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An Address ON IODINE IN EXOPHTHALMIC GOITRE.

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Introduction.

A RELATIONSHIP between endemic goitre and iodine appears to have been recognized for many years. Coindet¹ in 1820 reported that by the administration of iodine goitres could be diminished in size. Chatin,² a French chemist, wrote extensively in 1850 and the years following, reporting his investigations on the amounts of iodine in air and soil and water, and he drew attention to the high incidence of endemic goitre and cretinism in localities where the amount of iodine was low. He further maintained that endemic goitre could be prevented by increased ingestion of iodine.

Following Chatin's work, iodine was used extensively in the treatment of goitre until evidence accumulated to show that, following iodine treatment of endemic goitre, the subjects frequently developed tachycardia, tremor, loss of weight, etc. Krehl,³ Kocher,⁴ and others, pointed out that iodine treatment in simple goitre could bring about a condition of exophthalmic goitre, or Graves's disease, and warned against its use. Probably for this reason its employment became much less general. In recent years it has been revived, largely as the result of the work of Marine.

In 1896 Baumann,⁵ by demonstrating the presence of iodine in the normal thyroid gland, initiated a series of valuable investigations. The normal thyroid tissue, when dried, contains from 0.1 to 0.6 per cent. of iodine, and is eight to ten times richer in iodine than any other tissue in the body. Magnus-Levy,⁶ in 1895, showed that thyroid tissue has a powerful effect on heat production in the body, and Kendall⁷ in 1914 isolated in crystalline form the substance thyroxin, which has the same action on heat production as the whole gland substance, and which contains 65 per cent. of iodine. Marine and Lenhart⁸ showed that when the iodine content of human glands falls below 0.1 per cent. the gland shows changes of hypertrophy and hyperplasia, and that in glands showing a high degree of hyperplasia iodine is found only in traces or is absent. If the gland reverts to the resting condition—that is, to the colloid type of goitre—the iodine content rises. If the gland tissue contains over 0.1 per cent. of iodine histological examination will show no hypertrophic changes. Marine and Lenhart further showed that, after a partial thyroidectomy in experimental animals, hyperplasia of the remainder did not occur unless its iodine content fell below 0.1 per cent., but that if as much as three-fourths of a gland were removed and iodine administered to the animal, the hyperplasia that would otherwise have occurred could be prevented.

On the basis of these researches the prevention of endemic goitre by means of the administration of minute quantities of iodine is now practised in many parts of the world.

Exact knowledge of the cause of goitre is, however, still small. Whatever the cause, it would appear that iodine deficiency is one step in the process. It seems probable from the work of Marine, and of McCarrison⁹ in India, that this deficiency may result (1) from a lowered intake of iodine, or (2) from a normal intake and a raised demand for iodine on the part of the body. Their researches point to several ways in which this increased need for iodine may be brought about. At certain periods in life, such as puberty, pregnancy, lactation, there seems to be an increased need of iodine. Faulty dieting, and especially excess of fat in the diet, has been shown to lead to hypertrophy and hyperplasia, and the addition of iodine can prevent this response of the gland to excess of fats. McCarrison has postulated a fat-iodine-thyroid balance on the results of these experiments. Pollution of food and of water has also been shown to produce hypertrophy and hyperplasia, and that this is preventable by the ingestion of iodine. All these researches refer to the simple hypertrophy and hyperplasia that is seen in endemic goitre and sporadic goitre, or to experimental conditions in animals that show the same histological changes as are seen in these goitrous conditions in man. These conditions in the individual may lead to the subsequent development of myxoedema, and the offspring of goitrous females are frequently cretins. In myxoedema and cretinism there is indisputably a lack or absence of the iodine-containing thyroid substance, and Marine has pointed out that endemic goitre and sporadic goitre, as well as myxoedema and cretinism, must be regarded as deficiency diseases, and that in all of them there is a deficiency of iodine. The goitre is the result of a response on the part of the thyroid gland to this deficiency. In myxoedema and cretinism the gland is unable to respond because of atrophy or because of congenital deficiency.

In patients with exophthalmic goitre—which in many respects appears to be hyperthyroidism—symptoms of myxoedema frequently develop, and every gradation may be found between these two apparently opposed states. In exophthalmic goitre the thyroid gland shows an exaggerated and irregular hyperplasia, and the iodine content is extremely low.

In 1920 McCarrison¹⁰ reported that the hyperplastic thyroid glands that resulted in pigeons fed on an excess of butter without iodine showed on histological examination an irregular type of hyperplasia with vesicular budding similar to the picture seen in the glands of human cases of Graves's disease. In 1921 E. and M. Mellanby¹¹ reported that, in the course of their experimental work on rickets and on defective teeth in dogs, they found in the animals fed on an excess of butter a hyperplasia of the thyroid gland histologically resembling that seen in exophthalmic goitre, but that in the animals fed on an excess of fat in the form of cod-liver oil this hyperplasia did not result. They suggested that the high iodine content of the cod-liver oil was responsible for the difference.

These facts suggested that in exophthalmic goitre also an iodine deficiency might be present, and that the administration of iodine might have some therapeutic value in cases of this disease. Iodine therapy has been tried frequently in exophthalmic goitre, but an increased severity in the symptoms may result unless the dose is carefully regulated. This fact, and the frequently recorded examples of exophthalmic goitre symptoms developing during the treatment

of simple goitre with iodine, have led most authorities to issue strong warnings against its use if any symptoms of Graves's disease are present.

Such was the knowledge of iodine in relation to exophthalmic goitre a few years ago, when we commenced to study the therapeutic effect of iodine in cases of exophthalmic goitre. As so often happens, workers in other countries commenced similar studies at about the same time, notably in the Mayo Clinic, and after the results of our observations in the wards of the Medical Unit at St. Bartholomew's Hospital have been discussed reference will be made to several publications that have appeared in the last few months.

Preparation of Iodine Employed.

Throughout these observations the iodine preparation used has been the 10 per cent. tincture of the French *Codex*, in which the iodine is dissolved in 95 per cent. alcohol without the addition of any iodide. This preparation was selected because it contained no combined iodine. On adding it to milk the iodine is precipitated, but on stirring it is efficiently suspended, and the mixture is quite agreeable to take. It is probable that it is immaterial in what form the iodine is administered, so long as it is not in an inactive organic combination.

Results of Iodine Treatment.

Since March, 1921, we have been able to observe the action of iodine on 24 cases of exophthalmic goitre in the wards of the hospital. In addition to these cases there have been a small number who have received treatment as out-patients only, but in whom the conditions were not sufficiently under control to allow of deductions as to the effect of the treatment. In the following 8 of the 24 cases the results were sufficiently clear to justify detailed accounts of them in illustration of the action of the drug in exophthalmic goitre.

CASE I (Chart 1).

A woman, aged 27, who had noticed palpitation and shortness of breath in the beginning of 1922. In March they were sufficiently distressing to interfere with her work in the house, and swelling of the neck was noted. She was admitted on June 20th, 1922, as she had developed auricular fibrillation. This had disappeared by the next morning, but the heart rate was 120. Tremors were pronounced; exophthalmos was not pronounced, but von Graefe's and Joffroy's signs were present. The thyroid gland was symmetrically enlarged, soft, and pulsating. There was a muco-purulent discharge from a perforation of the right ear-drum, and both tonsils were septic. By July 3rd, when her basal metabolic rate was +48 per cent., the heart rate had settled to between 80 and 90 and the tremors were less, but she had lost weight steadily. The ear condition was being treated by syringing, and the general condition

CHART 1.

was but little improved when, on July 21st, tonsillectomy was performed. By August 8th considerable improvement had taken place, the basal metabolic rate being +28 per cent. and the heart rate 82. Iodine was commenced in doses of m xv daily, of the 10 per cent. solution in alcohol, and by August 11th the basal metabolic rate was +10 per cent. and the heart rate 76. On August 14th the basal metabolic rate was +3.5 per cent. and the heart rate 66, while she had commenced to gain weight. She was discharged from hospital, but in a few months' time was as bad as on admission. While an out-patient, although she felt better when taking iodine, it had no obvious effect, and when the auricles commenced to fibrillate again she was readmitted for surgical treatment.

CASE II (Chart 2).

A woman, aged 20, who for six months before admission in May, 1922, had noticed shortness of breath, swelling of the neck, prominence of the eyes, and nervousness. The heart rate was 110 to 120 on admission. The thyroid gland was symmetrically

enlarged, soft, elastic, and pulsating. All the classical eye signs of exophthalmic goitre were present. With rest in bed the heart rate fell to 94, but she continued to lose weight, and the basal metabolic rate, which shortly after admission was +54 per cent., had by June 22nd fallen to +47 per cent. only. Commencing June 22nd, m xv of the iodine solution were given daily, and this was increased to m xxx on June 29th. By July 10th the heart rate was

CHART 2.

76, the basal metabolic rate was not increased above the normal level, and the body weight was steadily increasing. On discharge from hospital the condition soon relapsed, and by October the greatly increased hardness of the thyroid gland caused the administration of iodine to be stopped. It was started again later at a smaller dose, as the patient thought she was better when taking it, but it had no noticeable effect, and she was readmitted in February, 1923, with a heart rate of 130, and basal metabolic rate of +68 per cent. With rest in bed the heart rate dropped to 110 to 120, and the basal metabolic rate to +56 per cent. Iodine was started, in doses of m ix of the solution daily, on February 13th. On February 24th the heart rate was 96, and the basal metabolic rate +25 per cent., and a few days later she was transferred to the surgical side for thyroidectomy.

CASE III (Chart 3).

A married woman, aged 49, who was said to have had exophthalmic goitre off and on since the age of 33. There had been a recent increase of palpitations, sweating, headache, and nervousness, and she was admitted in November, 1922, with auricular fibrillation, which disappeared, however, after a few hours' rest in bed. The following day the heart rate was 110 to 120. The thyroid gland was enlarged throughout, but the left lobe was larger than the right, and it was firm and elastic and not markedly vascular. Flushing and sweating were marked, and there was a fine generalized tremor. The eyes were somewhat staring and glistening, but no definite eye signs were present. With rest in bed for three weeks, the initial basal metabolic rate of +41 per cent. had fallen to +32 per cent., the heart rate was not altered, and the body weight had fallen steadily. Iodine was commenced on

CHART 3.

December 19th, in doses of m ix daily, and by January 15th, 1923, the basal metabolic rate was +3 per cent., the heart rate 94, and she had gained 16 lb. in weight. Her general condition was greatly improved, and she was discharged. After a few months at home her condition was as bad as on admission, and although she always felt better when taking iodine, it had no obvious effect, and partial thyroidectomy was ultimately performed. Some doubt existed as to the true diagnosis in this case, but the histological examination of the gland confirmed the diagnosis of exophthalmic goitre. While an out-patient, continued administration of iodine for several months, even in doses as small as m iij daily, caused the gland to become very hard, and increased the excitability of the patient and the rate of the heart.

CASE IV (Chart 4).

A man, aged 40, who for two years had noticed nervousness, palpitations, and weakness, and for six months before admission had noticed swelling of the neck. He had lost 2 st. in a year, and had frequent attacks of sore throat. On admission to hospital in April,

1923, the heart rate was 100 to 120, and the basal metabolic rate was +75 per cent. There was slight exophthalmos, the palpebral fissures were wide, and the conjunctivae glistening. The thyroid gland showed a uniform enlargement, it was soft and pulsating, and there was a loud bruit audible over it. A fine tremor was present. The tonsils were large and showed points of exudate. Tonsillectomy was performed on May 8th, and on May 16th the

CHART 4.

basal metabolic rate was +46 per cent., the heart rate was as on admission, and he had lost weight steadily. Iodine $m\ vj$ daily was started on May 16th, and later increased to $m\ ix$ and then to $m\ xii$, and he commenced to improve in a striking manner. By June 10th the heart rate was 94, and he had gained a stone in weight. On May 25th the basal metabolic rate was +29 per cent. Unfortunately no further estimations were made. Partial thyroidectomy was performed on June 21st.

CASE V.

A woman, aged 43, who complained of weakness and tremors following an attack of tonsillitis in November, 1921. In May, 1922, the swelling in the neck was noticed, and in December, 1922, she was told her eyes had become prominent. On admission, on February 23rd, 1923, the heart rate was 120, and the basal metabolic rate +61 per cent. The thyroid gland was uniformly enlarged, soft, and pulsating, and a loud bruit was heard over it. Exophthalmos and von Graefe's and Stellwag's signs were present. The patient's voice was husky, there was a dry cough, and the tonsils were enlarged and septic. There was a fine generalized tremor of the muscles. Considerable improvement resulted from rest in bed, and on March 7th, when iodine was commenced, the heart rate averaged 104, and the basal metabolic rate was between +30 per cent. and +40 per cent. Two weeks later the basal metabolic rate was +16 per cent., the heart rate 84, and the body weight was rising. On stopping iodine for a week, the basal metabolic rate rose to +39 per cent., the heart rate to 116, and the weight ceased to increase; after recommencing it the basal metabolic rate had dropped again to +16 per cent. at the end of two weeks, the heart rate to 90, and she was again gaining weight. In spite of continuing the administration of iodine, the improvement was not maintained. The onset of an attack of tonsillitis may have been responsible for this, or a less strict condition of rest, or both.

CASE VI.

A married woman, aged 41, who had had a history of exophthalmos for five years, palpitations, dizziness, and digestive troubles for more than one year, and a vague history of swelling in the neck from time to time. On admission, in November, 1923, general nervousness and excitability were marked. The heart rate was 112, and the basal metabolic rate +60 per cent. to +70 per cent. The thyroid gland was soft, symmetrically enlarged, and a bruit was audible over it. Besides exophthalmos, all the classical eye signs were present, but there was no tremor. With rest in bed the heart rate dropped to 98, but there had been little improvement otherwise when iodine was started in doses of $m\ vj$ daily on December 11th. On December 24th the basal metabolic rate was +29 per cent., and the heart rate had been as low as 86. The patient became very excited during the Christmas festivities, and this was held to account for the fact that for a period of three or four weeks the condition relapsed. Towards the end of January, although the dose of iodine had been reduced to $m\ iv$, the heart rate and the basal metabolic rate were again falling, but not so satisfactorily as in December. The body weight had, however, increased continuously since the commencement of the iodine treatment.

CASE VII.

A married woman, aged 43, who had noticed prominence of the eyes and shortness of breath on exertion for eighteen months, disturbed sleep for eight months, and severe weakness and tremor for four months. She was admitted in December, 1923, with a heart rate of 100, and basal metabolic rate of +46 per cent. Exophthalmos and all the classical eye signs were present. The skin was moist and flushed readily. Tremor was not marked. The enlargement of the thyroid gland was slight but symmetrical, and no bruit or thrill was noted. Under iodine, $m\ vj$ daily, the basal metabolic rate fell to +22 per cent. and the heart rate to 82, but the improvement was not maintained and no gain in weight resulted.

In this case there were serious family troubles owing to the patient's absence from home, and it was soon seen that

no further benefit would be derived from hospital treatment. The improvement that results from iodine seems to have a feeble hold, for in this case worries, in Case VI excitement, in Case V tonsillitis, and in Cases I, II, and III less strict conditions of rest, all caused it to disappear to a greater or less extent.

The following case is given in detail, not so much because it illustrates a typical action of iodine, but because the effect of the iodine was so striking, though unusual.

CASE VIII.

A woman, aged 31, who had had increasing symptoms of exophthalmic goitre for one year, but who was found after admission to have a staphylococcal septicaemia in addition. She was given iodine for four days, and received $m\ lxxv$ in all. At the end of the four days the heart rate, which had been 116, had fallen to 60, and after continuing at that level for two more days rose again rapidly to 100. No other cause for the fall in rate could be discovered, and no disturbance of cardiac mechanism was suspected, the heart's action being regular throughout the fall and subsequent rise of rate.

This case appears worth recording if only to show that iodine is capable of profoundly influencing certain functions of the organism in disease. Of the remaining 16 cases, in 9 there was evidence of beneficial action similar to that seen in the foregoing cases. In these the observations on the basal metabolic rate were not so complete, or other factors disturbed the action, so that they do not present such a clear picture. In others, again, a sufficient control period without iodine was not present. Among these 9 cases are examples illustrating further some of the points already brought out. It was frequently seen that on the patient being allowed up, and more particularly on leaving hospital, the condition relapsed in spite of continued iodine administration. On the other hand, such patients are almost unanimous in stating that they feel better when on iodine. In a man aged 40 the subjective distress and nervousness improved strikingly, and the heart rate was slowed, but there was little or no effect on the basal metabolic rate. In a woman aged 44 the improvement in the general condition and basal metabolic rate was striking, but persistent auricular fibrillation set in, and the picture of exophthalmic goitre became overshadowed by that of circulatory insufficiency. Two cases in whom constipation had been troublesome to manage developed a desirable looseness of the bowels after commencing iodine, and the ward sister states that in other cases a similar action was noticeable, though to a less extent.

In 5 cases no beneficial action could be noted, but in 3 of them coincident infections may account for this. In one, septic teeth and chronic appendicitis, in another tonsillitis, and in a third bronchopneumonia, may have prevented the evidence of iodine action being seen. In none of the five was any harmful effect discoverable. In 2 cases undesirable effects were prominent. In one, a woman aged 20, tonsillectomy and rest brought about considerable improvement, but the commencement of iodine in doses of $m\ xxx$ daily, and later $m\ lx$ daily, caused an increase in the severity of the symptoms—the thyroid gland became extremely hard, and troublesome diarrhoea appeared. The basal metabolic rate had before treatment with iodine been +20 per cent., and after the diarrhoea set in it rose to +90 per cent. The condition subsided somewhat on stopping the administration of the iodine, and partial thyroidectomy was performed. In the other case, that of a woman aged 27, considerable improvement occurred in the ward after tonsillectomy, and further improvement was seen on commencing iodine in doses of $m\ xl$, and later of $m\ lx$ and $m\ clxxx$; but on leaving hospital on this last dose the thyroid gland became hard and appeared increased in size, and distressing palpitations appeared.

Regulation of Dosage.

It will be seen that in those two cases in which harm resulted much larger doses than those usually given were employed. They were in the earlier days of our observation, and because of the very promising results obtained with the smaller doses, the larger doses were the result of an attempt to obtain even better results. As a result of experience we soon learnt that doses of $m\ ix$ and $m\ xv$ daily gave as good results as could be obtained with larger doses. If, however, such doses were continued for long, after a

varying number of weeks the thyroid gland would become gradually harder, and distressing symptoms of palpitations, pressure in the neck, choking sensation, and occasionally increased exophthalmos and tachycardia, would develop. After obtaining a decided benefit on daily doses of $m\ ix$ or $m\ xv$, and no further improvement occurring, the dose is reduced to $m\ vj$ or $m\ iij$, and the patient can continue on such doses almost indefinitely. In each case repeated examination is necessary to ascertain the optimum dose to maintain the improved condition. On the appearance of a rise in heart rate, or of the gland becoming harder, all iodine is omitted for one or two weeks and then recommenced on a lower dose.

Therapeutic Value.

In spite of such careful regulation of dosage, the ultimate results have not been as good as might be expected, for, as seen in the cases detailed, worry, excitement, and infections can undo all the benefit derived from the iodine. I think, further, that iodine cannot withstand the consequences that the daily contact with the world, either at work or at home, has on patients with exophthalmic goitre, and that so far it is of limited value in the medical treatment of the condition. If the patient can afford to lead a sheltered life it is a valuable addition to the other means at our disposal for managing a condition that in the majority of cases gradually subsides in time. But its very striking action has a much greater value than this, if it is combined with surgical treatment. The great majority of cases of exophthalmic goitre cannot afford to lead a sheltered life, and for them the only treatment that holds out the hope of a recovery sufficient to allow of successful competition in the struggle for a living wage is by means of surgery. Iodine treatment can so improve the patient's condition, even if temporarily, that surgical treatment by partial thyroidectomy becomes much simpler and much safer.

DISCUSSION.

In the last few months several reports on the action of iodine in exophthalmic goitre have been published. Plummer and Boothby,¹² reporting from the Mayo Clinic, base their deductions on their experiences with 600 cases in all, of which 43 were studied carefully. They administered the iodine in the form of Lugol's solution, which contains 5 per cent. iodine in 10 per cent. potassium iodide. In their summary they state that "it seems probable that approximately two-thirds of the patients with exophthalmic goitre will be greatly benefited, one-fourth will be slightly benefited, the remainder—or about one patient in twenty—will not be benefited." They consider that there is practically no probability of iodine doing any harm. In their recorded observations there is no mention of any attempt to use the larger doses which we employed at the outset, and which I think are capable of doing harm, and since their cases appear to have been in course of preparation for surgical treatment it is unlikely that they ever observed the action of even small doses of iodine over a prolonged period. Our results point strongly to the possibilities of harm even with such small doses as $m\ vj$ of the 10 per cent. tincture, if continued for several months or weeks. Plummer and Boothby employ doses of ten drops of Lugol's solution daily for the average case, and may in urgent cases give as much as thirty drops for a few days only.

Mason,¹³ reporting from Montreal, also uses Lugol's solution, and his experience is the same as that of Plummer and Boothby. He emphasizes the immediate relapse of the clinical condition on stopping iodine.

Jagic and Spengler¹⁴ used a 5 per cent. solution of sodium iodide in the treatment of various types of goitre, and they report that, in 5 cases with symptoms of exophthalmic goitre, 2 were improved, 2 others relapsed after a preliminary improvement, and the fifth became worse. They advocate the use of eight drops of the 5 per cent. solution of sodium iodide, three times a day, in cases of goitre with thyrotoxic symptoms.

Wahlberg¹⁵ used a 5 per cent. solution of potassium iodide in maximum doses of fifteen drops a day. In 2 cases out of 8 he found that after a preliminary improvement the disease became worse. The ultimate results on the

whole were not satisfactory, and he believes that the problem is largely one of dosage, and that the initial benefit is destroyed by a cumulative action of the iodine.

Starr, Walcott, Segall, and Means¹⁶ followed the lines reported by Plummer and Boothby, and, using Lugol's solution in the same doses, confirmed their results. They also noted the temporary character of the improvement, and use the term "iodine remission" to describe the benefits obtained, and also noted that in some cases no effect is observable.

Since the cause of exophthalmic goitre is at present unknown, it is not easy to decide on the meaning of this action of iodine. The recent experimental work of Marine¹⁷ on the result of damage to the cortex of the adrenal bodies is of interest in this connexion. He found that such damage in rabbits causes an increased heat production—that is, a rise of basal metabolic rate—and a loss of iodine in the thyroid gland. If the thyroid had been removed previously, this rise of heat production did not occur. Clinically these animals, in whom the adrenal cortex was damaged, showed features resembling those seen in exophthalmic goitre—namely, asthenia, exhaustion, myocardial damage, and loss of nutrition. These results appear to support the prevalent ideas that in exophthalmic goitre other organs of internal secretion besides the thyroid are essentially, and possibly primarily, involved.

It is tempting to try to bring exophthalmic goitre into line with the simpler goitres as an iodine deficiency disease, and to account for the different types of goitre by differences in the response of the thyroid and of the body generally to iodine deficiency. The results of iodine treatment in exophthalmic goitre, however, justify merely the view that in this disease there is an iodine deficiency relative to the needs of the body. It may be that the primary disturbance, whatever that may be, involves the thyroid gland in addition to other organs, and that the thyroid is stimulated to overactivity. This overactivity, by greatly increasing the need for iodine, would then result in a relative iodine deficiency. On this hypothesis, the administration of iodine would be of value in the treatment of what is merely a symptom, while it would have little if any effect in altering the course of the disease, and the administration of large doses would result in harmful effects, just as in the treatment of simple goitre.

SUMMARY.

1. The effect of iodine administration has been studied in twenty-four cases of exophthalmic goitre.

2. Iodine can bring about a lowering of basal metabolic rate, and of heart rate, and an increase of body weight, with a striking improvement in the general condition of the patient.

3. The improvement obtained with iodine does not as a rule persist.

4. The optimum dose at the commencement of the treatment appears to be about $m\ xv$ of a 10 per cent. solution in alcohol, but this dosage cannot as a rule be maintained more than a few days or weeks. If the administration is stopped the condition immediately relapses. For prolonged treatment the dose should be lowered as soon as the initial improvement has taken place, and the administration continued with doses of $m\ iij$ to $m\ vj$ daily. The dosage must be carefully regulated according to the condition of the patient.

5. Increasing hardness of the thyroid gland is an indication for a smaller dosage.

6. The condition of the patient may be made worse, instead of better, if too large a dosage is employed.

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