Effect of Carbutamide on Blood Levels of Glucose, Potassium and Inorganic Phosphate

Studies of the Serum in Diabetic and Healthy Man and Pancreatectomized Dogs

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I

Of the hormones influencing carbohydrate metabolism insulin, some steroids of the adrenal cortex,[1] and, according to some workers, adrenalin[2] bring forth an increase in K-level of the serum. It has been suggested in the literature that decrease in the K-level of the serum following insulin is partly due to enhanced glycogen synthesis in the liver and musculature, partly to increased sugar utilization.

In previous publications[3] the authors have presented evidence of the hypoglycemic effect of carbutamide* in diabetic subjects, and a favorable therapeutic response was seen in 71 per cent of our patients. This investigation was undertaken to determine whether the blood sugar changes occurring as an effect of carbutamide would be accompanied by changes in ion metabolism similar to those following hypoglycemia caused by insulin.

METHODS

After determination of an initial fasting blood sugar, serum-K and inorganic-P, the subjects were given 3 gm. Nadisan (carbutamide) per os, and these same determinations were repeated at 30, 60, 120, 180 and 240-minute intervals. The patients fasted throughout the examination. Blood glucose was determined according to the method of Schmör,[4] serum-K by the flame-photometer and serum-P by the Fiske-Subbarow methods.[5]

Carbutamide was considered effective if the fall of the blood sugar exceeded 20 per cent of the fasting value.[3] The change in serum-K level was considered significant if it was greater than 10 per cent of the control level, since it has been established previously in healthy individuals that the spontaneous serum-K level variation in four hours is within the ±10 per cent limit.

Our material was divided into three groups: 1. Twenty diabetics who responded to carbutamide. 2. Ten diabetics who showed no significant hypoglycemic response to carbutamide. 3. Control group of twenty patients with no demonstrable abnormality of carbohydrate metabolism.

RESULTS

In each of the twenty patients responding to carbutamide blood sugar fell over 20 per cent, as demonstrated by figure 1.

Serum-K determinations in seventeen of the twenty patients revealed decreases of more than 10 per cent. Decrease of the serum-K level paralleled the blood sugar fall.

There was not a single case among the ten unresponsive diabetics of a clinically effective, i.e., more than 20 per cent, blood sugar fall. The majority of this group consisted of young diabetics of the labile type (figure 3).

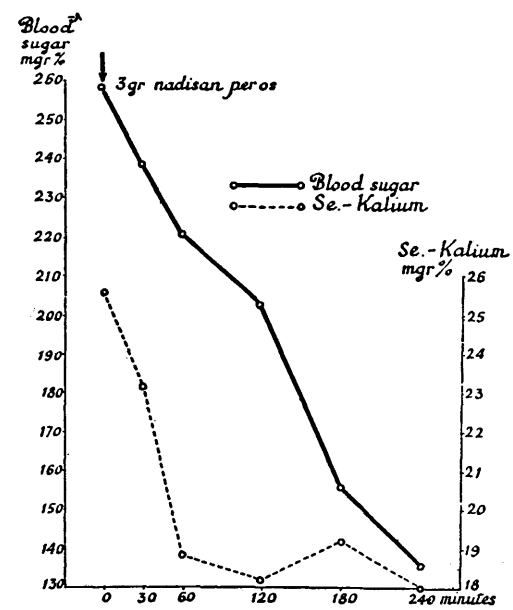

FIG. 1. Blood sugar and serum potassium change in diabetic patient responding well to Nadisan.

* BZ-55 (Nadisan or carbutamide).

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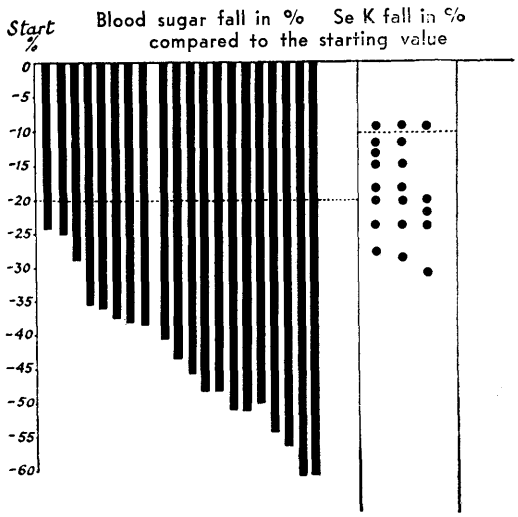

FIG. 2. Diabetic patients responding to Nadisan.

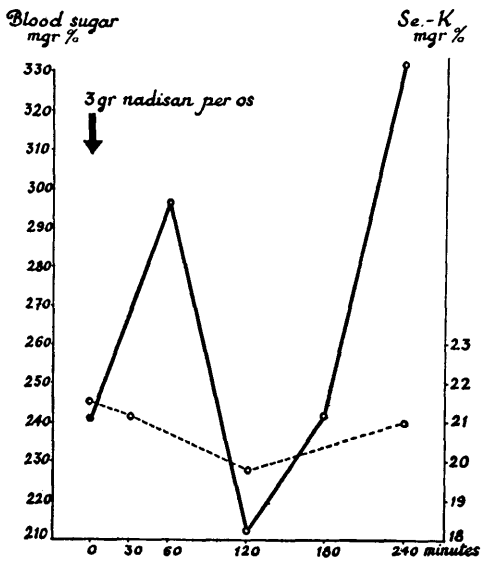

FIG. 3. Blood sugar and serum potassium change in a diabetic patient not responding to Nadisan.

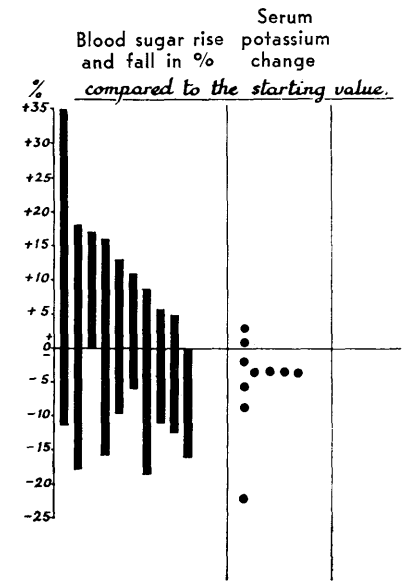

FIG. 4. Diabetic patients not responding to Nadisan.

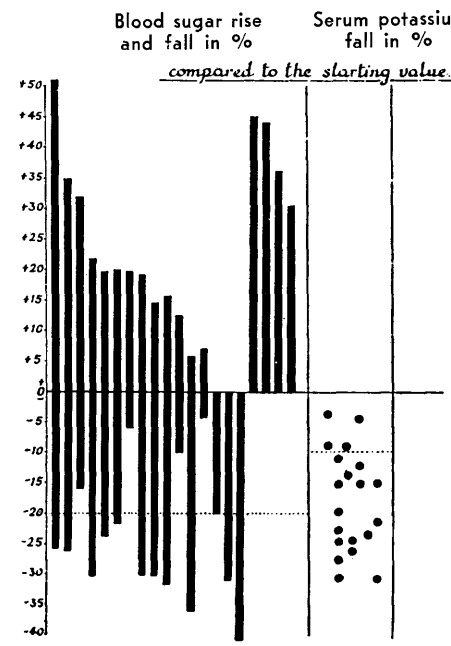

FIG. 5. Normal group.

There was no significant change in the serum-K level of these patients, as illustrated by figure 4. One case excepted, the fluctuation remained within the 10 per cent limit.

In the control group of twenty patients with normal carbohydrate metabolism, the blood glucose showed extreme fluctuation (figure 5) preceded by an initial rise; in others the initial blood sugar decrease was followed by a rise above the fasting level.

A prolonged decrease of blood glucose was seen in only three cases of the twenty experiments. Clinical hypoglycemia was not observed in any of the cases. While blood glucose decrease becomes more marked in responsive diabetic patients from hour to hour, the fluctuating blood glucose level in the normal subject suggests increased activity of the blood glucose regulating system. The serum-K level behaves like that of the responsive diabetic patients. As can be seen in figure 5,

the fall of serum-K exceeds 10 per cent in seventeen cases out of twenty.

Simultaneous serum inorganic-P determinations in all three groups showed no significant changes corresponding to the fluctuation of the blood glucose and serum-K levels.

DISCUSSION

Mohnike and Bibergeil[6] formerly reported changes of serum-K and inorganic-P occurring after administration of D-860 in the normal dog. In their experiments there was a parallel decrease in both serum-K and blood sugar; on the other hand, serum-P significantly rose after an initial fall. As is known from numerous publications[7-9] K is required for glycogen synthesis. Animal experiments of several workers [10-12] demonstrated that both carbutamide and tolbutamide increase the glycogen content of the liver. In patients responding to carbutamide, parallel decreases in serum-K and blood glucose might be explained by increased glycogen synthesis in the liver and subsequent glycogen deposition. It appears that in unresponsive diabetic subjects this glycogen synthesis in the liver is not increased enough to produce serum-K decrease. Serum-K decrease in normal individuals may be similarly explained by enhanced glycogen formation, despite the marked fluctuation of the blood sugar level after oral carbutamide, for which supposedly an increased compensating reaction of the adrenal may be responsible. It has been demonstrated in animals[13,14] that after substantial doses of sulfonylurea and IPTD, a pronounced hyperglycemia occurs which can be prevented by adrenalectomy. It is postulated that a similar mechanism is responsible for the failure to show a sustained decrease in blood glucose levels in the intact, nondiabetic human.

There was no change in the serum inorganic-P level in any group. This suggests that peripheral glucose utilization is not increased by the administration of Nadisan in the dose employed by us.

II

In the following an attempt has been made to elucidate what sort of changes do occur in blood sugar, serum-K and P after carbutamide administration in an organism deprived of endogenous insulin by pancreatectomy.

METHODS

Our experiments were performed on totally pancreatectomized dogs of 7 to 10 kg. body weight. Following operation the animals were maintained on a free diet and crystalline insulin. The experiments were performed at least two to three weeks following the operation. The animals obtained the last insulin dose forty-eight hours prior to the experiment and in addition were fasted for eighteen hours. After determination of fasting blood sugar, serum-K and P, 0.5 gm./kg. body weight of carbutamide was given intravenously. At intervals of 30, 60, 120, 180 and 240 minutes, samples of blood for glucose, inorganic serum-K, and -P determinations were taken. The animals were fasting throughout the experiments. Blood sugar was determined by the method of Somogyi, serum-K with a flame photometer and serum inorganic-P by the Fiske-Subbarow procedure.

RESULTS

Altogether sixteen experiments were performed on eight totally pancreatectomized dogs. Figure 7 illustrates the range of variation of blood sugar and serum-K expressed as per cent of the initial values. As can be seen, a significant blood sugar fall occurred six times; there was no change at all in six experiments, and in four there was a pronounced rise of blood sugar. The values shown in the blood sugar curve in figure 8 represent an average of all sixteen experiments; a successive decrease of blood sugar lasting until the fourth hour is seen, but this change does not appear to be statistically significant ($p>0.1$).

The effect of intravenous carbutamide on serum-K is shown in figure 7. In all but two cases a decrease is noted. A statistically significant decrease in the serum-K is seen to reach a minimum value in the fourth hour in figure 8 ($p<0.02$). The gradual rise of serum inorganic-P shown in figure 8 is statistically significant ($p<0.05$).

DISCUSSION

The experimental data here presented on diabetic and normal persons and pancreatectomized dogs tend to support the hypotheses stated in the literature that carbutamide increases glycogen synthesis in the liver but has no effect on peripheral glucose utilization.

In the mild type of diabetes mellitus, the secretion of endogenous insulin is not sufficient to maintain adequate carbohydrate metabolism. By means of mechanisms not yet elucidated, carbutamide, in the presence of endogenous insulin,[15,16] stimulates glycogen formation in the liver. As a consequence, glycosuria is diminished, resulting in amelioration of the diabetic symptoms. The endogenous insulin is needed not for the stimulation of glycogen synthesis but rather to maintain peripheral sugar utilization.

Our experiments are in accord with this hypothesis. The decrease of serum-K after the intravenous administra-

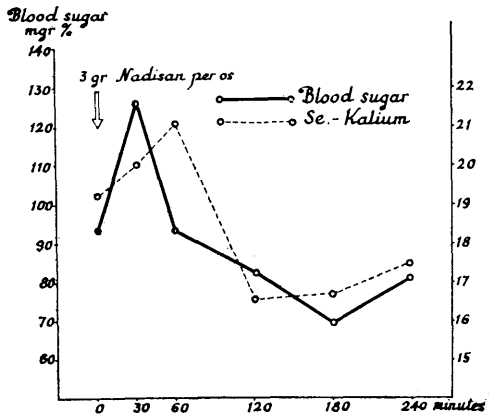

FIG. 6. Blood sugar and serum potassium change on effect of Nadisan in a normal individual.

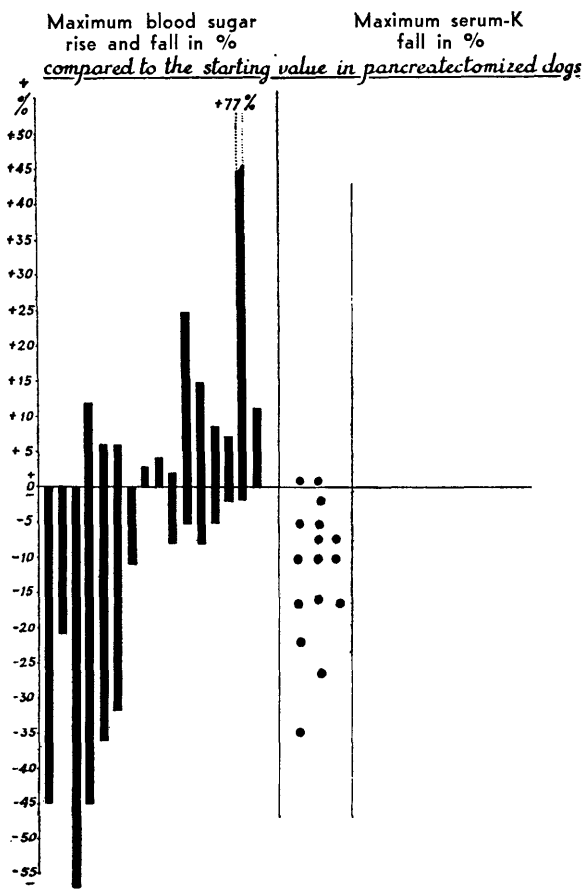

FIGURE 7

tion of carbutamide in the pancreatectomized dogs suggests that there is a stimulus to deposition of glycogen, insufficient, however, to maintain the animal in carbohydrate balance. As can be seen in figure 8, there is some decrease in the blood sugar level of the animals,

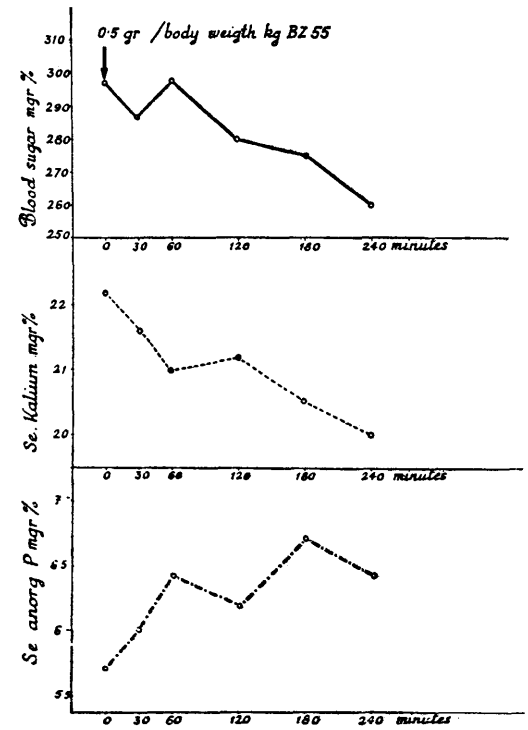

FIG. 8. Blood sugar, serum potassium and serum inorganic phosphorus change on effect of carbutamide in pancreatectomized dogs.

but since there is no peripheral utilization of glucose, suggested by the increasing inorganic-P levels, the organism progresses to increasingly severe carbohydrate decompensation.

These observations would explain why insulin must be present in order to develop significant hypoglycemia after the administration of carbutamide.

This interpretation is supported by an event that occurred during the experiments. A dog was erroneously given his usual insulin dose immediately after intravenous administration of carbutamide. Even though the animal was fed, he succumbed to hypoglycemia in two hours.

SUMMARY

We believe our investigations show that carbutamide, through its effect on glycogen synthesis, is able to maintain an organism in carbohydrate balance if the organism is producing some endogenous insulin. In the absence of this, i.e., the pancreatectomized subject, the help afforded by increased glycogen formation is far from sufficient, as peripheral sugar utilization is not affected by carbutamide. Thus the sulfonylureas, even though they are able to stimulate glycogen synthesis in the absence of insulin, are not effective in preventing ultimate diabetic coma unless insulin is also present.

SUMMARIO IN INTERLINGUA

Le Effecto Acute De Carbutamido Super Le Nivellos De Glucosa, Kalium, E Phosphoro Inorganic In Le Sero De Individuos Diabetic E Normal E De Canes Pancreatectomisate

Nos crede que nostre investigationes ha monstrate que carbutamido, per su effecto super le synthese de glycogeno, es capace a mantener un organismo in equilibrio carbohydratic, providite que le organismo produce un certe quantitate de insulina endogene. In le absentia de isto—i.e. in le individuo pancreatectomisate—le succurso representate per un augmento del formation de glycogeno remane nettemente insufficiente, proque le utilisation peripheric de sucro non es afficite per carbutamido. Assi le sulfonylureas—ben que illos es capace a stimular le synthese de glycogeno in le absentia de insulina—non es efficace in prevenir un ultime coma diabetic, excepte in caso que insulina es etiam presente.

ACKNOWLEDGMENT

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The Use of Isotopic Tracers in Estimating Rates of Metabolic Reactions

Since the introduction of practical methods for the production and measurement of substances containing isotopes of elements common in biological systems—such as hydrogen, carbon, nitrogen, and phosphorus—these have found expanding uses as "tracers" in biological systems. For the identification of intermediate compounds and the qualitative description of biochemical pathways and reaction mechanisms, they have allowed unprecedented advances; and some isotopically labeled substances also have been useful in analytical measurements—by the "isotope dilution" principle—of the quantities of material present or of their volumes of distribution in biological systems. A further type of use, of great potential importance theoretically, has often been attempted: by observation of the "movement" of labeled material to measure the absolute or relative *rate* of movement or of chemical transformation of unlabeled substance already present in the system. To the uninitiated in this field, this process would seem to be quite simple in principle. A substance containing a known quantity of the isotopic element would be introduced into the animal or surviving metabolizing system, and after a time one would find out how much of the isotope was present in a particular place or form. This might be feasible if one were dealing only with a single simple transfer of material from one "compartment" of known dimensions to another. In biological systems, however, this is very seldom the case. Instead, one finds that the transfer may be reversible; that what appears to be a simple transfer is in fact a series of reactions (some of them reversible, perhaps); that the substance introduced is itself being replaced with nonisotope material as fast as it is used; or that it can exchange with not one but many other forms. Hence the interpretation of rates of movement of the isotope in terms of the rates of movement of unlabeled materials is seldom simple and may be deceptively complicated.

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