CLXXXVI. A NOTE ON THE HYPOGLYCAEMIC ACTION OF DIHYDROXYACETONE IN MAN.

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SEVERAL interesting and apparently conflicting observations have accumulated about dihydroxyacetone.

(I) When administered to dogs [Campbell and Soskin; Himwich, Rose and Malev, 1926] or human beings [Cathcart and Markowitz, 1927], it causes a much prompter rise in the R.Q. to unity or over than does an equivalent quantity of glucose.

(II) It augments considerably the hyperglycaemia of depancreatized dogs, by whom it is quantitatively excreted as glucose. During this process the R.Q. shows a slight fall [Campbell and Markowitz, 1927].

(III) It exerts no curative influence on the hypoglycaemia following hepatectomy [Markowitz and Campbell, 1927].

(IV) When injected into eviscerated nephrectomized preparations, it enters unchanged into the tissues, the concentration of this substance in the tissues, at the end of several hours (as calculated from the concentration of the triose in a muscle), being sufficient to account for most of the triose administered [Markowitz and Campbell, 1927].

(V) It has no influence on the respiratory metabolism of excised amphibian muscle [Meyerhof, Lohman and Meier, 1925].

Observation (I) suggests that the triose is burnt with much greater facility than glucose. However, observations (II)–(V), if taken in conjunction, make it reasonably certain that dihydroxyacetone cannot be used as such, but must first be converted into glucose by the liver. The explanation for the high R.Q. following the administration of the triose is somewhat conjectural, but (as stated in our previous communication [Cathcart and Markowitz, 1927]) we believe it to depend on the following consideration. A depancreatized dog of only about 6 kg. can excrete nearly 20 g. of dihydroxyacetone as glucose in less than 6 hours. It is therefore a fair assumption that, following the administration of the triose to the intact animal, the tension of carbohydrate in the liver is considerably increased. Presumably the increase is sufficient not only to stop glyco-neogenesis out of fat and protein, but also to bring about a considerable synthesis of fat.

In agreement with the finding that dihydroxyacetone is a sugar-former in the animal body is the observation that it can act as an antidote to the hypoglycaemia following overdosage with insulin both in man and the lower animals [Campbell and Hepburn, 1926; Kermack, Lambie and Slater, 1926]. In decided contrast to this latter property of dihydroxyacetone is the observation, first made by Isaac and Adler [1924] and confirmed by Rabinowitch [1925], that the triose has a hypoglycaemic action in the human subject.

In the course of an investigation which had quite a different object, we found that, following the ingestion of 50 g. dihydroxyacetone on a *fasting* stomach, the subject developed muscular tremor, flushing, restlessness and general malaise. The condition was not recognised until routine blood-sugar determinations, which were made during the course of the experiments, revealed that the symptoms coincided with the existence of hypoglycaemia.

Since dihydroxyacetone thus resembles glucose in that it can both relieve insulin hypoglycaemia and definitely induce hypoglycaemia in man, it was deemed necessary to confirm its blood-sugar-lowering properties.

METHODS.

Five experiments in all were done on two subjects. One of these experiments was reported in Fig. 5 of our previous communication [1927]. The results of the remaining four experiments are presented in the form of a chart. Blood-sugars were estimated by MacLean's method. No correction for the presence of dihydroxyacetone in the first few samples has been introduced. Mason [1926], Campbell (personal communication) and others have shown that the quantity appearing in the blood after such doses is insignificant.

DISCUSSION.

It requires to be explained why a substance which forms sugar so readily in the animal body should have a hypoglycaemic action. The possible mechanism of this action can as yet be only conjectured.

The sugar of the blood is normally a balance between (1) the production of sugar by the liver [Soskin, 1927], (2) the utilisation or storage of sugar by the tissues, and (3) the secretion of insulin by the pancreas. A fall in the blood-sugar must be due to one or more of these factors, each of which will be discussed in turn.

(1) Although there is a considerable rise in the oxygen consumption immediately following the administration of dihydroxyacetone, this is by no means comparable to that occurring even in mild muscular exercise, in which condition there is no hypoglycaemia. It is, therefore, justifiable to conclude that the hypoglycaemia is not due to the increased energy requirement of the organism, although this latter may be a contributory cause.

(2) Before one can state that the hypoglycaemia of dihydroxyacetone is not insular in origin, it must be shown that when administered to *surcically* hepatectomised dogs, it does not accelerate the rate of fall of the blood-sugar, which it should do if it evoked a secretion of insulin in normal animals. Markowitz and Campbell [1927] found that when injected into a *functionally* hepatectomised dog, there was no evidence that the triose accelerated the rate of fall of the blood-sugar. However, this effect could have been masked by the presence of a slight amount of functioning liver tissue.

In favour of the insular origin of the hypoglycaemia following dihydroxyacetone may be mentioned the observation that the administration of the triose considerably augments the hyperglycaemia of a depancreatized dog. This finding, however, may possibly be dependent on the inability of the diabetic liver to hold glycogen, and not on the absence of insulin *per se*.

The ability of dihydroxyacetone to induce hypoglycaemia may be compared with the similar ability of glucose, under certain conditions, to bring about hypoglycaemia [Gibson and Larimer, 1924]. The administration of 50 g. glucose to a fasting normal human subject is regularly followed by hypoglycaemia after the initial hyperglycaemia has passed away. In some cases the hypoglycaemia is so profound as to cause symptoms like those of insulin overdosage. There is some evidence that the hypoglycaemia from glucose is dependent on an over-secretion of insulin. It is possible that dihydroxyacetone brings about hypoglycaemia in a similar fashion, although there is no evidence for this as yet.

(3) The liver is quite possibly concerned with the hypoglycaemia of dihydroxyacetone. Since the mechanism of the normal constant secretion of glucose into the blood by the liver is not known, the possible mechanism of this can only be vaguely conjectured. In our previous communication we put forward the tentative hypothesis that the extraordinarily high R.Q. following the administration of dihydroxyacetone was dependent on an increased tension of carbohydrate in the liver, an increase so great as not only to stop glyco-neogenesis out of fat and protein, but also to result in a considerable synthesis of fat. In the light of present knowledge it seems possible that a similar explanation may obtain in the case of the hypoglycaemic action

of this triose. Normally the cause for a greatly increased tension of carbohydrate in the liver is an excessive quantity of sugar of alimentary origin in the blood. Under these conditions it is possible that the hepatic secretion of blood-sugar ceases. When the tension of carbohydrate in the liver increases from any other cause, it is possible that an inhibition of the blood-sugar-secreting function of the liver ensues, which soon leads to hypoglycaemia, since the existing blood-sugar becomes rapidly used up.

In any case, there is no evidence for regarding the hypoglycaemic action of dihydroxyacetone in man as other than an adventitious one, being in this regard similar to glucose. It is therefore not dependent on any anti-diabetic qualities that the substance may possess. This viewpoint is in harmony with the fact that neither anti-diabetic nor hypoglycaemic functions of the triose have been demonstrable in the lower animals.

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