Group Discussion

GEORGE E. ANDERSON, M.D., (*Brooklyn*): We observed a dog for seventy-two days on 250 mg. per kg. per day. There were no observable changes whatsoever in the islet cells, certainly none in the alpha cells. This corresponds with Dr. Goldner's findings.

A. E. RENOLD, M.D., (*Boston*): I was interested in Dr. Izzo's observations on prolonged glucagon administration. It was not quite clear when the last dose of glucagon was administered before the fasting blood sugar was done. I also wanted to ask whether or not you have given glucagon over prolonged periods of time as in studies on normal subjects. It seems to me perhaps a little questionable whether one can interpret rises in blood sugar as meaning exacerbation of the diabetic state when the glucosuria did not increase. Perhaps the glucosuria is a better indication of over-all diabetic control than just one blood sugar value after giving an agent which affects blood sugar per se.

JOSEPH L. IZZO, M.D., (*Rochester, New York*): The glucagon was given at 7 o'clock, and the blood sugar was taken at 8:30. The administration of 6 mg. of glucagon daily caused a change in blood sugar from 100-150 mg. to about 300 mg. The most interesting feature is that this person then instead of having little or no glucose output increased it to 60 or 80 gm. per day. In addition there was a change in nitrogen balance and a fall in plasma inorganic phosphorus. But the most significant finding is this consistent effect on nitrogen balance. Whether this is due to glucagon itself or to some impurities in the glucagon, I can't say at the present time.

As for your other question about experiments on normals—we plan to use normals as controls. One of the difficulties in interpreting experiments on glucagon in normal individuals is that glucagon stimulates the pancreas to secrete insulin because of the increase of the blood sugar. We wanted to study the effect of the drug where the central secretion did not compensate for rises in blood sugar. We were surprised that glucagon could have a marked effect on blood and urine sugar if there is presumably no compensatory secretion of insulin.

LAURANCE W. KINSELL, M.D., (*Oakland, California*): As an assumption, those patients who respond to sulfonamide also make insulin. Also by assumption they don't do quite a normal job of it; otherwise they wouldn't be diabetic. The fact that they do respond and are not in the proteinuric-ketonemic group means that unquestionably they make perhaps quite appreciable amounts of insulin. Second, as I recall your figures, your increases, with perhaps one exception, were in urinary sugar predominantly in those patients who initially had high levels of blood sugar.

FRANCIS D. W. LUKENS, M.D., (*Philadelphia*): Dr. Izzo, what diet did you put those patients on?

DR. IZZO: Diets of approximately 2,000 calories with 90 gm. of protein, 200 gm. of carbohydrate, and about 100 gm. of fat.

Effects of Sulfonylurea Drugs in Hospitalized Diabetic Patients

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The published literature available to us now (September, 1956) contains reports of at least 1,035 patients treated with the sulfonylurea compounds, and doubtless many times this number have actually received the drugs. As nearly as can be ascertained, all but thirty of these patients have been studied and evaluated by methods which are either incompletely described or, in our opinion, inadequate to permit valid conclusions as to the efficacy of the treatment. Unpublished reports presented at this symposium are not included in this survey.

Methods that are satisfactory for such studies include the use of patients with well-established diabetes of relatively remote onset, hospitalization (preferably on a metabolic ward), a sufficiently long fore-period to ensure a stabilized diabetic state, provision of a diet that maintains body weight, administration of the test substance when blood and urine sugars are fairly constant or rising, and the employment of changes in well-marked hyperglycemia and glycosuria rather than changes in the so-

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called insulin requirement as the criterion for judging the results of drug therapy.

The present study is concerned with the effects of carbutamide and tolbutamide in seven diabetic patients observed under conditions which as nearly as possible approximated those just described. Samples of blood for determination of glucose were obtained four times each day, and daily twenty-four-hour specimens of urine were collected for quantitative analysis. Dosage of the drugs was from 1.5 to 3 gm. daily, and blood sulfonamide levels in the cases in which they were determined were in the accepted therapeutic range of 15 to 20 mg. per 100 ml.

Results are shown in the accompanying table.

DISCUSSION

Of the seven patients studied, five would be expected to respond satisfactorily to drug therapy on the basis of earlier reports, i.e., they were obese, middle-aged or elderly individuals with mild to moderately severe diabetes of only a few years' duration. Of the five, two (cases 1 and 7) showed a partial response but insufficient for proper diabetic control without insulin; one (case 3) responded partially in the hospital but very well later on ambulatory management; one (case 5) had no response; and one (case 6) obtained a striking therapeutic result. Of the two patients in whom a favorable effect was not anticipated, one (case 4) was a juvenile diabetic whose condition was unchanged by the drugs and the other (case 2) was a patient with diabetes of sixteen years' duration which could not be properly controlled with drug therapy alone.

Hypoglycemia did not occur in any of these cases with drug alone. With two exceptions, no evidence of toxicity was found by the usual clinical and laboratory tests. In one patient (case 2) the white blood count was 5,750 per cu. mm. with 46 per cent granulocytes prior to treatment. After treatment with tolbutamide followed by carbutamide, the white blood count was 3,300 per cu. mm. with 29 per cent granulocytes. In a second patient under similar circumstances, the initial white blood count was 12,000 per cu. mm. A fall to 4,300 per cu. mm. was noted on treatment with carbutamide.

CONCLUSIONS

1. Carbutamide and tolbutamide have hypoglycemic activity in some but not all diabetic patients.

Summary of results in hospitalized patients

Case, age, sex, nutritional state	Duration diabetes (years)	Duration insulin therapy (years) usual dose (units)	Duration hospital observ. (days)	Insulin dose while on drugs (units)	Average blood sugar level (mg./100 cc.) Average daily urinary glucose (gm.) Control period	Drug period	Recovery period	Drug period	Remarks
(1), 36, F, obese	1	1 40	63	10	200 44	C* 160 12	200 34	T* 187 10	
(2), 70, F, obese	16	10-12 30-35	57	0	262 32	T 237 15	286 43	C 251 26	
(3), 68, M, obese	0.25	0	37	0	271 50	T 260 13	—	—	Urine became sugar-free and blood sugars normal on drug at home.
(4), 24, M, nor. wt.	5	4 45	54	45	199 34	C 241 58	—	T 206 50	On anti-convulsant drugs for mild epilepsy. No potentiation of barbiturates noted.
(5), 59, F, obese	1	0.6 25	17	0	149 0	C 160 0	—	—	Total adrenalectomy 1 year previously. Maintained on 50 mg. cortisone daily.
(6), 60, F, obese	4	4 50	90	0	365 61	T 120-140 0	280-300 9	C 120-140 0	
(7), 47, F, obese	1	2 days 10	56	0	311 50	T 282 18	287 23	—	On carbutamide at home. Urine is essentially sugar-free. Postprandial blood sugars, 198 and 172.

*C=carbutamide.
*T=tolbutamide.

2. Even among patients who, on the basis of previous reports, might be expected to respond favorably, the drugs are in some cases incapable of controlling diabetes adequately without injected insulin.

3. The results of clinical studies under carefully controlled conditions suggest that the usefulness of these preparations may be considerably more limited than was originally expected.

4. The occurrence of leukopenia in two patients of this group treated with carbutamide after receiving tolbutamide calls attention to the toxic potential of these drugs.

Observations in Diabetic Subjects Treated with Sulfonylurea Compounds

Stanley J. Talpers, M.D., Thomas Stanford Splitter, M.D.,† Roger Friskey, M.D.,‡ Frederick Brown, M.D.,§ Laurance W. Kinsell, M.D.,‖ Oakland, California*

This report summarizes some of the experience of members of the Institute for Metabolic Research with the oral hypoglycemic agents during the period January-October, 1956.

OUTPATIENT STUDIES

An initial group of twenty-eight patients was selected in March and April of 1956. None of these was an "ideal" diabetic in terms of precise adherence to a diet, etc. These patients, for the most part, were obese, middle-aged or elderly, nonketonuric, diabetic patients whose insulin dose varied from zero to forty units. As shown in figure 1, the average fasting blood sugar values were unchanged after insulin withdrawal. (Some of these data have been reported by Splitter et al.)[1] In only one patient was it necessary to resume insulin because of ketonuria and rising blood sugar. All but four of the patients in this group showed significant reduction in blood sugar values while on carbutamide or tolbutamide. A mild granulocytopenia in one patient while under carbutamide therapy was the only side effect noted. Hypoglycemic episodes were not encountered, nor have patients become unresponsive to the drug.

The second group of thirty-two patients included five "unstable diabetics." These five and three others have failed to respond to sulfonylurea therapy (figure 2). Withdrawal of insulin for four weeks prior to oral *treatment produced little change in average fasting*

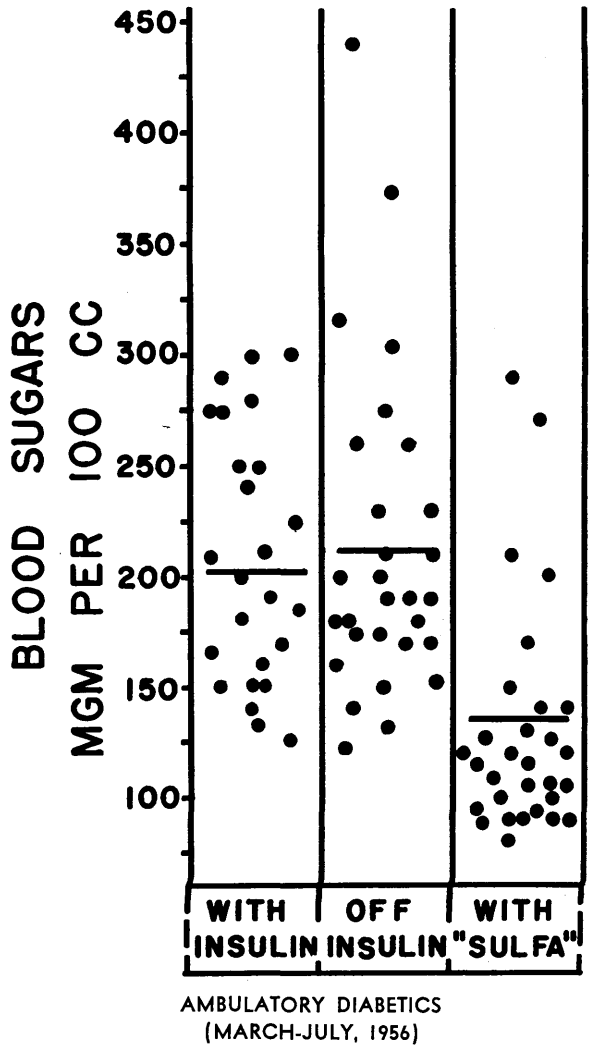

FIG. 1. Fasting blood sugar determination in twenty-eight ambulatory diabetics (a) during treatment with insulin, (b) following cessation of insulin therapy and (c) during sulfonylurea therapy.

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