsides only to light up again and again with greater or less severity over a number of years. In those with repeated relapses or exacerbations the thyroid gland is usually found to be nodular. There are still other patients, who, when they come under observation for the first time because of toxic symptoms, present a nodular gland. We know that the gland responds to physiological stimuli, such as puberty, pregnancy and lactation, by increased activity; and it responds in a similar way to pathological stimuli, such as infections; but in both conditions signs of thyroid intoxication are rare, and the gland usually returns by involution to a normal condition. If the involution is not perfect, and areas of hyper-involution and of hypo-involution result on repeated occasions without the occurrence of symptoms of intoxication, then a nodular gland might be expected to develop in time. This accounts for those patients in whom such a gland is found on the first appearance of toxic phenomena. The absence of nodules and of fibrosis is not evidence that hypertrophy, hyperplasia, and involution have not occurred, but a nodular goitre is good evidence of a past history in which the thyroid gland has had to respond to stimuli and then has involuted, perhaps repeatedly and over a number of years. These nodules are not adenomas, but true adenomas may occur, though much more rarely; and pathological processes, other than those that result from the involutionary changes described by Rienhoff, are met with in glands associated with toxic goitre, such as the small fibrous gland described by Williamson and Pearse⁶ as primary arterio-capillary sclerotic goitre, and the large gland resembling that of simple colloid goitre. But an advance has been made, and we are in a better position to understand the condition of our patients.

The cause of the disease is unknown, but it cannot be doubted that there is some stimulus that causes increased activity, with hypertrophy and hyperplasia, of the gland, and manifestations of hyperthyroidism or thyroid intoxication. The stimulus, whatever it may be, will vary in

* Read in opening a discussion in the Section of Medicine at the Annual Meeting of the British Medical Association, Eastbourne, 1931.

strength. A gland that is healthy previous to the stimulation of its activity is capable of responding with marked increase of activity, and, consequently, with manifestations of severe hyperthyroidism or intoxication; but a gland that has undergone hypertrophy and involution, perhaps many times, and that is altered in structure, with numerous areas of hyper-involution and degeneration, is not capable of reacting with the same vigour, and the degree of intoxication will therefore be less for equal degrees of stimulation. These nodular goitres are usually found in middle-aged persons, whose organs and tissues are not able to stand the stress of thyroid intoxication as can those of a young adult. Even a moderate degree of intoxication will, in the elderly, produce auricular fibrillation, though in a young girl it would only have produced

problems. There is ample evidence that the thyroid glands of fatal cases, and the glands removed at operations, contain very variable amounts of iodine²; and it is reasonable that the effect of iodine administration will be greater in a patient whose thyroid gland is almost completely lacking in iodine stores, and will be less striking in a patient whose gland already contains large stores of available iodine. During the course of the disease spontaneous remissions and relapses are continually occurring, and iodine cannot prevent these, though there is much to suggest that it modifies the severity of the relapses. If a relapse occurs in a patient who has been taking iodine continually for many months, and the administration of the iodine is then stopped, the severity of the relapse is immediately increased, and it is again

Diagrams (by Means, Thompson, and Thompson) showing the effect of iodine in toxic goitre. The upper outline indicates the hypothetical course of the disease when iodine is not administered, the lower outline when iodine is administered. Iodine commenced at (a) and (e); iodine stopped at (c).

a tachycardia. In the same way the vasomotor system, the digestive organs, the excretory organs, and the higher cortical functions, are profoundly disturbed in the elderly by a grade of hyper-activity that is easily borne by the young. In the elderly such stresses and strains may cause changes that overshadow the evidences of the thyroid disease, and that threaten the life of the patient. Dunhill⁷ has suggested that by variations in the strength of stimulus, in the capacity of the thyroid to react, and in the state of the organs of the patient, it is possible to account for the varying symptomatology of the disease. These factors can account for many of the variations in symptoms, but there are still large gaps in our knowledge.

IODINE

Since Plummer and Boothby⁸ in 1923 awakened renewed and widespread interest in the subject of iodine in the treatment of thyroid disease, by pointing out its value in the pre-operative management, much work has been done, and much has been written, on this subject. We are still ignorant of the mode of its action, and there is still much controversy as to its value. There is general agreement that by its use the severity of the disease can, in many cases, be profoundly lessened, and that, by administering it for a week to ten days before operation, the risks of operation are materially diminished. There is general agreement that it is not curative, and that the course of the disease is not shortened by means of it. Some observers maintain that after ten days or so it loses its effects, and that it is useless to give it for a longer period, while others believe that by its continuous administration the disease runs its course at a lower level of activity. It is difficult to reach a clear decision on these

lowered by re-administration of the iodine. The iodine content of the blood is being studied by many workers, and when the methods for its quantitative estimation are more satisfactory, so that reliable figures are available for the different phases in the course of the disease, it is possible that this subject will be clarified.

By repeated estimations of metabolic rates during iodine administration, Means, Thompson, and Thompson⁹ have come to conclusions that agree closely with our clinical experience. They say:

"In any given patient at any particular time iodine will reduce the intensity of the thyrotoxicosis, but the disease seems to continue even though in a modified form. Iodine does not reach its cause, but merely alters its effects. There seems to be a course which will be followed when iodine is supplied, another when it is not."

Our practice is to give iodine continuously, and I am convinced that by it, and by rest in bed, and by the numerous other details of management, which I do not propose to enter into now, we bring our patients to a minimum of thyroid intoxication, and an optimum condition for operative treatment, at a time after the commencement of iodine treatment which may be much longer than the ten days so dogmatically stated in the literature. When operative treatment is unnecessary, iodine is one of the most valuable methods of treatment available.

PROGNOSIS

In 1930 I published¹⁰ an analysis of the results of treatment in 50 cases that had been carefully observed in my wards during 1920-1925, and in which the results, after a period varying from five to ten years, had been ascertained. The group of cases treated by operations on the

thyroid gland and the group treated by means other than surgical were roughly comparable, and it was concluded that in a number of the younger patients whose thyroid glands show no evidence of previous disease, recovery may take place without surgical treatment, but that surgical treatment is indicated in those with nodular goitres, and in those who do not improve rapidly, or continue to relapse and become chronically ill in spite of satisfactory management, and in those who for financial or other reasons cannot submit to adequate observation and treatment. During the years 1926-1930 I have tried to profit by the lessons of the previous period. The groups of cases are, therefore, in no way comparable, as the patients were urged to submit to the treatment indicated, and much less difficulty was experienced in obtaining consent to surgical treatment than was experienced in the earlier period. In 1931, the results of treatment were ascertained in 86 patients who were in the wards during the period 1926-1930, and these are shown in the table along with the results for the period 1920-1925.

Results of Treatment

Years.	Total No.	SURGICAL				Total	NON-SURGICAL				Total
		Good	Poor	Bad	Died		Good	Poor	Bad	Died	
1920-25 ..	50	15	5	1	3	24	10	4	2	10	26
1926-30 ..	86	29	15	1	3	48	13	11	1	13	38
	136	44	20	2	6	72	23	15	3	23	64

It will be seen that there is no striking difference. The mortality in those treated by operations on the thyroid gland is halved, but it is little altered in those treated by non-surgical methods. If the patient is capable of full work, the result is classed as "good"; if working with difficulty, it is classed as "poor"; and if leading an invalid life, as "bad." It will be seen that the proportion of poor results is increased in the second period in the patients treated either by surgical or by non-surgical methods. With a few exceptions, α rays and radium were not employed.

Of the thirteen deaths in the group treated without operations on the thyroid gland, only one was inevitable; the patient had what were probably multiple secondary carcinomatous growths in the abdomen. One patient refused operation and discharged herself, but had had the disease for eight years, during which treatment should have been possible. Two others died before they could be brought to a suitable condition for operation, and had been ill for 18 months and 5 months, respectively, before admission. Eight patients improved so satisfactorily that operation was not considered necessary, but they relapsed and died, and in three of them the deaths followed operations carried out in other hospitals. In the case of the remaining patient, who was extremely unstable mentally, and subject to repeated attacks of tetany, we did not consider that any operation on the thyroid gland was likely to succeed in improving the condition, but she was admitted to another hospital and died, following an operation. In ten, or possibly eleven, of these thirteen cases, therefore, the lives of the patients might have been saved if treatment had been carried out earlier to diminish the amount of functioning thyroid gland tissue.

The high proportion of "poor" results in the second period is to some extent due to the fact that sufficient time has not yet elapsed for the full effects of treatment to be manifest. Undoubtedly some of these results will later be classed as "good." Even when this factor is allowed for, the high proportion of "poor" results to "good" results of surgical treatment is worthy of notice. When the cases are divided into age groups, it is found

that the proportion of "poor" results increases with the age of the patient; and when the cases are subdivided according to the duration of the disease before admission to hospital, it is found that the proportion of "poor" results increases with the duration of the disease. The figures are too small to be of statistical value, but the "poor" and "bad" surgical results together expressed as the percentage of surgically treated cases in the age groups 20-29, 30-39, 40-49, and 50-59, are 20 per cent., 36 per cent., 27 per cent., and 46 per cent. respectively; and in the groups with durations 1-4 years, 5-9 years, and 10 years or over, they are 31 per cent., 33 per cent., and 57 per cent. respectively. It is reasonable to expect that the older the patients the greater will be the deleterious effect of the illness on the various organs and functions, and the less likely are they to be restored to the health they previously enjoyed, but it is not fully appreciated that the longer the thyroid intoxication continues, even if it is of a very mild degree and interrupted by numerous remissions, the less likely is the patient to be restored to health.

In considering prognosis, etiology must be taken into account. The fundamental cause of the disease is unknown, but in many cases the factor that finally brings about the manifestations of thyroid intoxication is clear. In some patients it is an infection, in others mental strain and worries, in others sexual disturbances; frequently it is a combination of two or more of such factors. If the intoxication is mild and the patient is brought under medical care early, and the causal factor can be removed, there appears to be a possibility of recovery without an operation on the thyroid gland. In ten of the thirteen cases in which the results have been classed as good, and in which thyroidectomy was not performed, there was a definite association with attacks of tonsillitis, and the condition improved strikingly after tonsillectomy; they were all mild cases; the average age of the patients was 29 years, and the average duration of symptoms 2½ years. In one case appendicectomy was performed in addition, and in another, treatment with α rays contributed to the recovery. The longer the duration of symptoms the more difficult it is to discover a causal factor, and the factors that can be discovered are such as must be experienced by most people in the course of their lives, but the incidence of the disease is small. It is reasonable to suppose, therefore, that there is a constitutional factor. Examples of two generations being affected, and of two or more members in the second generation, are sufficiently frequent to indicate that the constitutional factor may be inherited and inborn. The following cases illustrate this:

Mrs. J., aged 62 years. Always nervous, and eyes always rather prominent. In 1918, aged 50 years, 3 years after menopause, exophthalmic goitre diagnosed. July, 1921, B.M.R. +70 per cent., partial thyroidectomy; November, 1921, B.M.R. +20 per cent., further partial thyroidectomy; June, 1922, B.M.R. +15 per cent., further partial thyroidectomy. 1931, in fair health.

Jessie J., daughter of Mrs. J., aged 31 years. Developed exophthalmic goitre in 1920, when aged 20 years. August, 1922, B.M.R. +45 per cent., partial thyroidectomy; June, 1926, further partial thyroidectomy. 1931, doing full work, tired and nervous at times.

Mary J., daughter of Mrs. J., aged 23 years. Developed exophthalmic goitre in 1926, aged 18 years. September, 1929, tonsillectomy. 1931, recovered well, now married and has a child.

J. O., aged 11 years. His mother had exophthalmic goitre when aged 17 years; she recovered without operation, but always nervous. In 1928, when aged 10 years, he developed exophthalmic goitre. October, 1929, B.M.R. +60 per cent., ligation of superior thyroid arteries; November, 1929, treatment by radium. December, 1929, died.

Warthin¹¹ has discussed this factor and speaks of it as the Graves' constitution, but at present it must be regarded as theoretical, because it cannot yet be recognized in the absence of the disease. It appears as if this factor is strong in some patients so that no other factor is needed to produce the disease, but that in other patients it is less strong, and in them some additional factors are necessary. The prognosis will be influenced by these considerations, and the restoration to health, even after thyroidectomy, will be less complete the stronger the constitutional factor. In some of the cases in which the result is recorded as "poor," the patients gave histories of nervousness and excitability all their lives, and appeared to have been below the normal standard of physical efficiency before the onset of symptoms of thyroid intoxication. This was clearly a factor in the results in the two following cases:

Mrs. A. B., aged 55 years. Nervous and excitable all her life. In 1923, aged 47 years, developed exophthalmic goitre; symptoms more severe following tonsillitis in 1922. January, 1923, tonsillectomy; continued to be nervous and excitable, and unable to do her work. April, 1928, B.M.R. +20 per cent., very emotional and mentally depressed, and these symptoms were more prominent than those of thyroid intoxication, which were mild. April, 1928, partial thyroidectomy. 1931, improved, no evidence of thyroid intoxication, but always grumbling and unhappy, and not able to do her house-work.

Miss F. B., aged 46 years. Never strong, always tired, numerous fainting attacks, frequent tonsillitis. In 1905, aged 20 years, developed exophthalmic goitre; remissions and relapses frequent, and very emotional. 1926-1929, repeated attacks of tetany caused by emotion, but no disturbance of calcium metabolism, no alkalosis. July, 1926, tonsillectomy; July, 1929, B.M.R. +40 per cent., x-ray treatment; August, 1920, B.M.R. +30 per cent., partial thyroidectomy. 1931, no tetany, but emotional storms, and unfit for any exertion.

TREATMENT

From the analysis of the results of treatment in the 136 patients, who have been carefully studied and followed, it seems clear that surgical treatment is indicated in most cases severe enough to be admitted to the wards of a general hospital. Of those selected as suitable for treatment without operation, nearly a third relapsed and died after discharge from hospital, so that it would appear difficult to decide when it is safe to allow such cases to return home away from close observation and experienced treatment; and the logical conclusion is that it is safer to operate at the earliest suitable opportunity than to hope for spontaneous recovery. So long as cases present themselves for treatment at the stage in the disease at which they now come to us, some means of reducing the amount of functioning thyroid tissue is necessary to save life and restore efficiency. As alternatives to surgical treatment there are x rays and radium, but both methods require such long courses of treatment, and are at present so comparatively uncertain in their results, that operation by a surgeon with special experience of operations on the thyroid gland is preferable, to save time and to avoid the risk of serious relapse during the course of radiation. Unfortunately, such surgeons, in whose hands the operative treatment has a negligible mortality, are to be found only in a few centres in this country. Even in their hands the proportion of "poor" results is greater the longer the duration of the disease and the older the patients; and it would seem unnecessary that they should be called upon, as they are at present, to perform an extremely difficult task when an earlier operation would be easier and safer, and the result for the patient would be better. If treatment by x rays or by radium were more easily controlled and more certain, these difficulties could be to a great extent avoided by commencing treatment as soon as possible after the diagnosis is made, by utilizing either x rays or radium

to diminish the amount of gland tissue, by giving iodine to reduce the intoxication, and by removing any causal factors that can be discovered. If this were done while the case was mild and the patient still fit for work, the delay in obtaining the desired result, due to the longer time required by radiation as compared with operation, would not be important, and the number of late cases and severe cases, which can only be treated efficiently by means of thyroidectomy, would be so reduced that the few surgeons of sufficient experience could attend to them. Perhaps treatment by radiation is already sufficiently advanced to permit of this policy being adopted, and such treatment should certainly be tried if the case is seen early, and if the best surgical aid is not available.

CONCLUSIONS

Cases of thyroid intoxication, or toxic goitre, should be treated as early as possible by removing any causal factors that can be discovered, by the administration of iodine, and by reduction of the amount of functioning thyroid tissue. This can be accomplished with the greatest certainty by operative treatment, but if a surgeon with special skill and experience in such cases is not available, treatment by x rays or radium should be tried while the case is still mild and the patient able for work.

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PSYCHIC PAIN AND THE PSYCHOSES*

BY

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Taking the psychoses as a whole, the psychiatrist can scarcely fail to gain the impression that external stresses play but a relatively small part in their development. Financial disaster, the loss or inaccessibility of a beloved object, persistent domestic strain, the pangs of physical disease, the loss of social esteem, and even the disgrace of imprisonment for some delinquency—such traumatic events might reasonably be expected seriously to upset the psychic equilibrium; but generally speaking they do not have this effect. They may, and often do, bring about enduring psychic pain, and tend, no doubt, to diminish efficiency; but they are usually met with courage, endurance, or resignation, for life has to be accepted as it is; we know that it can never be moulded after the pattern of our own desires. Should, indeed, a psychosis develop under severe stress, some pre-existing abnormal sensitivity or some inadequacy in meeting the demands of everyday life would probably be revealed in the history. A negative history of recent trauma does not, of course, exclude the possibility that external events may have taken a part in the causation of a psychosis. In all cases it is necessary to make an exhaustive inquiry into the past, with a view to discovering the extent to which the symptoms manifested can be traced to subtle

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