IODINE IN THE TREATMENT OF DISEASE OF THE THYROID GLAND.

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Iodine in one form or another has been used unknowingly from the earliest times in the treatment of goiter. The beneficial effects on goiter of substances now known to contain iodine is said to have been known to the Chinese fifteen centuries B.C. Of these iodine containing substances, sponge ash is the best known, and was extensively used at the time of Hippocrates. In addition to its used by the Greeks as an important remedy in the treatment of diseases in general, Dioscordes specifically mentions the use of sponge ash in the treatment of goiter. Galen and Pliny also refer to its use. Humboldt,[1] in 1824, described the occurrence of endemic goiter in the United States of Colombia, and refers to the interesting fact that these people knew one salt deposit was more beneficial than another. A young French physician, Roulin,[2] came to Colombia after graduating from the University of Paris, where he had learned of Coindet's work on iodine in the treatment of goiter. He became interested in this subject and had analyses of these salts made for iodine, and found that the deposit containing the most iodine was the one which the natives had found most useful.

Another very interesting reference to the use of iodine, unknowingly in the treatment and prevention of goiter, is given in Mrs. Lucy Crawford's "History of the White Mountains."[3] After referring to the frequency of swelling of the thyroid gland in Coos county, New Hampshire, at the close of the seventeenth century, she relates that her grandfather brought sea salt, a bushel at a time, eighty miles over the mountains on his back. She states that it was generally believed by the early settlers that the swelling of the thyroid was due to the almost exclusive use of meat (deer, moose and other game) which the nature of the country necessitated, together with the lack of salt. They noted that children were more susceptible than adults

and recommended that they be given larger quantities of salt, particularly if it was impossible for them to live near the sea a part of each year. This account clearly establishes the fact that long before the discovery of iodine our early settlers knew the value of sea salt (for this was the only salt available) in the treatment and prevention of goiter. They also were aware of the fact that a diet consisting largely of meats was potent cause of thyroid enlargement.

Iodine was first knowingly used in the treatment of goiter by the Geneva physician, Coindet,[4] in 1820—nine years after its discovery and isolation by the French chemist, Courtois,[5] of Dijon. Within a year after its introduction as a remedy against goiter by Coindet, untoward effects were noted in certain classes of cases. These untoward effects were vividly described by Gairdner,[6] who noted "peculiar, great and persevering anxiety, depression of spirits, emaciation, diarrhea, tremor, and nervous excitement simulating chorea" were produced in certain individuals. This symptom complex was designated "Iodine Basedow's" by Kocher,[7] some seventy-five years later. These early observations on the untoward effects of iodine started a controversy which has now continued for more than a century, whether iodine should be used in the treatment of any form of goiter. There have always been supporters on each side of this controversy. Up to about 1890 the balance of medical opinion seemed to favor its use in small doses. Then, due to the influence, particularly of surgeons under the leadership of Kocher and to the overuse of desiccated thyroid introduced in 1891, the pendulum began to shift the other way.

Since 1910, however, there has been a gradual return to the older views. This return to the use of iodine has been in great measure due to the rational application of the great mass of physiological facts acquired by and since Baumann's discovery in 1895 of the normal presence of iodine in the thyroid. The gist of all this recent research as applied to modern therapy may be summed up in one sentence, that the thyroid requires an exceedingly small amount of iodine for the carrying out of its function, which, so far as we now know, consists in the elaboration of an iodine-containing hormone, first suggested by the discovery of Baumann and isolated in crystalline form by Kendall in 1914. Undoubtedly, the use of massive doses of iodine was the major factor in bringing iodine into ill repute in the earlier

empiric treatment of goiter. And, if one may draw a conclusion from the recent literature and from my own experience, this is still the major cause of untoward effects. All the facts at present known support the view that minimum amounts of iodine are required for the normal physiological needs. Only three of these facts need be mentioned in illustration: 1. That 25 mg. of iodine represents about the maximum storage capacity of the normal human thyroid. 2. As shown by Marine and Lenhart, 1 mg. of iodine given at weekly intervals by mouth will prevent thyroid enlargement in dogs living under conditions which would otherwise produce thyroid enlargement. 3. As shown by Boothby and Sandiford, 1 mg. of thyroxin may exert its accelerating effect on metabolism for as long as seventy days. With this general background in mind, what would seem the most rational plan of applying these and kindred physiological facts in the treatment and prevention of goiter?

For the sake of simplicity and, in my opinion, accuracy and clearness as well, we may group the diseases due to functional disturbances of the thyroid as follows:

I. Thyroid Insufficiencies.
   1. Simple goiter (endemic, sporadic, epidemic, etc.).
   2. Myxedema.
      (a) Infantile (cretinism).
      (b) Adult (Gull's disease).

II. Graves' Disease.

Simple Goiter.

The most recent view of the etiology of simple goiter assumed that it is a work hypertrophy depending upon a relative or an absolute deficiency of iodine. The causes of this deficiency may be grouped under three headings:

1. Factors which bring about an abnormally low intake, as is known to occur in districts of endemic goiter. The normal source of iodine is mainly from food and water, and it has been abundantly shown, first, by Chatin,[8] in 1852, that the food, soil and water are deficient in iodine in districts of endemic goiter. It has also been shown that thyroid enlargement may be induced by the experimental deprivation of iodine. It may be accepted, therefore, that an absolute deficiency of iodine is one important cause in endemic goiter.

2. Factors which divert an otherwise adequate supply of iodine. This is purely hypothetical. It is conceivable, however, that intestinal bacteria or parasites might prevent the absorption or utilization of an otherwise adequate supply.

3. Factors which temporarily increase the needs of the organism for the iodine containing hormone, that is, factors which create a relative insufficiency. Among the most important of these are: (a) Diet, as shown by the production of goiter in brook trout on a diet of pig's liver, or in pigeons on an excessive diet of lard or other iodine free digestible fat; (b) Infections, as in pulmonary tuberculosis and syphilis; (c) Pregnancy; (d) Puberty, and (e) Graves' disease.

The first group depends upon a definite, simply defined and easily understood factor, an actual deficiency in iodine, whereas the third group, which depends upon a relative or temporary insufficiency, is more difficult to define, less understood and by far the most important, since no living animal with the ductless thyroid is ever free from the possible influence of one or another of the factors enumerated. These factors of diet, pregnancy, puberty, infections, etc., are active as well in goiterous as in nongoiterous districts, and when combined with a real iodine starvation the effects are exaggerated. As will be pointed out later, it is important to distinguish between groups 1 and 3 when planning or evaluating treatment. Emphasis on the iodine deficiency has been so prominent of late that we are liable to overlook more important elements in the treatment, particularly in the so-called sporadic goiter.

Prevention of Goiter.

The principle of prevention depends upon the fact that if the iodine store in the gland is constantly maintained above 0.1%, dry weight, no enlargement occurs.

Simple goiter may be easily prevented in man by the administration of 1 mg., and possibly less, of iodine daily. Iodine in any form and administered in any manner is effective. This fact introduces difficulties and advantages—difficulties regarding the selection of the best form and manner of administration, and advantages in that the desired result may be accomplished with certainty in a great variety of ways. The amount of iodine necessary and the ideal plan of administration for such purposes have not yet been worked out. The

most effective means, and to my mind the least objectionable, would be the use of a salt containing 1 mg. of sodium or potassium iodide per each 10 gm. of salt, that is, 0.01%. Such a plan would provide universal prophylaxis at a nominal expense. Where small units of population are to be protected, as for example, school populations, iodostarin or starch-iodine tablets containing 5 to 10 mg., administered once a week, may be used. Such a plan could also be readily applied by physicians in the prevention of thyroid enlargement during pregnancy and lactation. Iodine may be introduced periodically into the drinking water, following the plan first used by us in preventing goiter in brook trout. For this purpose, iodine in a concentration of one part per million for a period of two weeks each autumn and spring would seem ample. In individual cases, in private practice, syrup of hydriodic acid is a very convenient and easily obtained form for administration. One or two ounces twice each year is ample. Desiccated thyroid also completely protects the thyroid against enlargement, but is too dangerous a drug to recommend for this purpose.

Much has been written about the danger of causing or of aggravating Graves' disease by the use of iodine. The use of iodine in the amounts above recommended in the prevention of goiter is, in my opinion, not associated with any noteworthy dangers. Occasionally iodism may be observed, and some authors have claimed that this can be prevented or lessened by the use of calcium iodide. It is of such rare occurrence that attempts to administer iodine in a form which would not cause iodism may be neglected until the susceptible individuals have been discovered. It is possible, though improbable, that cases of early Graves' disease may be aggravated by the administration even of these small amounts of iodine. Most, if not all, instances of the alleged production of Graves' disease by the use of iodine that have appeared in the literature and all that have come under my observation have occurred in predisposed individuals and have been due to the gross abuse of iodine or desiccated thyroid alone or combined.

Treatment of Goiter.

Regarding the use of iodine in the treatment of thyroid enlargements, we cannot be so dogmatic as in the case of prevention. When the treatment can be instituted in the early stages of development of the thyroid enlargements of endemic goiter districts, the methods and

the amounts of iodine recommended for prevention bring about a cure. In our Akron experiment, where 2 gm. of sodium iodide were administered over a period of two weeks twice yearly for prophylactic purposes, 773 thyroids out of a total of 1,182 with enlargement showed reduction. Similar results have been reported from Switzerland by Klinger and others, and from Italy by Pighini. In sporadic goiter the cause of the relative or temporary thyroid insufficiency must be sought for and corrected if iodine therapy is to be of permanent value. In the long standing cases no plan of medical treatment can with certainty accomplish more than relieve any existing functional insufficiency. In these cases the functional insufficiency is usually already relieved or outgrown and the patient seeks the physician's advice largely for the correction of the cervical deformity. Occasionally striking curative results are observed even in long standing cases. Such cases are anatomically of the simple or colloid form, free from hemorrhages, cyst formation, calcification or adenomata, so characteristic of long standing human goiter. Whether a curative effect is produced or not, and certainly if the individual expects to seek surgical intervention in the event of failure of medical treatment, iodine should be given. The best plan of medical treatment, in my opinion, requires the administration of standard U. S. P. desiccated thyroid in 1/10 to 2/10 gm. doses daily for a period of two weeks, and if there has been no change in pulse rate, loss of body weight or other evidence of injury, the same treatment may be repeated. Then, after an interval of one to two weeks, some form of iodine, as, for example, syrup of hydriodic acid in 2 to 4 cc. doses daily, should be given for a period of two or three weeks. This combined treatment with desiccated thyroid and iodine may be repeated three times during the year, and for the maximum reduction at least a year is required. Desiccated thyroid unquestionably causes a greater reduction in the volume of the thyroid and more rapidly than does iodine. The administration of large amounts of iodine suddenly, often causes the thyroid, in about seven days, to become very firm to the touch, painful, and clinically even larger than before its administration. This is due to the rapid accumulation of colloid in the alveoli which iodine induces. The untoward effects of the excessive use of iodine in the treatment of goiter are real and often serious. Coindet, in 1821, first noted these effects in certain types of goiter, and Gairdner, as above mentioned,

in 1822 observed and described all the essential features as we know them today. This effect of iodine usually occurs in women with long standing goiter, during or after the menopause, which is in some unknown way a factor in causing the increased susceptibility.

Exophthalmic Goiter.

In sharp contrast with simple goiter we know almost nothing concerning the etiology of Graves' disease, and until this is known a rational therapy cannot be expected. The prevailing opinion now favors the view that Graves' disease is not primarily a thyroid disease, but is in some way dependent upon a deranged function of the visceral nervous system. This view is only a return to that held by the older internists and neurologists, including Charcot, Trousseau, Buschan, Gowers, prior to the introduction of the Gauthier-Moebius hypothesis in 1865. My own view is that underlying the typical clinical picture of Graves' disease there is a long standing constitutional anomaly which may be acquired or inherited, the acquired form coming on usually in association with or after the menopause, the thyroid hyperactivity being secondary and a result of a powerful stimulation either through the sympathetic nervous system or through the blood stream or both. To determine the origin of this stimulation of the thyroid, as well as that of other tissues, particularly the lymphoid (thymus and lymph glands), is the major problem in connection with this disease. After a careful study of the literature, together with observations and experiments on a large series of our own cases, Marine and Lenhart[9,10,11] came to the conclusion in 1910 that the thyroid reaction in Graves' disease was in no way different from that seen in other clinical associations. To quote: "There were eleven cases in which the patients were treated with iodine from one to three weeks prior to operation. In all of the cases the iodine contents of the thyroids were markedly raised and in none had complete involution to the colloid state occurred. There were four cases which had received iodine for periods varying from two months to eighteen months, and in all complete involution to the colloidal state was present at the time of operation. We can therefore reasonably conclude that the active hyperplasia of exophthalmic goiter has the same characteristic of rapidly taking up iodine that characterized all other active functional thyroid hyperplasias and also that iodine induces a similar series of morphological changes in the exophthalmic goiter

hyperplasia as in other active thyroid hyperplasias, and that these changes are histologically identical with those occurring in spontaneous involution (recovery)." From these studies we concluded "the essential physiological disturbance in the thyroid in exophthalmic goiter is insufficiency, its reaction compensatory, and its significance symptomatic." Oswald[19] in 1902 and A. Kocher[20] in 1912 also fully described the effect of iodine administration in Graves' disease.

We are, however, concerned more particularly with the use of iodine in the treatment. Its beneficial effects are limited, while its injurious effects may be serious. These are limited to relieving any real or relative insufficiency of the thyroid. This iodine undoubtedly does, but unless and until the cause of the thyroid stimulation which produces the relative or temporary insufficiency can be relieved, no lasting benefit occurs merely from supplying the means with which the thyroid can manufacture more thyroxin more easily or more quickly. As above mentioned, Coindet in 1821 noted untoward effects from large doses of iodine in certain types of cases, and Gairdner in 1822 fully described the symptoms of Graves' disease in connection with his observations on the untoward effects of iodine in certain cases of goiter at least twelve years before Graves recognized the syndrome. From the earliest literature on exophthalmic goiter, more than one hundred years ago, just as today, distinct benefit has been reported from the use of iodine. On the other hand, highly injurious effects have been noted. A great increase in the injurious has been noted since the introduction of desiccated thyroid into goiter therapy in 1891. These effects became so serious that many of the ablest students under the leadership of Theodore Kocher opposed the use of iodine in any form in this disease, indeed, in any form of goiter. Beginning about 1910 the pendulum began to swing back again to the view of the earlier observers, namely, that iodine could be used without danger if administered in doses somewhat approximating what might be called physiological. Why some patients undergo remarkable improvement and others do not is not understood. Patients with Graves' disease getting iodine even in small doses should be under hospital or other means of daily control. With this safeguard it is my opinion that every case should be treated with iodine in doses not greater than 1 mg. daily over a period of at least two months. The older observers used much larger doses than this, as in the case of the

recently much quoted therapeutic accident of Trousseau, who, through mistake, gave iodine instead of digitalis. Much more to the point are the numerous references in the literature of the deliberate administration of iodine in Graves' disease. Thus Cheadle[12] in 1869 reported nine cases of true Graves' disease showing "immediate and extraordinary improvement" in two cases and no injurious effects in the other cases. These effects he pointed out could hardly be referred to as a coincidence. Although the prevailing opinion was that iodine always was injurious in Graves' disease, this observer regularly recommended its use in all cases. In 1875 Cheadle reported a second series of six cases, one, a very severe case, showed great improvement during the first two weeks of iodine administration and then relapsed. This case illustrates very vividly the outcome which is so well emphasized today. Cheadle concluded his paper with the following statement: "Be the explanation of the beneficial effect of iodine what it may, the fact remains that the only decided improvement obtained by medical treatment in any of these cases followed the administration of iodine."

In 1911 Dr. Ohlemann,[13] a sufferer from Graves' disease, published an account of the treatment of his own case, which he states he cured by taking approximately 150 cc. of tincture of iodine together with the occasional use of potassium iodide over a period of three years.

Neisser[14] in 1920 pointed out that small doses of iodine are well borne by cases of Graves' disease and that such doses may notably improve their condition.

Loewy and Zondek[15] in 1921 reported a series of twelve cases in which they showed that the administration of potassium iodide in doses of a few mg. daily would improve not only the nutrition but also the general subjective condition of the patients. They reported three cases in which the respiratory exchange was reduced 19.9, 28.8, and 29.5% respectively by the use of these small doses of potassium iodide.

In 1924 Plummer and Boothby[16] reported a series of 400 cases of Graves' disease where large doses of Lugol's solution (10-15 mm. once or twice daily), as a preoperative measure, had been used and in which they also observed a lowering of the respiratory exchange, just as Loewy and Zondek had previously found. This, however, was the first large series of cases in which respiratory exchange measurements

had been made in connection with iodine administration. Subsequent reports of even larger series by Plummer and Boothby[47] showed this initial fall in metabolism occurred in most of the cases. Since then numerous reports by other observers have confirmed this temporary decrease in metabolism following iodine administration and its subsequent rise again in most of the cases where the use of these heroic doses of iodine is continued longer than two weeks. The mechanism of this temporary fall in metabolism and consequent improvement of the disease is not clear. Plummer has supported the view that in Graves' disease the thyroid is producing an incomplete thyroxin of a highly toxic nature which the addition of iodine completes. This is purely speculation without at present any foundation in fact. As we have repeatedly pointed out, this old view that the thyroid in Graves' disease is producing an abnormally toxic secretion was introduced by Moebius in 1886 and is open to many serious objections.

In the first place the most serious cases of Graves' disease in general are those with the greatest degree of active thyroid hyperplasia, and therefore associated with the lowest iodine store. Secondly, it is this type of case which is most commonly benefited temporarily by iodine administration. Thirdly, all the pharmacological effects of thyroid administration are proportional to its iodine content in whatever way this effect is tested, whether by measurement of the respiratory exchange or the nitrogen excretion, or by the Gudernatsch tadpole test. Fourth, feeding desiccated thyroid from cases of Graves' disease to cases of Graves' disease produces pharmacological effects in proportion to its iodine content. We have fed as much as 11 gms. of desiccated Graves' disease thyroid to severe cases of Graves' disease during eleven days and have noted no alteration in their clinical condition, whereas the feeding of 1/10 to 1 gm. of standard desiccated thyroid may produce a very marked reaction. In other words, if the Graves' disease thyroid contains no iodine it has no effect. This is just the opposite of what should occur if the severe cases associated with marked hyperplasias were producing a more toxic secretion and we considered this experiment as proof that the thyroid in Graves' disease was not different from the thyroid of similar morphological and chemical constitution of other clinical associations.

A much more rational view of the beneficial effects of iodine in cases of Graves' disease with marked hyperplasia is that the admin-

istration of iodine causes a rapid accumulation of colloid in the alveolar spaces, just as the administration of iodine to cases with marked hyperplasia of other clinical associations in man, dogs, sheep, birds and fish. The rapid distention of the alveoli with colloid brings about a *pressure retention* which temporarily blocks excretion until the thyroid cells have accommodated themselves to the increased tension. Excretion is then reëstablished and the metabolism begins to rise. A similar effect of the rapid administration of iodine is regularly seen in simple goiter, both in man and in animals. This is well known, and most physicians have seen cases where, in about seven days after beginning iodine treatment, the patient returns, complaining that the thyroid is even larger than before, is very hard to the touch and painful. Even with the continued use of iodine this effect generally wears off within two or three weeks. We have studied this phenomenon, particularly in dogs, where, as early as the fourth day after the administration of large doses of tincture of iodine, the gland, previously soft and spongy, because of the marked hyperplasia, becomes very firm, and numerous histological examinations have shown that this firmness is due to the accumulation of colloid. When desiccated thyroid is administered this rapid accumulation of colloid and consequent firmness of the gland does not occur, because involution proceeds without the rapid storage of iodine.

It has been asserted that Graves' disease, associated with adenomata—the so-called toxic adenoma—is not even temporarily improved by iodine administration. This statement is in general true, but there are numerous exceptions. The reason why iodine so seldom causes a lowering of metabolism of cases of Graves' disease associated with adenoma, I believe, is that the adenomata seldom react to iodine administration with involution and the storage of colloid and iodine. On the other hand, the cases of Graves' disease associated with adenomata that have reacted favorably to iodine administration are those cases in which a rapid accumulation of colloid with the storage of iodine occurs, just as in the true hyperplasias. In an experimental study of the relation of iodine to the adenomata,[18] we pointed out that certain adenomata would react to iodine with involution and storage, just as ordinary thyroid hyperplasia, but that most of them had, more or less, lost this physiological attribute and that it was not

possible to tell even from an histological examination which adenomata would and which would not react to iodine.

SUMMARY.

Goiter is a compensatory or work hypertrophy of the thyroid in response to a real or a relative deficiency of iodine. The factors which may produce this deficiency of iodine may be grouped under three headings:

Group 1 includes factors bringing about a real deficiency, as occurs in endemic goiter. Water and food are the main normal sources of iodine, and it has been abundantly shown that in goiter districts the iodine may be greatly reduced in both.

Group 2 includes factors which divert an otherwise normal intake of iodine. This is hypothetical at present, but it is conceivable that intestinal bacteria or parasites might prevent the absorption of an otherwise adequate intake.

Group 3 includes factors which create a temporary or relative insufficiency, as, for example, diet, pregnancy, puberty, infections, Graves' disease, etc.

The first group depends upon a definite, simply defined and easily understood factor—an actual deficiency in iodine, whereas the third group is more difficult to define, less understood, and by far the most important. No animal with the ductless thyroid is free from the possible influence of one or another of the factors enumerated. In planning and evaluating treatment, it is important to distinguish between Groups 1 and 3. Emphasis on iodine starvation has been so prominent of late that the underlying cause of the iodine deficiency, whether real or relative, is often not taken into consideration. For example, the thyroid enlargement of hereditary syphilis might not be noticeably influenced by iodine, whereas salvarsan might have a highly beneficial effect on both the syphilis and goiter.

The greatest value of iodine in thyroid disease will always be in prevention. Its value in treatment is limited and conditioned. Simple goiter should be treated with desiccated thyroid combined with iodine. This will relieve any functional insufficiency, but, as regards the deformity, much depends on the duration of the enlargement and the presence of complications like hemorrhage, cysts, calcification and adenomata. The beneficial effects of iodine in the treatment of

Graves' disease are limited, while its injurious effects are serious. Its benefits are limited to relieving in real or relative functional insufficiency of the thyroid. This iodine undoubtedly does, but until the cause of the thyroid stimulation in this disease can be relieved, no lasting benefit occurs merely from supplying the means with which the thyroid can manufacture more thyroxin more quickly. Nevertheless, iodine should be given in all cases in doses not exceeding 1 mg. daily for a period of at least two months. Iodine has generally been used in much larger doses, and recently Plummer and Boothby have revived the temporary use of large doses, particularly as a preoperative measure. Unfortunately, the use of iodine in these large doses cannot be limited or controlled by the profession at large as Plummer recommends, and much harm has and will continue to result from the abuse of these large doses.

The mechanism of the temporary beneficial effect of iodine in Graves' disease is not thoroughly understood. My own view is that iodine, by causing a rapid accumulation of colloid in the alveolar spaces, produces a *pressure retention* of the secretion until the cells accommodate themselves to function under the increased tension.

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DISCUSSION.

DR. HENRY S. PLUMMER, Rochester, Minn.: I am not a member of this Society, but I have taken a great interest in listening to the papers, not thinking I was to be asked to discuss them. You can't talk in the same words of the adenomas and of exophthalmic goiter. Just as soon as you apply the term "exophthalmic goiter" to hyperthyroidism and the adenomatous goiters you have a misnomer.

Regarding the nervous symptoms, we recognized them in taking our basic things in exophthalmic goiter very definitely for twenty years, and announced fifteen years ago the peculiar psychic status of the patient. Now, the thing in the exophthalmic goiter in the psychic reaction is that they do not vary, but closely resemble the neuroses of the anxiety neurosis. They resemble almost all of the things that are toxic on the nervous system. They resemble alcoholism. The patient is emotional and laughs and cries and does all those things just as a man with whiskey in him. I do not know about the hyperfunctioning goiter, whether it is the nervous phenomena of anybody who is tired or the nervous phenomena of a laborer who has worked all day and is tired from fatigue. In that type of case, if he is nervous, there is nothing striking in that, as there is in exophthalmic goiter.

Now as to the use of iodine. Iodine was tried on the wholesale in the Mayo Clinic, but I had never used it. I ordered it and called upon the men to use it when I was leaving for Mexico; I called for it because I believed that the things I knew about were true. And most of the men who were interested in the thyroid couldn't see the spectacular results which followed the big doses of iodine.

I want to express again my appreciation of how much the world will owe to Dr. Marine for introducing and pushing iodine in the prevention of goiter. Iodine, I think, always benefits the function of a gland that is being driven hard to function, and that is the reason iodine prevents goiter and prevents diffuse colloidal goiter. It makes a gland that can't deliver thyroxin to the tissues able to do so, and a gland that can't deliver thyroxin produces endemic goiter. When you stimulate it hard, as is done where there is shortage of iodine in this country, you drive out the thyroxin and you drive out an abnormal agent, and this abnormal substance or agent may produce everything characteristic of exophthalmic goiter as in contradistinction to hyperthyroidism as you will get in giving it.

DR. ———— ————: I think we must divide these cases into those which are adenomatous and those which are not, just as in the case of diseases of the skin we must divide them into those which are eczema and those which are not. If we make the distinction between these two, it makes a difference in the treatment. Those which are adenomatous will not do well under the X-ray. In fact, in two cases treated by X-ray there was a terrible destruction of the blood, and both cases died, and I am satisfied that had they been operated upon they would have lived. I think the adenomatous cases should be operated upon and not have X-ray.

DR. HENRY S. PLUMMER, Rochester, Minn.: Iodine to exophthalmic goiter, probably given from the inception of the disease, will make a different picture. You will bring fewer cases up to that crisis stage. But as far as giving iodine, we absolutely know that cases will get well in two weeks with small doses of iodine. That dose has got to be five grains of iodine or five drops of Lugol's solution; and there are cases that are involuting, which, given five to seven drops of Lugol's solution, will be absolutely well within a week.

DR. EDWARD A. STRECKER, Philadelphia, Pa.: I believe that there is a differential diagnosis to be made between the neuroses and hyperthyroidism. Furthermore, I am inclined to think that very often the reason such a differential diagnosis must be made is a very basic one and goes back to the probability that imbalance of the endocrine apparatus may be an etiological factor in the production of the neuroses. In my experience the differential diagnosis is especially necessary in certain cases of so-called anxiety neuroses. Here, as you know, we have a definite chain of events, physical and psychological or psychological and physical, I do not know which. However, I am convinced that at some point in this vicious circle the endocrine glands are disturbed and corresponding physical reactions are produced.

DR. JOHN P. SAWYER, Cleveland, O.: We have seen the effect of a thoroughly convinced statement on the patient. I believe the assurance given the patient in anxiety neurosis helps the patient.