and the other a young girl with juvenile, unstable diabetes of recent onset. The hypoglycemic capacity of the drug varied among the patients studied. The most striking response was obtained in the young patient. In the other two patients the responses were mild to moderate.

2. The lowering of blood and urinary sugar by carbutamide was not associated with any consistent changes in the number of circulating eosinophiles or the urinary excretion of reducing corticosteroids. Carbutamide did not appear to have any direct effect on nitrogen, sodium, potassium or water balances, or body weight. In one patient the administration of carbutamide was associated with retention of inorganic phosphorus.

3. The repeated administration of glucagon for several days produced more or less sharp, sustained rises in blood and urinary sugar and a fall in serum inorganic phosphorus. In the unstable patient, the hyperglycemia and glycosuria induced by glucagon was associated with negative nitrogen balance. Effect of glucagon on nitrogen balance was also seen in lesser degree in one of the stable patients. These results are in agreement with other studies on glucagon in our laboratory and will be reported later.

4. The blood sugar lowering effect of carbutamide could be quantitatively antagonized or counterbalanced by the administration of glucagon. Conversely, the blood sugar raising effect of glucagon could be quantitatively antagonized or counterbalanced by the administration of carbutamide. The capacity of glucagon to raise the blood sugar appeared to be diminished to a greater or less degree in the presence of carbutamide in the two patients in whom this effect was investigated. Inhibition was noncompetitive. This inhibitory effect of carbutamide appeared to be directly proportional to its blood sugar lowering capacity. While carbutamide markedly decreased the hyperglycemic and glycosuric response to glucagon in the unstable patient, it did not proportionately diminish the effects of glucagon on nitrogen balance and serum inorganic phosphorus.

5. In the patient with unstable diabetes carbutamide produced not only a marked lowering but a stabilization of the blood sugar levels. This stabilizing effect was also reflected in the levels of plasma inorganic phosphorus, sodium balance and Na:K ratio.

CONCLUSION

These preliminary studies are consistent with the reported experimental observations that carbutamide reduces hepatic glucose output.

Studies of the Mechanism of Action of Sulfonylurea Derivatives

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Since most of the presented experimental and clinical data are in print elsewhere,* only a brief summary will be given here. In addition, there appears in this issue a report of a joint project with Doctors Berson and Yalow of the Veterans Hospital, Bronx, New York, to which brief allusion was made during the symposium.

In the present study, no histologic changes of the pancreatic α cells of the rabbit were noted after oral or parenteral administration of hypoglycemic sulfonamides in various doses and over various periods of time. Degranulation of beta cells was observed after prolonged Orinase treatment.

No inhibitory effect of the action of exogenous glucagon by the hypoglycemic sulfonamides could be demonstrated in acute experiments in rabbits and in man, normal as well as diabetic. The height and the duration of the glucagon hyperglycemia showed no significant differences when induced with or without pretreatment with sulfonylureas.

Adrenalectomized dogs responded to the drug with unusually severe and prolonged hypoglycemia, while cortisone-pretreated rabbits responded like normal rabbits, but a single daily dose of the drugs was not sufficient to control the cortisone induced hyperglycemia and glycosuria over a twenty-four hour period.

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* *Metabolism* 5:894-903, 1956.

No evidence of increased peripheral glucose utilization was found in man when the arteriovenous blood sugar difference was estimated after a glucose meal before and after sulfonylurea medication.

Clinically, generally satisfactory results were obtained in a group of twelve elderly diabetics treated over prolonged periods of time. It appeared that carbutamide was slightly more effective than tolbutamide when equal doses were employed. Only minor and transitory side effects of carbutamide were noted. In general, not more than 20 to 25 units of insulin per day could be replaced by the sulfonylurea derivatives.

The Effect of Sulfonylureas on the Rates of Metabolic Degradation of Insulin-I^{131} and Glucagon-I^{131} in Vivo and in Vitro

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Recent studies on the hypoglycemic action of various sulfonylureas have not elucidated the mechanism by which their action is effected. However, the absent or diminished response of the blood sugar to these agents in the pancreatectomized or completely alloxan-diabetic animal has suggested that the hypoglycemic effect may be mediated through inhibition of insulin destruction or stimulation of insulin secretion. The possibility of an influence on glucagon secretion or glucagon degradation has also not been excluded. The present study was designed to evaluate the effect of the sulfonylureas on the rates of metabolic degradation of I^{131} labeled insulin and glucagon.**

METHODS

The preparation of the I^{131} labeled hormones, and the evaluation of alterations induced during preparation have been discussed in detail in previous communications.[1, 2, 3] A small moiety of the labeled hormones is frequently damaged, by irradiation or through other causes, and binds to serum proteins so that it leaves the blood stream less rapidly than the unaltered labeled hormone.[1, 2, 3] Since the fraction altered varies with each preparation, experimental and control studies were performed simultaneously with every lot of labeled hormone, with a single exception noted below. In vivo studies were performed in rabbits fasted for about eighteen hours; in vitro studies were carried out with rat liver homogenates. Equivalent doses of insulin–I^{131} or glucagon–I^{131} were administered intravenously to control rabbits and to sulfonylurea-treated rabbits and its disappearance from the blood stream was followed by an assay of radioactivity in washed trichloracetic acid precipitates of the plasma. The labeled hormones were given three to four hours after oral administration of 1-butyl, 3-p-aminobenzene sulfonylurea (BZ-55, U6987)* or 1-butyl, 3-p-tolylsulfonylurea (U-2043, D860, Orinase) or one to two and one-half hours following the intravenous administration of the sodium salt of Orinase (U7064). Both BZ-55 and Orinase† (orally and intravenously) were used in the insulin–I^{131} experiments but only Orinase sodium (intravenously) was employed in the glucagon I^{-131} studies.

The effect of Orinase sodium was tested on insulinase glucagonase and adrenocorticotropinase activity of rat liver homogenates at various concentrations of

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** We are indebted to Dr. O. K. Behrens and Dr. C. W. Pettinga of Eli Lilly and Company for a generous supply of crystalline regular insulin lot No. 535664 and to Dr. O. K. Behrens for a generous supply of crystalline glucagon.

* We are indebted to Dr. F. B. Peck, Sr., and Dr. W. R. Kirtley of Eli Lilly and Company for a generous supply of BZ-55.

† We are indebted to Dr. Cornelius J. O'Donovan of the Upjohn Company for a generous supply of Orinase.