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J. EARL ELSE, M.S., M.D.
University of Oregon Medical School
PORTLAND

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THE RELATIONSHIP OF IODINE TO THYROID HYPERPLASIA AND FUNCTION*

J. EARL ELSE, M.S., M.D.

Clinical Professor and Chairman Department of General Surgery,
University of Oregon Medical School

PORTLAND, ORE.

The literature upon thyroid disease is so voluminous, the ideas expressed are so varied and many of the papers are so abstract that physicians who have not made a special study of goiter are more confused after reviewing the literature than before beginning such a study. It is time for those who are making an actual study of the thyroid and its pathology to sift carefully the wheat from the chaff and state in a definite, clear and concise manner the present status of our knowledge.

The clinician's interest in goiter centers around three major problems. First, the insuring of a normal thyroid gland at birth; second, the prevention of goiter; and third, the treatment of goiter in those patients in whom it has been permitted to develop.

Halstead in 1896 stated that congenital goiter could be produced by the removal of a greater portion of the thyroid gland of a pregnant female dog, but that the removal of a major portion of the thyroid gland of the male had no influence upon the thyroid of the progeny. Experimental work has confirmed Halstead's observation. A study of the patients with congenital goiter whom I have seen in private practice and in the goiter clinic of the University of Oregon has led me to the conclusion that congenital goiter in the human is of exactly the same origin. That is, if the mother's thyroid gland is not secreting enough thyroxin during pregnancy, a demand is thrown upon the child's thyroid gland to function in utero. As the result of this demand, there is either a secretion of colloid resulting in a colloid goiter, or a hyperplasia resulting in one of the types of hyperplastic goiter. Congenital goiter thus produced is not then an hereditary disease, but is instead a congenital condition developing as a compensatory process. So true is this that whenever we see a family in which all or nearly all of the children have goiter, we can with practically a hundred per cent of accuracy predict that the mother had a goiter, and although the thyroid gland may have been able to produce sufficient secretion under ordinary conditions, it was deficient when the added load of pregnancy was thrown upon it. I have yet to see the first patient with congenital goiter borne by a woman with hyperthyroidism, and I do not believe it occurs. By that, I do not mean to say that a woman who has a deficient thyroid during pregnancy may not as a result of the stimulation thrown upon that gland, develop a toxic goiter subsequent to the pregnancy.

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The problem then in preventing congenital goiter is assuring a sufficient amount of thyroxin to care for the needs of both mother and child. In women with normal thyroid glands, this can be done by maintaining an iodine intake sufficient to enable the thyroid gland to produce the necessary thyroxin. If the iodine in the food and water is deficient, more must be added. To the woman with a thyroid so deficient that it cannot produce the necessary amount of thyroxin, dessicated thyroid is given. Iodine should not be given to the woman with a non-toxic goiter of the adenomatous type, as it is liable to be made toxic thereby. Some time ago I conceived the idea of giving the patients of this group a small amount of dessicated thyroid. This has been done by my associate in the goiter clinic, Dr. C. E. Brous, and although his experience at the present time is too limited for a positive statement, we believe that this is going to be the solution of the prevention of congenital goiters in children of women with glands of the type which make it unsafe to give iodine.

The causes of goiter may be classified as primary and secondary. The primary causes of goiter are first, and chief, a deficiency in the iodine intake; second, anything that lowers the ability of the thyroid to utilize iodine; and third, anything that increases the thyroxin need above that which a partially deficient thyroid can produce. Iodine deficiency as a cause of goiter is an undisputable fact and is universally accepted by everyone who has made a really scientific study of the problem. The relationship of the existence of goiter and iodine deficiency in the great goiter belts, such as the Great Lakes Basin and on the Pacific Coast where the surface water, and hence, the vegetation, is deficient in iodine, cannot be doubted. The best proof of this statement occurs in northern Michigan, where there is one district in which practically everyone has an enlarged thyroid and in which the surface water is absolutely devoid of iodine.

The iodine intake in food and water may be sufficient, deficient, or relatively deficient. It is sufficient when there is a sufficient amount of iodine to meet the demand for thyroxin at any time and in any amount. It is deficient when there is not enough iodine to meet the need even under minimum activities. It is relatively deficient when there is a sufficient amount of iodine to produce the necessary amount of thyroxin under ordinary conditions but not enough to produce the necessary amount of thyroxin when there is an extra load demanding an increased amount of thyroxin. Examples of this are seen in individuals who, under ordinary conditions, have normal functioning thyroid glands, but who develop a goiter as a result of excessive physical or mental strain or disease.

The thyroid in its ability to utilize the iodine furnished to it must be classified as efficient, deficient, or relatively deficient. The efficient thyroid gland is able to utilize iodine and produce the necessary amount of

thyroxin under all conditions. The relatively deficient gland is the gland that under ordinary conditions is able to produce a sufficient amount of thyroxin, but when the demand comes for more thyroxin, it is not able to produce it even though there is a sufficient amount of iodine. The deficient thyroid gland is the gland that is not able to produce thyroxin enough under any circumstances even though there is plenty of iodine at all times. Both the deficient and the relatively deficient glands may be unstable either because of a congenital abnormality or acquired changes.

Glands that are relatively or absolutely deficient, or in which there is a relative or absolute deficiency in the amount of iodine intake because of the regenerative power of the gland, may develop any of the hyperplastic forms of goiter. If the congenital goiter in man, as that in experimental animals, is the result of a maternal thyroxin deficiency, we can trace back most of those goiters which have not been the result of an actual disease of the gland to a primary iodine deficiency in the maternal ancestor, and while there are other determining factors that have an influence in the development of goiter, they are, in reality, playing secondary rôles. The perfectly normal thyroid gland, which is receiving a sufficient amount of iodine, will not develop a goiter, but a perfectly normal thyroid gland receiving an insufficient amount of iodine or a thyroid gland with lowered efficiency produced by infection or toxins or other lesions so that it cannot utilize the iodine that it receives, usually results in the production of some form of goiter.

The prevention of goiter in the individual born with a normal thyroid gland is merely that of supplying a sufficient amount of iodine. We hear a great deal said about the danger of iodized salt, but the experience of using the iodides in syphilis in the days gone by has demonstrated conclusively that it does not carry any danger to the ordinary individual. The danger is only to the individual with the abnormal thyroid gland and it is my personal opinion that it occurs only in the thyroid which has undergone a hyperplasia so that there is a markedly increased number of cells which have been lying dormant and may be stimulated into activity by the giving of iodine over a long period of time.

A comparative study of the acini of the colloid goiter with that of the normal thyroid gland indicates the type of treatment required. The cells secrete two known substances; one, thyroxin, and the other, colloid. Colloid appears to be an inert substance filling the acini, its purpose being either that of holding the iodine in suspension until needed for the production of thyroxin or holding thyroxin in suspension until needed. I am personally inclined to believe that it is the former. When in the presence of an iodine deficiency, a demand is thrown upon the thyroid gland for more thyroxin, the cells set about trying to produce it. In this attempt, there is an over-secretion of colloid distending the acini. As the acini become distended with colloid, the margin is stretched, flattening the cells both by the stretching their bases and the increased intra-acinar pressure due to increase in colloid. In well marked cases, the cells become so flattened that the protoplasm at the sides of the nuclei is not as thick as the nuclei. Such cells can not be expected to secrete normally.

A few years ago in the goiter clinic of the University of Oregon Medical School, we divided our patients with simple colloid goiter into four groups. One group was given ten milligrams of iodine daily, one group was given one grain of sodium iodide three times daily, another group was given larger amounts, and another group was given one grain of dessicated thyroid daily. The patients were seen every two weeks and the thyroid gland examined, the neck measured, the pulse counted, and other observations made as indicated. The length of the treatment varied from a few weeks to two years.

Later three of us independently went over the records and came to the same conclusion, viz.: iodine does not cure simple colloid goiter in a majority of cases, but dessicated thyroid does. In the iodine series, the results were practically the same regardless of the amount. A few were cured. The most of them were not. Some of the goiters on iodine decreased in size and then increased while iodine was being given. Experimentally, we have shown that the increase in colloid begins within two days after reducing the thyroid capacity by operation and that if there is not some relief, the hyperplasia begins within a week. That hyperplasia does not take place in all glands is, I believe, due to the fact that the added stimulation enables the thyroid to utilize the iodine to a better advantage. There is no organ in the body that is one hundred per cent efficient, and we have no right to believe that the thyroid gland is absolutely efficient. With an increased activity on the part of the cells, it may utilize the iodine to a greater degree of efficiency than it was doing before. This I think explains the reason for not getting the early hyperplasia in all colloid goiters.

The fact that the giving of iodine to patients with colloid goiter does not produce results in a majority of such patients is due to this deficiency of the cells. The treatment then is to put these cells at rest by supplying the thyroxin already prepared until the colloid can be absorbed and the cells come back to normal. It has been our custom in the goiter clinic of the University of Oregon to give patients with a simple colloid goiter one grain of dessicated thyroid three times a day. Occasionally some patients require more. It has been our general experience that patients with a simple colloid goiter are cured within a period of two or three months. So firmly are we convinced of the truth of this statement that to those patients in whom cure does not result in that period of time, we state that there has been error in the diagnosis. We have seen the patient too late when hyperplasia had already occurred. This we have proved by operating upon some of them who later became toxic and finding a diffuse adenomatous type of goiter.

In the treatment of toxic goiter, iodine in the form of Lugol's solution has been found invaluable in the preparation of the patient for operation, regardless of the type of goiter. It must be used, however,

with caution. It must not be used indiscriminately, as some patients are harmed by the prolonged use of Lugol's solution. It has been our experience that when this has occurred, these patients do not readily yield to Lugol's solution again.

So far I have dealt with the use of iodine in the preparation of the patient for operation. In reviewing the literature, we find frequent references to patients who have not been cured. Some time ago I made a study of the patients seen in the goiter clinic who have been operated upon without a complete cure. As a result of this, we were able to classify the patients of this group as follows: First, errors in diagnosis, that is, the symptoms the patient had were not due to a thyroid lesion; second, late operation, the patient having had permanent lesions produced previous to the operation. The operation had cured the goiter and there was no longer any hyperthyroidism, but the patient still had a damaged heart and nervous system and symptoms of goiter present because of these permanent lesions; third, incomplete operation, in which case the patients have never been cured; fourth, true recurrences.

To study the cause of true recurrences, we carried on experimental work on dogs and rabbits and found, first, that it was possible to remove a minimum amount of thyroid without producing any reaction in the thyroid gland at all. In other words, we left enough thyroid gland to produce the necessary amount of secretion so that there was no need for any compensatory change. Second, we found that when the maximum amount of the thyroid gland was removed, leaving only a very small portion, there were certain uniform changes that always occurred. These were first, an increase in the amount of colloid which appeared within two days, and second, a hyperplasia that began at the end of the week. Third, we found that when an amount between these extremes was removed, if the animals were given iodine there would be no reaction; but, if they were not given iodine, hyperplasia occurred. Our experimental animals could be classified in their relationship to thyroxin production as follows: first, thyroxin efficient, in which there was enough thyroxin produced to meet the animal's need; second, relatively deficient, in which, when iodine was not given, the hyperplasia took place because there was a thyroxin deficiency, but when iodine was given, hyperplasia did not take place because the cells were able, with an excess of iodine, to produce enough thyroxin; and third, thyroxin deficient, in which there was not enough thyroid tissue to produce the necessary amount of thyroxin even though the gland was kept saturated with iodine. In this group, hyperplasia always took place.

We next studied the influence of iodine upon the hyperplasia. There had appeared in the literature a discussion between Loeb and Marine as to the effect of iodine upon hyperplasia. We found that when the gland was kept saturated with iodine by giving Lugol's solution, the hyperplasia continued usually up to about the end of the third week, occasionally a few days longer, there being two exceptions in which it was not completed

within a month. We found, further, that when iodine was not given, the hyperplasia was much more extensive and in two instances it produced an actual goiter in dogs that had a normal thyroid gland before operation. In no instance did we see a goiter develop in a dog that received a sufficient amount of iodine during the period of regeneration.

We then applied this to our patients. The patients all have the thyroid gland saturated with iodine previous to the operation by giving Lugol's solution in 10 to 25 minim doses, three to four times daily, according to the severity of the goiter. Following the operation, we give Lugol's solution in 15 to 30 minim doses by rectum the first two days, three or four times a day. After this, we give 10 minims by mouth three times daily for the first month following the operation, and then 10 minims once a day for the next month, and then follow up with iodized salt or iodine tablets. Since we have followed this regime, we have seen just one patient who has returned with a toxic goiter, due to excessive regeneration. This occurred in a foreigner who could not understand English well and had neglected to take the Lugol's solution as directed.

SUMMARY.

We may sum up our present knowledge of the relationship of iodine to the thyroid gland as follows:

1. Iodine constitutes a high percentage of the thyroxin molecule and is therefore essential to its secretion.
2. Goiter develops as the result of the continued iodine deficiency in the diet.
3. Congenital goiter occurs in the presence of a thyroxin deficiency in the mother and can be prevented by maintaining a sufficient iodine intake for the mother with a normal thyroid gland and giving dessicated thyroid to the mother with a deficient thyroid.
4. Goiter can be prevented in those born with a normal thyroid gland by maintaining sufficient iodine intake unless the efficiency of the thyroid is later lowered by disease.
5. Iodine relieves hyperthyroidism but does not cure in the majority of cases and should be used only for preparing patients for operation.
6. The thyroid gland should be kept saturated with iodine following subtotal thyroidectomy in order to prevent excessive regeneration.
7. Following regeneration a sufficient iodine intake must be maintained in order to prevent recurrence.