FOUR CASES OF EXOPHTHALMIC GOITRE TREATED WITH INSULIN.

A Preliminary Report to the Medical Research Council.

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THE idea of treating hyperthyroidism with insulin was founded on the hypothesis of an antagonism between the hormones of the thyroid and the pancreas. Such an hypothesis admits of no definite proof, but the pathological and experimental evidence in its favour seemed to warrant the hope that insulin might prove useful in the treatment of hyperthyroidism and exophthalmic goitre. Since this work was begun, Goffin¹ has published a report of four cases of Graves's disease treated with insulin, three of which were greatly ameliorated. His work may be criticized on the grounds that no estimations of basal metabolism were made and therefore hyperthyroidism was not definitely established, nor is there a record of the conditions of his experiment being carefully controlled. Of the four cases here reported two were successful, and, though it is too early to generalize on these few cases, they seem to give an indication of the type of case most likely to benefit from insulin. As each case requires very thorough and prolonged investigation to be of real experimental value and few can be adequately undertaken at a time, the following four cases are recorded now in detail in the hope that others may be tempted to investigate the question.

Evidence of an Antagonism between the Thyroid and the Pancreas.

The clinical picture of hyperthyroidism and exophthalmic goitre is well known. The condition is due to an increased production and perhaps a qualitative change in the specific hormone thyroxin, an iodine compound. When this is present in excess, as in exophthalmic goitre, the metabolism as judged by the minimal heat production—the basal metabolic rate as it is called—is markedly increased, katabolism exceeds anabolism, the tissues are rapidly broken down and nitrogenous excretion is increased, weight is lost, the pulse and respiration are rapid, and the temperature often elevated. In brief, thyroxin acts as an excessive draught to the fires of the body. In addition, the sympathetic system is over-active, and to this the symptoms of nervousness, tremors, and exophthalmos are commonly ascribed. The carbohydrate metabolism is frequently upset and spontaneous glycosuria and hyperglycaemia may occur. More often this appears only on a glucose tolerance test, which shows a high and prolonged blood sugar curve. Usually the fasting blood sugar is normal, and it would seem that the oxidation of carbohydrates is normal and only the glycogenic function² of the liver defective at first. This may lead subsequently to a true diabetes mellitus, presumably by prolonged overstrain of the pancreas.

On the other hand, although we do not know of any condition of excessive production of insulin by the body (hyperinsulinism), the effects of insulin are the opposite of thyroxin in several directions. Its total effect on metabolism apart from diabetes is little known, but it would appear to retard metabolism, especially when the blood sugar is reduced to a low level (Macleod, 1924). Its effect on the weight of non-diabetics is also unknown, although Harrison³ has failed to fatten rabbits on large doses of insulin. But Garrelon and Santenaise⁴ have recently shown its action as a vagotonic agent, apart from its hypoglycaemic effect, but owing to the importance of its therapeutic possibilities this point requires confirmation. Certainly some of the early symptoms of hypoglycaemia—the hunger pains, the occasional colic, and the heavy slow palpitation—are suggestive of parasympathetic vagus stimulation, the opposite of the sympathetic effect of hyperthyroidism. Insulin reduces the blood sugar and undoubtedly restores the glycogenic function⁵ of the liver of a diabetic, or at least

enables it to store glycogen. Loewi's adrenaline eye test for dilatation of the pupil may be cited as further evidence, for in Graves's disease it is often positive from increased sympathetic tone, and in diabetes (hypoinsulinism) often positive from failure of the pancreatic hormone to counterbalance the sympathetic tonus—or so the theory goes.

Some experimental work on animals is definite in support of a thyroid insulin antagonism. Ducheneau⁶ showed that thyroidectomy makes rabbits more sensitive to insulin. Burn and Marks confirmed this,⁷ and went further by showing that thyroid feeding makes a thyroidectomized rabbit again more insensitive to insulin. Falta⁸ states that—

"extirpation of the thyroid raises the assimilation limits for carbohydrates and reduces the protein metabolism during fasting. Extirpation of the pancreas reduces the assimilation limits very strongly and increases the protein metabolism during fasting. Simultaneous extirpation of the thyroid and pancreas produces indeed a diabetes; this, however, pursues a milder course to the extent that the increase of the protein destruction is not so high and the diminution in weight does not increase so rapidly. . . ."

Friedman and Gottesman⁹ have recently confirmed this. There is thus much scattered evidence to suggest a correlation between the thyroid and the pancreas, but so far mostly that the thyroid is an antagonist to insulin than the other way about.

Plan of Author's Investigation.

Spontaneous variations in the clinical condition of a case of Graves's disease are notorious, and the consequent difficulty in estimating the specific effect of any treatment is recognized. In this investigation care has been taken to allow time for the preliminary improvement that rest in hospital usually brings about before starting insulin treatment. The patients were placed on a fixed diet to avoid changes in weight and metabolism due to diet alone and to make it safe to give large doses of insulin with blood sugar control. Improvement was to be judged by changes in the general condition of the patient, the size of the thyroid, the nervous symptoms, the weight and the pulse rate, and, most important of all, the basal metabolic rate. It was intended to estimate the nitrogenous excretion also, but so far this has not been done. All the patients were confined to bed throughout the investigation, and indeed were too ill to be allowed up. The progress of the cases is recorded in the tables, which show the weekly change in weight, morning and evening pulse rate, basal metabolic rate, the units of insulin per day, and the respiratory quotient. The modified Tissot spirometer supplied by the Sanborn Company was used for the basal metabolic estimations and the air analysed in a Haldane's apparatus. The tests were carried out uniformly sixteen hours after the last meal, although a cup of tea was allowed four hours before the test for the comfort of the patient and seemed to make no difference. As all the patients presented ocular and nervous symptoms, tremors, tachycardia, and dilatation of the heart, and enlarged thyroid, these are not mentioned again in detail unless of special interest.

CASE I.

An unmarried woman, aged 23, was admitted to hospital on April 29th with a history of swelling in the neck since childhood, which had rapidly enlarged and begun to cause symptoms only in the last six months. She presented all the cardinal symptoms of exophthalmic goitre; the right lobe was more enlarged than the left and caused deviation of the trachea and dysphagia. The apex beat was 4½ in. from the mid-sternal line. She did not improve under medical treatment, and in Dr. Firth's opinion was too bad a surgical risk for operation. I wish to take this opportunity of expressing my indebtedness to him throughout this investigation, and especially for help in the estimations of basal metabolism. She had no glycosuria and neither fasting nor post-absorptive hyperglycaemia.

Before starting insulin her average diet was observed for several days, and estimated at 350 grams of carbohydrate, 120 grams of protein, and 150 grams of fat. She was accordingly placed on this diet arranged in four meals in the day (that is, 80 calories per kilogram of body weight) and insulin A.B. commenced with 15 units twice a day before breakfast and tea. Her progress is shown in Table I. I do not think that the beneficial suggestive element of the injections has to be reckoned with, as she had been having other

injections before and hardly knew they were changed. Yet even after four days of insulin she was positive that the neck was less tense and that she could swallow better. The insulin was increased in ten days up to 90 units, and four days later she had mild symptoms of hypoglycaemia (blood sugar 0.069 per cent.) coinciding with the use of a new batch of insulin. The dose was subsequently dropped to 80 units, which caused no inconvenience either locally or generally.

At the end of three weeks the tremors and exophthalmos were quite gone and she felt much better and walked better. The basal metabolism had dropped, but the pulse rate took longer to follow suit. As she felt very hungry (an insulin effect) her diet was raised at the fourth week by 100 grams, after which she increased much more rapidly in weight. Her general improvement was marvellous; insulin was discontinued after nine weeks, but her progress was still maintained, and all this during the hottest period of the summer, which is often fatal to these cases. The thyroid obviously diminished in tenseness and size; but the measurements were unfortunately not made by the same person throughout the investigation and vary too much to afford any real indication. As her weight increased the added fat tended to mask any diminution in the size of the gland, but at the end of her treatment it was still slightly enlarged. The heart had returned to the normal position, and the pulse rate remained steady during the last fortnight, when she was allowed to walk about the ward.

TABLE I.

Weeks.*	Weight in lb.	Pulse.		Basal Metabolic Rate per Cent.	Respiratory Quotient.	Insulin Units per Day.
		Morning.	Evening.			
7	111	116	122	—	—	0
4	98	120	120	+66	0.74	0
2	95	112	108	—	—	0
1	92	100	120	+58	0.71	0
0	91	114	122	—	—	30 to 50
1	90	100	128	+41	0.79	70 to 80
2	93	96	120	+33	0.82	90
3	95	104	120	+19	0.76	80
4	97	80	120	+14	0.78	80
5	100	88	100	+13	0.87	80
6	105	84	100	+24	0.83	60 to 40
7	112	92	72	+24	0.81	40 to 20
8	117	84	96	+27	0.77	20 to 0
9	119	88	108	+16	0.77	0
10	125	78	100	+13	0.79	0

* Weeks before and after insulin treatment. Insulin commenced at 0. This applies to the four tables.

CASE II.

A married woman, aged 28, was admitted to hospital with a history of swelling in the neck for six months and exophthalmos and extreme nervousness since a miscarriage three months ago. The Wassermann reaction was negative. She was excessively nervous and restless on admission and the heart was slightly dilated. She had glycosuria (2 per cent. in the twenty-four hours urine), normal fasting blood sugar but hyperglycaemia after meals. The variations in the carbohydrate metabolism throughout the experiment are very interesting.

After two weeks of rest her basal metabolic rate had become stable, and she was put on a diet of 350 grams of carbohydrate, 120 grams of protein, 150 grams of fat, and 40 units of insulin given in two doses. She became sugar-free in three days and developed an enormous appetite, an effect which insulin produced on three of the four cases. Instead of losing weight she gained a pound in the first four days. Accordingly 100 grams of carbohydrate were added to her diet in the form of bread and the insulin raised gradually to 100 units a day. At the end of the second week she had greatly improved; she had gained 5 lb. and the pulse and basal metabolic rates were dropping. The fasting blood sugar was normal, and five and a half hours after the morning dose of 50 units was 0.074 per cent. She never had any hypoglycaemic symptoms, except that she was always very hungry even after a large meal. I had now got her into the state at which I was aiming, in which I hoped insulin would have its maximal beneficial effect either by the low blood sugars *per se*, by a direct antagonism to an excess of thyroxin, or by its general restraining influence on metabolism. It seemed to be having the desired effect, but she then received some very worrying domestic news which upset her completely, and she relapsed in every way except that she still continued to gain weight. She was kept on the same diet, and in spite of 100 units of insulin a day began to pass much sugar in the fourth week, and by the end of the fifth week the blood sugar was 0.179 per cent. fasting level, and 0.372 per cent. two hours after dinner—figures which showed that

the condition of the carbohydrate metabolism had become typical of diabetes rather than of hyperthyroidism. The interesting question arises whether this was caused by the mental upset, by an increased secretion of thyroxin rendering the insulin ineffectual, or by a diminished tolerance accompanying the rise in weight, or by a combination of these factors. The carbohydrates were reduced to 350 grams a day in the fifth week, to 250 grams in the sixth, and 200 in the seventh week, but in spite of the large dose of 100 units insulin a day, it was not till the eighth week that she became sugar-free with normal blood sugars. Her source of worry was removed in the sixth week, and after this she rapidly improved and felt so well that she decided to go home. In spite of a diet ample in bulk and calories she complained of always feeling hungry, even when the blood sugar estimates were high, an effect probably due to insulin apart from the blood sugar level, and noticeable in many diabetics under insulin. This, I would suggest, is a vagotonic effect. It is interesting to note that insulin raised the respiratory quotient markedly except in the fifth week, when the blood sugars showed her to be in a diabetic condition. She never showed any ketosis.

On discharge from hospital she declared herself better than she had been for months. Her muscular power had greatly improved and the tremors almost disappeared. The exophthalmos and the pulse rate were only slightly diminished. The circumference of the neck diminished one inch in spite of the fact that the weight increased 26 lb. The change in size and pulsation was most noticeable in the left lobe, but there was no sign of any residual adenoma in the right lobe to account for the fact that it hardly diminished at all.

The insulin was suddenly discontinued during the last three days, as the patient was anxious to leave, and slight glycosuria reappeared. It is hoped to continue the investigation of this patient as soon as she can be readmitted to hospital.

TABLE II.

Weeks.	Weight in lb.	Pulse.		Basal Metabolic Rate per Cent.	Respiratory Quotient.	Insulin Units per Day.
		Morning.	Evening.			
2	81	120	120	+61	0.74	0
1	79	112	120	+43	0.79	0
0	78	110	120	+41	0.75	40
4 days	79	112	120	+41	0.76	60
1	82	109	100	+30	0.81	60
2	84	90	120	+26	0.81	80 to 100
3	89	130	140	+46	0.85	100
4	93	120	115	+46	0.87	100
5	98	130	140	+35	0.77	100
6	100	122	120	+41	0.80	100
7	103	108	112	+35	0.82	100
8	105	100	120	+24	0.82	100

CASE III.

A married woman, aged 50, a severe case with marked tremor and muscular weakness, was admitted with a history of swelling in the neck, nervousness, and palpitation for two years, and exophthalmos for sixteen months. A carcinoma of the right breast had been removed four years previously and showed no sign of recurrence. A deep-seated adenoma could be felt in the right lobe,

TABLE III.

Weeks.	Weight in lb.	Pulse.		Basal Metabolic Rate per Cent.	Respiratory Quotient.	Insulin Units per Day.
		Morning.	Evening.			
2	92	96	104	—	—	0
1	90	100	100	+42	0.77	0
0	89	96	100	+39	0.81	40 to 50
1	92	96	100	—	—	60 to 80
2	95	108	112	+46	0.82	80
3	98	96	104	+57	0.76	90
4	101	100	124	+66	0.74	90
5	104	104	142	+52	0.82	40
6	105	88	120	—	—	20
7	105	84	108	+46	0.77	20
8	105	88	112	+40	0.76	0

which was larger than the left. She had transient glycosuria, normal fasting blood sugar, but gave a typical prolonged curve of slight hyperglycaemia with 50 grams of glucose.

Insulin was commenced with 40 units on a diet of 450 grams of carbohydrate, 120 grams of protein, and 150 grams of fat—somewhat higher than she had been eating before. At first this proved too much for her, but her appetite improved as the insulin was increased to 90 units and she rapidly gained in weight. She did not improve in other respects, and after a month the insulin was reduced to 20 units a day. On this the gain in weight was not maintained, perhaps partly because appetite diminished, although she was still able to eat a very liberal diet. When insulin was discontinued her general condition was little if at all improved, although the tremors were appreciably less. The neck measurement remained unchanged, but it must be remembered that she had gained 14 lb. to offset this. The left lobe was decidedly diminished and the adenoma in the right lobe was more obvious, as the remainder of the lobe seemed to have shrunk. After the insulin was reduced below 40 units she ceased to gain weight but had no recurrence of glycosuria. The pulse and basal metabolic rate fell somewhat, probably because she began to sleep better under the influence of bromides.

CASE IV.

A married woman, aged 47, was admitted on May 26th with a history of dysphagia for eighteen months and noticeable thyroid enlargement and exophthalmos for twelve months. She presented all the symptoms of Graves's disease, and a dilated heart was found, but from the presence of several nodules in the thyroid she was rather a case of toxic adenoma than of simple exophthalmic goitre. Glycosuria and hyperglycaemia were absent. The Wassermann reaction was weakly positive, but this is common in hyperthyroidism, and no significance was attached to it.

She was treated with x rays for a month with no benefit, except that the thyroid became harder; she continued to lose weight, as shown in the table. Accordingly she was put on a diet of 350 grams of carbohydrate, 120 grams of protein, and 150 grams of fat—approximately what she was eating at the time—and 40 units, and later 60 units, of insulin were given. She got worse and developed pressure symptoms on the trachea, so that the insulin was discontinued after a month. Unlike the other three cases, she did not even gain weight appreciably, although the loss was checked for a time.

TABLE IV.

Weeks.	Weight in lb.	Pulse.		Basal Metabolic Rate per Cent.	Respiratory Quotient.	Insulin Units per Day.
		Morning.	Evening.			
3	79	96	98	—	—	0
2	76	100	100	+37	0.78	0
1	72	88	122	+34	—	0
0	71	92	93	+35	0.80	40
1	71	110	100	+50	0.82	40 to 60
2	72	98	92	+69	0.74	60
3	73	100	112	+64	0.79	60
4	72	106	120	+58	0.81	60
5	71	104	112	+61	0.77	20 to 0

The possible mode of action of insulin in hyperthyroidism, whether by direct chemical or physiological antagonism, by primary effect on carbohydrate metabolism, or as a vagotonic with a general anabolic action, will be discussed in a later publication when more evidence, including some animal experiments, has accumulated. But it already seems possible to correlate the results in these four cases with different types of hyperthyroidism. Two cases were successful, one strikingly so, and these were uncomplicated though severe cases of Graves's disease in young women. In one the carbohydrate metabolism was never abnormal, so that insulin did not act primarily by correcting this. The two unsuccessful cases were older women and the disease of longer standing. One of them, Case III, was definitely a toxic adenoma (Graves's syndrome associated with adenoma of the thyroid), and though she gained in weight and felt better she did not fundamentally improve. Case IV, a complete failure, was admitted as a case of toxic adenoma, but when I examined her after the thyroid had become hard, following a course of x rays, I could not be sure of this. Therefore it would appear that hyperthyroidism arising from an adenomatous condition of the thyroid is not likely to benefit from insulin, and that the

most hopeful are simple cases of Graves's disease. Indeed, on *a priori* grounds, we could hardly expect insulin to influence an adenomatous condition of the thyroid to which the general metabolic disturbance seems to be secondary.

Nothing definite can be said regarding the dose of insulin. On theoretical grounds big doses would seem most likely to succeed, and certainly small doses were no more effective than large in Case III. Goffin, however, reports improvement in his cases with 10 units a day and never gave more than 20.

The rise in the respiratory quotient under insulin was marked in the two successful cases, but indefinite or absent in the failures. Such a rise may prove to indicate whether the treatment is likely to be successful in any case. It can hardly be due to the direct action of additional circulating insulin, as the estimations were made eighteen hours after the last dose of insulin. It would seem to indicate a check on the former excessive katabolism of protein accompanied by improved glycogenic function of the liver; or at least a storage of carbohydrate under the influence of insulin which remains available for oxidation even when the insulin effect wears off, as occurs in diabetes.

The gain in weight was striking in three of the cases, and in the first two was not due to any change in diet, because they were kept on the same diet before and after the commencement of insulin, and the gain in weight was evident before the diet was increased in response to the appetite created by insulin. This suggests the use of insulin in the treatment of under-nutrition and emaciation in cases other than diabetes and hyperthyroidism. It is probable that insulin will acquire a much wider therapeutic field with the progress of time.

SUMMARY.

1. Four severe cases of Graves's disease with hyperthyroidism were treated with large doses of insulin, 60 to 100 units a day. The insulin was well borne and caused no inconvenience.

2. Two of the cases were greatly improved, one being practically normal on discharge from hospital. In both the disease was uncomplicated and of less than a year's duration in women under 30. It seems unlikely that their improvement was spontaneous or caused by any factor other than insulin.

3. The two others were not essentially benefited, although one gained much in weight and felt better. They were cases of toxic adenoma of the thyroid rather than of simple Graves's disease, occurring in women of about 50 and of over a year's duration.

4. The treatment was carried on under strict standard conditions of diet and close blood sugar control, but, should its value become established, these should hardly be necessary.

5. The subject is still in its experimental stage, and these four cases are recorded now mainly in the hope that other workers may investigate its possibilities.

I wish to thank the physicians of King's College Hospital for permission to observe these cases, the sister for her careful dietetic control, the house-physicians for their close co-operation, and Mr. L. Hewlett for many of the blood sugar estimations.

REFERENCES.

- ¹ Goffin, J.: *Le Scalpel*, April 15th, 1924.
- ² Cramer, W.: *Proc. Roy. Soc. London*, 1913, 85, 550; and *British Journ. of Exper. Path.*, 1924, vol. v, p. 128.
- ³ Harrison, G. A.: Unpublished personal communication.
- ⁴ Garrelon and Santenaise: *C. R. Soc. de Biologie*, 1924, 90, 470.
- ⁵ Lesser, E. J.: *Die innere Sekretion des Pankreas*, 1923.
- ⁶ Ducheneau: *C. R. Soc. de Biologie*, 1921, 90, 248.
- ⁷ Burn, J. H., and Marks, H. P.: *Proc. Phys. Soc.*, 1924.
- ⁸ Falta: *Endocrine Diseases*, 1923.
- ⁹ Friedman and Gottesman: *Journ. Amer. Med. Assoc.*, 79, 1228.

THE seventh Congress of French-speaking Medical Practitioners in North America has recently been held at Quebec under the presidency of Professor Vallée of Laval University. The French Government was represented by Professor Sergent and Dr. Ribadeau-Dumas of Paris and Professor Jeanneney of Bordeaux, on whom honorary degrees were conferred. Papers were read on cancer, tuberculosis, and infantile mortality.