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

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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*

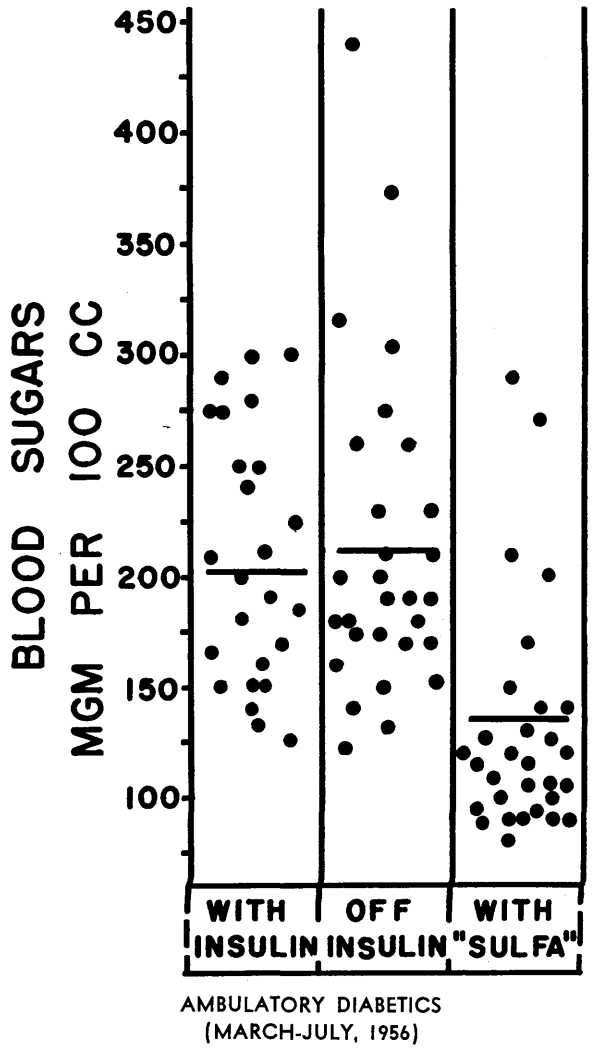

FIG. 1. Fasting blood sugar determination in twenty-eight ambulatory diabetics (a) during treatment with insulin, (b) following cessation of insulin therapy and (c) during sulfonylurea therapy.

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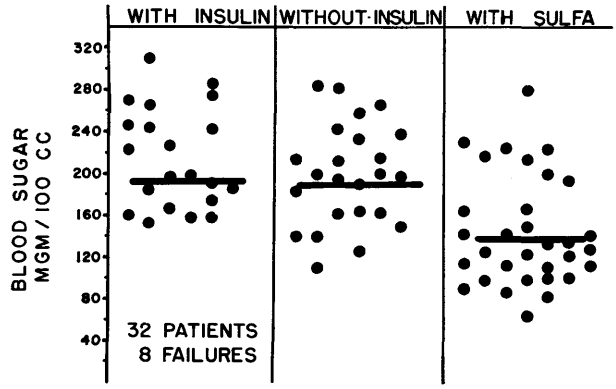

FIG. 2. Fasting blood sugar determination in thirty-two ambulatory diabetics with and without insulin and with sulfonylurea.

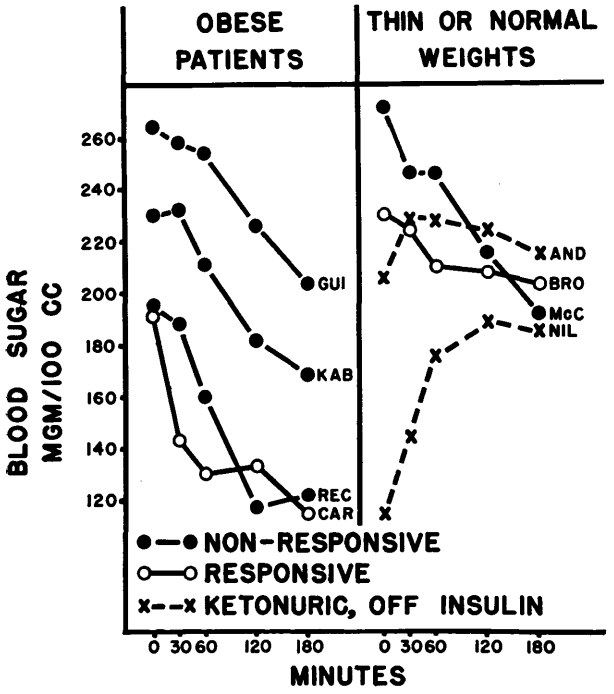

FIG. 3. Representative responses (in fasting state) to 2 gm. of sodium Orinase administered intravenously in eight diabetic patients.

blood sugar values. Dosage for patients in this group varied from 0.5 to 3.0 gm. per day, usually in one morning dose.

Side effects in this group have been minimal. There have been no rashes or drug fevers. One patient has noted desquamation of one palm.

In both groups we have been puzzled by the occasional nonketonuric diabetic who fails to respond to sulfonylurea treatment. For that reason, we have attempted to "screen" patients by administering sodium tolbutamide intravenously. A three-hour test, using 2 gm. of sodium

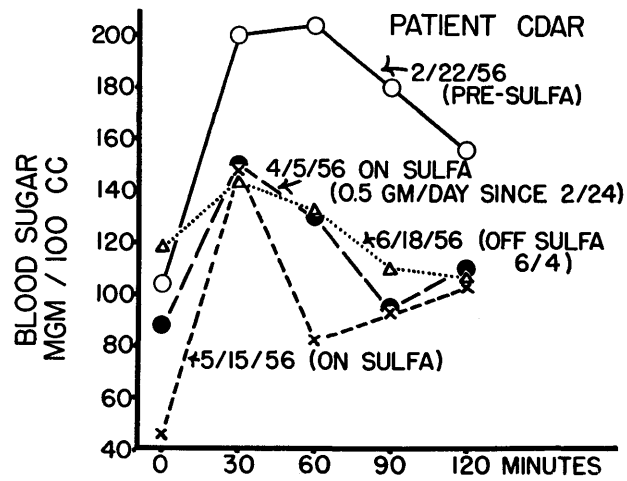

FIG. 4. Normalization of glucose tolerance in response to sulfonylurea therapy in an early juvenile diabetic.

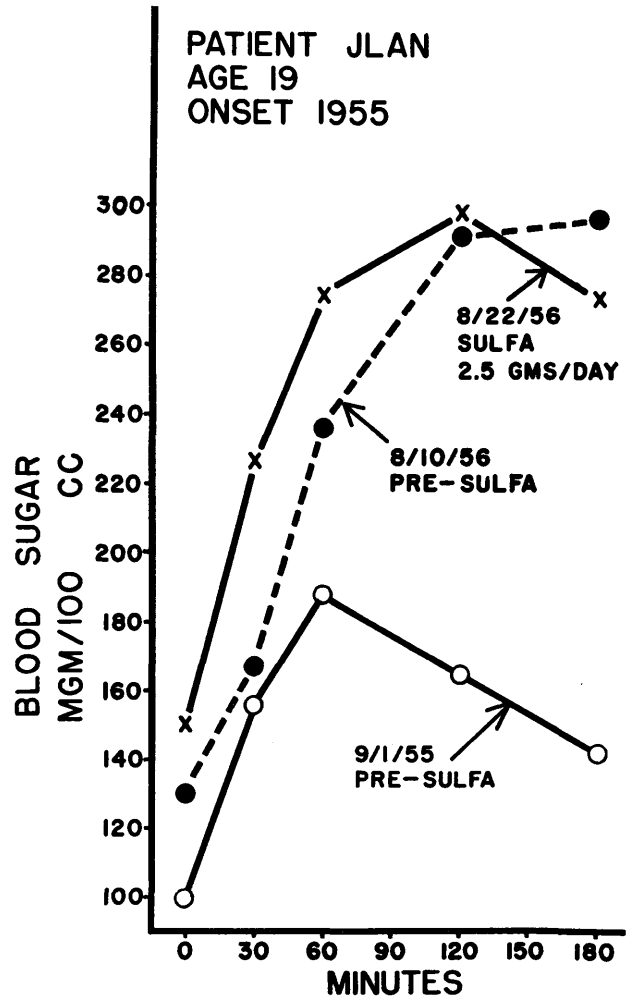

FIG. 5. Lack of response to sulfonylurea in a juvenile diabetic (duration of the disease more than one year).

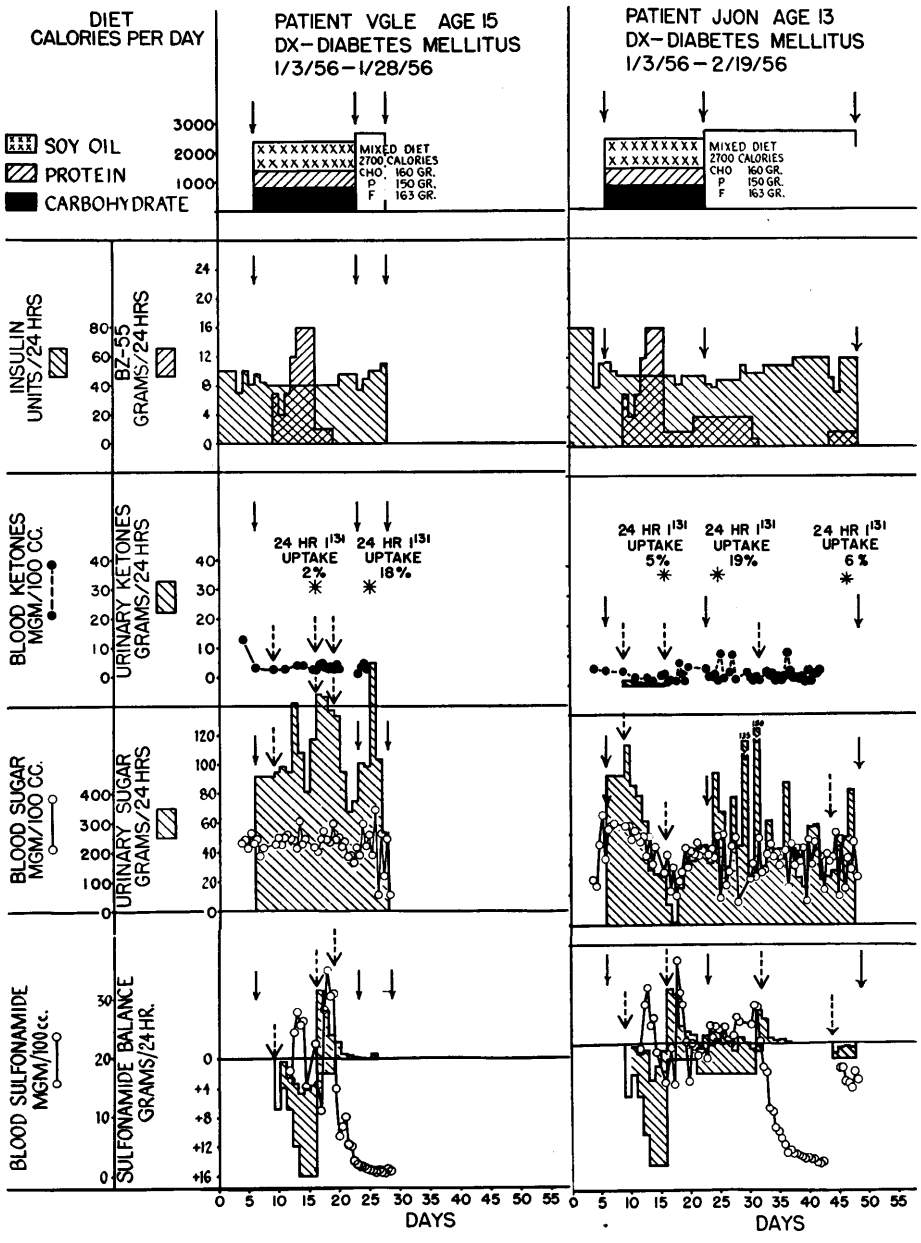

FIG. 6. Effects of massive carbutamide administration to unstable juvenile diabetics, age 13 and 15.

tolbutamide, has been performed on twenty patients. Figure 3 shows some representative results. Except for "ketonuric diabetics" it is apparent that the three-hour intravenous test will not separate responsive from non-responsive patients.

The juvenile diabetic is reported to be usually unresponsive to sulfonylurea therapy. In figure 4 are shown glucose tolerance curves in a child with "preclinical" diabetes. Glycosuria was noted in a routine urinalysis in February 1955. Glucose tolerance at that time was grossly abnormal. He was placed on a high protein, high fat diet, and observed until February 1956. Glucose tolerance at this time was still grossly abnormal. Response to carbutamide is shown. In June 1956, it was necessary to discontinue therapy temporarily because of the appearance of hypoglycemic symptoms. He is presently satisfactorily maintained on 250 mg. every other day.

In contrast to this patient, figure 5 shows glucose tolerance curves of a nineteen-year-old college student with progressive diabetes of one year's duration in whom a dose of 2.5 gm. of carbutamide per day was ineffective.

METABOLIC WARD STUDIES

Two juvenile diabetics (previously reported[2]) age 13 and 15, were studied on the metabolic ward simultaneously. The degree of severity of their diabetes was similar and their programs were identical in a quantitative chemical sense. Insulin was gradually withdrawn until both were spilling approximately 100 gm. of urinary sugar per day. Carbutamide was then added in doses ultimately reaching 16 gm. per day. Figure 6 shows the results in both boys. The first was responsive to the large dosage used. The second showed increased glycosuria without a concomitant increase in blood sugar, suggesting a renal effect. During this study it was noted that the responsive youngster was excreting the carbutamide mostly in the acetylated form, in contrast to the nonresponsive boy in whom the major portion of the drug was present in the free form. Further studies which we hope will throw light on this variation are in progress.

SUMMARY

We have reported some of our experiences with two oral sulfonylurea compounds in sixty ambulatory diabetics. The drugs were effective in approximately 75 to 80 per cent of the cases and side effects were not a serious problem. Initial experiences with an intravenous sodium tolbutamide response test suggest that it is of little value in predicting which patients will be responsive.

The diabetic glucose tolerance test of one nine-year-old boy was changed to normal by small doses of carbutamide. In another juvenile there was no change in the curve while on the drug. Balance studies in two hospitalized diabetics were paradoxical in that, while on identical programs one youth was responsive, the other, unresponsive.

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Sudden Death in a Diabetic Subject During Treatment with BZ-55 (Carbutamide)

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Sulfonylurea derivatives have been recently introduced as antidiabetic agents.[1-4] The drugs are receiving wide clinical trial, and to date reports of toxicity have been limited to several cases of drug rashes[3] and two cases of neutropenia.[5, 6] We recently observed a patient who died suddenly while on a sulfonylurea compound, (N_1-sulfanilyl-N_2-n-butyl-carbamide, BZ-55, carbutamide). Autopsy disclosed lesions similar to those reported previously in association with drug toxicity.[7-10] In view of the interest in these new agents the following case is reported in detail.

CASE REPORT

F.W., Number 5337, a forty-eight-year-old colored female domestic, was admitted to the Clinical Center on Feb. 24, 1956, for study of periodontal disease and diabetes. Diabetes had been discovered in 1954 and had been controlled with 10 to 15 units of insulin and a 1,200 calorie diet for eight months. At that time, one year prior to admission, she discontinued insulin because "injections were raising knots in my skin." Thereafter, except for some pruritus which she associated with dietary excess, the patient had no symptoms attributable to diabetes. There was a positive family history for diabetes.

Past history and review of symptoms were unremarkable except for history of moderate to excessive intake of alcohol.

Physical examination on admission revealed a moderately obese colored female in no distress. Blood pressure was 140/84, pulse 88 and temperature normal. Funduscopic examination revealed some "silver wire" changes in the arterioles but was otherwise normal. Mouth showed partial edentia, gingivitis and periodontal disease. The tongue was deviated to the right. There was no goiter. The lungs were clear to percussion and auscultation, and the heart was normal. There were no organs or masses palpable in the abdomen. Examination of the extremities and neurologic examination were within normal limits.

Laboratory findings were hemoglobin 12.7 gm. per 100 ml., white count 4,100 cells per mm^3, differential count was 43 per cent polymorphonuclear cells, 54 per cent lymphocytes, 1 per cent monocytes and 2 per cent eosinophiles. Urinalysis revealed a specific gravity of 1.017, no albumin, 1+ sugar

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