EFFECT OF THYROID FEEDING ON SUGAR TOLERANCE.

By H. P. MARKS.

(*From the National Institute for Medical Research, London.*)

In a recent communication from this laboratory (1), evidence was presented in support of the view that one of the effects of increasing the amount of thyroid hormone in the body is to render the liver more sensitive to such stimuli as promote glycogenolysis and consequent discharge of sugar into the blood stream, while, conversely, elimination of the hormone by thyroidectomy diminishes the readiness with which the liver converts its glycogen into sugar. We were there concerned exclusively with this function of the liver, and did not consider the inverse one of conversion of sugar into glycogen. Various workers have suggested that sugar tolerance, *i.e.* the ability of an animal to dispose of ingested (or injected) sugar, is determined by the power of the liver to remove excess of sugar from the circulation, and convert it into glycogen. It is now generally recognised, however, that the liver is not the only organ involved, and that the pancreas plays an essential part.

On the relation of the thyroid hormone to sugar tolerance, the evidence of previous workers is conflicting. Thus, Cramer and Krause (2) state that, in dogs, sugar tolerance is slightly lowered by thyroid feeding, and Holm and Bornstein (3), that the glycosuria following an injection of sugar is less after thyroidectomy. Underhill (4), on the other hand, reports a diminished glucose tolerance in dogs after complete thyro-parathyroidectomy, while Kurijama (5) fails to find any alteration in the sugar tolerance of rats subjected to thyroid feeding. A large amount of clinical evidence of a similarly conflicting nature has also been put on record. Here it will suffice to mention the following case cited by Maclean (6); it is of interest as affording an approach to the experimental conditions obtaining in our own investigations on thyroid-fed rabbits. A patient, suspected of being a diabetic on account of the character of his sugar tolerance curve, was subsequently found to be taking a course of thyroid tablets by mouth. After discontinuance of this treatment for some weeks, a repetition of the sugar tolerance test gave a curve of the usual, non-diabetic type.

In view of the unsatisfactory nature of the available evidence, a more detailed investigation of the changes in sugar tolerance of rabbits, during a period of thyroid feeding, was undertaken, and the results obtained appear to throw new light on the mechanism of blood-sugar regulation.

Effect of thyroid feeding on response to glucose administration.

In Fig. 1 are shown, for comparison, two curves depicting the course of the blood-sugar in a rabbit, following the injection into the ear-vein of one-eighth of a gram of glucose per kilo. of body weight. Curve A

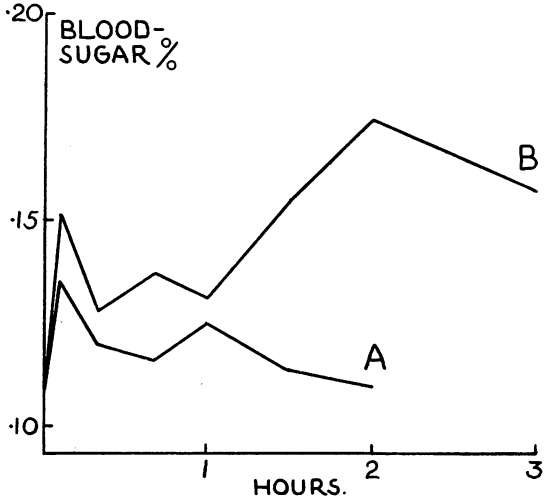

Fig. 1. Blood-sugar changes following an intravenous injection of glucose into a rabbit (A) when normal, (B) after 20 days' thyroid feeding. Note the late hyperglycæmia in Curve B.

shows the result obtained before thyroid feeding, Curve B that obtained after a period of 20 days' thyroid feeding. A comparison of the curves during the first hour following the glucose administration affords no evidence of such inability to dispose of excess of sugar as is seen in the diabetic organism. The injected glucose would appear to be removed from circulation equally rapidly in the normal and in the thyroid-fed animal. The point of particular interest, is that, in the thyroid-fed animal, the return of the blood-sugar to normal limits is followed by a secondary, pronounced hyperglycæmia, far exceeding in magnitude and duration that directly produced by the injection of the sugar.

Had the blood-sugar changes immediately after the sugar injection

not been closely followed, the return to the normal level might have been missed, and the curve taken to indicate a diminished power of the organism to dispose of the injected sugar. Actually, we see such a conclusion to be erroneous; the late rise in the blood-sugar may probably be ascribed to a discharge of sugar from the liver, rendered, by thyroid feeding, hypersensitive to the action of some glycogenolytic stimulus, occurring as a sequel to the administration and normal disposal of sugar.

This late rise in the blood-sugar may also follow the administration of sugar by mouth, or subcutaneously; but it has not been observed in all our experiments on thyroid-fed rabbits, and would appear to come into prominence only in the later stages of thyroid feeding. A summary of the experiments in which this phenomenon has been observed is given below:

No. of days thyroid feeding	Amount of glucose per kilo. and method of administration	Maximum value % of blood-sugar during late rise	Time in hours after the administration of glucose at which this maximum occurred
20	·125 gm. intrav.	·157	2
20	·125 „ „	·174	2
14	·125 „ „	·133	5
23	·125 „ „	·131	2
29	·125 „ „	·133	2
26	·125 „ subcut.	·152	3½
26	·125 „ „	·145	2
23	1 „ „	·224	3
27	1 „ by mouth	·152	5–7
35	1 „ „	·133 and ·132	4–7
6	1 „ „	·123	4
37	1 „ „	·126	6
19	1 „ „	·126	3

Since it has been shown that continued thyroid feeding ultimately results in the complete exhaustion of the glycogen reserves of the body (2), the late rise in the blood-sugar should not be observed in the extremely advanced stages of thyroid feeding, if the explanation put forward above is true. Our experiments show, not only that this is the case, but, further, that the secondary hyperglycæmia is then replaced by a hypoglycæmia. Curve A in Fig. 2 illustrates the effect of giving $\frac{1}{8}$ gram glucose per kilo. to a rabbit, after 20 days of thyroid feeding. It is seen that the slight secondary rise at $1\frac{1}{2}$ hours was cut short by a progressive fall in the blood-sugar, ending in hypoglycæmic collapse, from which recovery was only effected by the injection of 1 gm. of sugar, and the giving of food as soon as this had produced its effect. The change produced by sugar injection in this rabbit was so surprising that the experiment was repeated on the following day, with the result indicated in Curve B, Fig. 2. It is seen that for over 3 hours, in the absence

of any injection, the blood-sugar did not fall. 0·6 gm. of glucose was then injected by the ear-vein. After a preliminary rise to over ·2 p.c.,

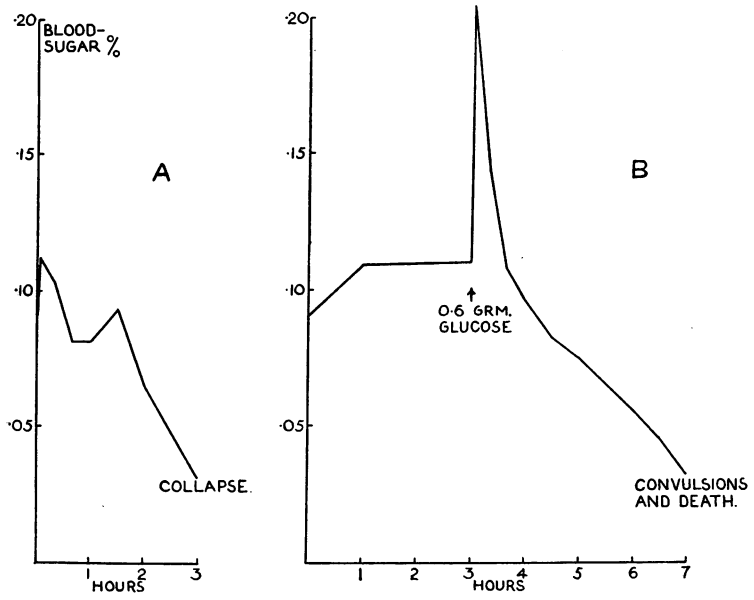

Fig. 2. Hypoglycæmia produced by injection of glucose into a thyroid-fed rabbit. Note in A, the transient rise in blood-sugar, and in B, the constancy of the blood-sugar prior to the injection of glucose.

the blood-sugar rapidly fell; in 2 hours it was down to ·075 p.c., and after 4 hours the rabbit died after a few convulsive kicks, with a blood-sugar of ·032 p.c. An examination of the liver showed it to contain no detectable amount of glycogen.

This phenomenon has also been observed to follow the administration of glucose by mouth. Indeed, the apparently spontaneous hypoglycæmia which has invariably terminated our experiments on thyroid feeding, in the absence of other treatment, is presumably the result of the ingestion of carbohydrate food. This final stage is usually reached in from three to four weeks, when the rabbit receives the equivalent of 1·3 gm. dried thyroid gland per day, but occasionally a rabbit will survive for six or eight weeks.

Effect of thyroid feeding on the response to small doses of insulin.

A study of the response of rabbits to small doses of insulin at different stages of thyroid feeding affords an interesting parallel to these blood-

sugar changes following an injection of glucose. Thus Curve A, in Fig. 3, illustrates the production of a late rise of blood-sugar, similar to that already described as following glucose administration. In this case, a dose of $\frac{1}{20}$ unit of insulin per kilo. was injected intravenously

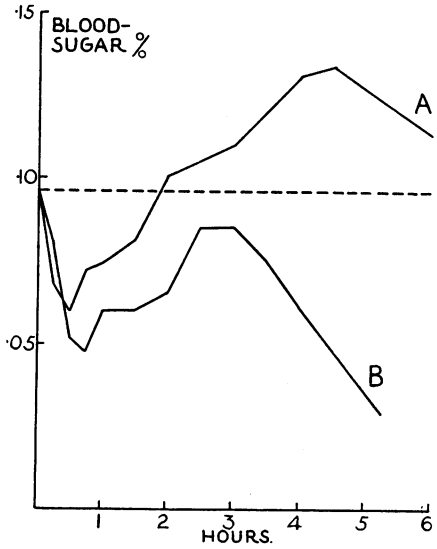

Fig. 3. Late hyperglycæmia produced by injecting a small dose of insulin into a thyroid-fed rabbit. In (B) the late rise is insufficient to compensate the hypoglycæmic effect of the insulin.

into a rabbit on the 23rd day of thyroid feeding. The late hyperglycæmia observed in this case would appear to represent the discharge of the last trace of glycogen from the liver, for, on the following day, an injection of glucose gave rise to a rapidly progressive hypoglycæmia, as a result of which the animal died in convulsions 2 hours after the glucose injection.

In the experiment illustrated by Curve B, the remaining glycogen reserve was apparently insufficient to restore the blood-sugar to the normal level, the slight rise in blood-sugar at the third hour being soon replaced by a second hypoglycæmia, ending in convulsions and death, $5\frac{1}{4}$ hours after the injection of the insulin. Here, again, no glycogen could be detected in the liver.

Response to adrenalin.

It has been stated(7) that the injection of adrenalin into animals previously rendered glycogen-free will still give rise to glycosuria, and

even cause the deposition of glycogen in the liver. According to Geelmuyden(8), this indicates that the sugar plethora following injection of adrenalin has some other source, besides the glycogen reserve in the liver, namely, the increased conversion of fat into sugar. Laufberger(9) also suggests that insulin opposes this action, by stopping the conversion of fat into carbohydrate.

On the basis of this theory, it might be expected that an injection of adrenalin would arrest the hypoglycæmia following injection of glucose into a glycogen-free, thyroid-fed rabbit, by rendering sugar available from other sources. We find, however, that adrenalin has no effect on the course of the hypoglycæmia. In fact, the injection of ·5 mgm. adrenalin into a rabbit in the advanced stage of thyroid feeding usually by itself brings on a fatal hypoglycæmia in a short time. Whether or not this is preceded by a detectable hyperglycæmia depends on the completeness with which the glycogen reserves have been exhausted.

Discussion.

Many observers have drawn attention to the fact that, even in normal individuals, the rise in blood-sugar after the ingestion of sugar is frequently followed by a fall to slightly below the normal level. Folin(10), indeed, considers that this secondary hypoglycæmia is as regular a consequence of sugar ingestion as is the primary hyperglycæmia, and attributes it to the lessened need for sugar transport, as a consequence of the tissues having absorbed the ingested glucose, and thus become amply supplied with nourishment. He based this view on the observation that the ingestion of olive oil and of gelatin also give rise to a hypoglycæmia. Maclean(11), on the other hand, suggested that the liver was the organ chiefly concerned with the absorption and storage of the ingested sugar, and that this absorption might continue after the blood-sugar had been reduced to the normal level. More recently, Sevringhaus and Smith(12), among others, have advanced the suggestion that the blood-sugar is reduced to the normal level through the agency of insulin discharged from the pancreas, a hypoglycæmia ensuing if this discharge of insulin is more than sufficient to deal with the sugar ingested. In these circumstances, they suppose, the liver then again adjusts the balance by a discharge of sugar into the blood. The results reported in the present paper are in complete harmony with this conception.

Let us consider first the blood-sugar changes following a small dose of insulin. In the normal animal, the return of the blood-sugar to the

normal level after the initial hypoglycæmia is due, according to Macleod, to a compensatory discharge of glycogen from the liver. According to Burn and Marks(1) thyroid feeding renders the liver over-responsive to such stimuli (*e.g.* adrenalin) as promote a discharge of sugar into the blood. The secondary hyperglycæmia observed in the thyroid-fed rabbit after insulin may therefore be attributed to an over-compensation by the liver, carrying the blood-sugar above the initial level. As the exhaustion of the glycogen reserves proceeds, this over-activity of the liver, although still present, is seen to become less and less effective, until finally, when the liver has no more glycogen to discharge, the hypoglycæmia produced by even a small dose of insulin proceeds unchecked to a fatal termination.

Turning now to the parallel changes observed in the behaviour of the blood-sugar after an injection of glucose, the disappearance of the excess of glucose is to be ascribed, according to our theory, to a stimulation of the pancreas to secrete insulin. Such an assumption receives direct support from the experiments of Spiro and Staub(13). In the normal animal, any excessive action of the liberated insulin is compensated by a discharge of sugar from the liver, so that the normal blood-sugar level is restored. In the thyroid-fed animal, however, the over-responsiveness of the liver again comes into play, and the excessive discharge of sugar may be sufficient to cause a marked secondary hyperglycæmia. If every carbohydrate meal is followed by such an excessive breakdown of glycogen, it is easy to see how the glycogen reserves may in time become completely exhausted. The effect of the progressive depletion of the glycogen stores may be followed here, just as in the case of insulin injections. The effectiveness of the compensatory function of the liver is seen to diminish progressively, until finally only the insulin effect remains. Then the insulin, secreted in response to the entry of sugar into the blood-stream, removes from the circulation not only the excess of sugar, but, in addition, the whole of the small remnant of available glucose in the body, so that the fall in the blood-sugar continues, unchecked by any compensatory discharge of sugar from the liver, until it is terminated by the death of the animal in hypoglycæmic convulsions.

A similar observation on the clinical side has recently been reported by Weil and Laudat(14). These workers describe a case of renal glycosuria, in which the ingestion of 30 gm. glucose was followed by a fall in the blood-sugar to ·048 p.c., accompanied by weakness and a sense of hunger, but none of the other symptoms of hypoglycæmia.

Here, also, we may expect that the glycogen reserves of the patient are depleted, and the hypoglycæmia is presumably due to the uncontrolled action of insulin, discharged from the pancreas under the stimulus of the ingested sugar.

It was thought that the phenomenon might be observed, even in the presence of ample glycogen reserves, if these reserves could be rendered inaccessible by paralysing the sympathetic endings by means of ergotamine. Under such conditions, the hyperglycæmia caused by an injection of glucose was followed by a fall in the blood-sugar to ·07 p.c., but no hypoglycæmia, of the severity of that encountered in thyroid-fed rabbits, was observed.

It is not possible at this stage, however, to say how far the other effects of thyroid feeding may contribute to the production of the intense hypoglycæmia observed in thyroid fed animals. The recent work of Cramer(18), and of Kojima(19) suggests that excessive thyroid feeding leads to hypertrophy of the islet tissue of the pancreas, accompanied by atrophic changes in the pituitary body, while Burn(16) has demonstrated the antagonism between pituitary extract and insulin. It may well be, therefore, that the operation of these factors, in conjunction with the depletion of glycogen reserves, will account for the dramatic and paradoxical results here described.

It seems clear that maintenance of the normal blood-sugar level involves the balanced action of a number of opposing factors. Just as the liver compensates for a fall by accelerated output of glucose, the pancreas compensates for a rise by accelerated output of insulin. Even under normal conditions, a temporary over-compensation may occur in one direction or the other, but the balance is maintained, on the whole, with remarkable accuracy. The balance can be disturbed by the influence of other endocrine glands, and of various drugs. Adrenalin, and sympathetic stimulation, certainly accelerate the output of glucose from the liver, and there is some evidence (Clark(15)) that vagal stimulants cause the pancreas to secrete insulin.

The thyroid hormone sensitises the liver to influences promoting glycogenolysis, among which we must presumably include the secretion of insulin *per se*; for glycogenolysis may apparently be elicited without the previous occurrence of hypoglycæmia (Fig. 1 B). Whether the insulin acts here as a direct liver stimulant, or by exciting the suprarenal glands to output of adrenalin, is a point on which no complete evidence is available; but Houssay's(17) demonstration, that the secretion of adrenalin is accelerated by injecting insulin, is suggestive.

SUMMARY.

1. A secondary hyperglycæmia is observed to follow the injection of glucose or of a small dose of insulin, into the thyroid-fed rabbit whose liver still contains glycogen.

2. When the liver is depleted of glycogen, a small dose of insulin, or an injection of glucose, produces a fatal hypoglycæmia.

3. The bearing of these observations on the mechanism of blood-sugar regulation is discussed.

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