Clinical Experience with Carbutamide (BZ-55)

A Progress Report

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From December 1955, through August 1956, we used sulfonylurea compounds in 620 patients with diabetes. Of this number 380 received BZ-55, 230 were given Orinase and 10 SPTD (sulfapropylthiodiazole). In the present paper our experience with BZ-55 alone is reported. This is in the nature of a progress report; a more complete and detailed presentation of results will be made at a later date.

Among the 380 who have received BZ-55, 187 patients, including 101 of fifteen years of age and under, were studied only following a single administration of the drug in the course of a response test (see below). The remainder, 193 patients, was observed while being maintained on BZ-55. Of these, in sixteen cases the period of observation was insufficient, in twenty-four the drug was discontinued because of complications and in three the preparation was stopped for other reasons. The results in the remaining 150 patients form the basis of the present discussion. These patients have been maintained on BZ-55 for periods varying from less than one month (thirty-one cases) to more than six months (twenty cases).

Of the 150 patients, 66 were males and 84 females. Most of them (116, or 77 per cent) were between the ages of 40 and 70 years; 14 were under 40 and 20 over 70. Diabetes had been present in 42 (28 per cent) of the group for 10 to 20 years; in 99 (66 per cent) the duration was under 10 years and in 9 (6 per cent) over 20 years. Of the 150 patients, 65 had never received insulin and 75 had been taking less than 40 units daily.

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RESPONSE TEST

It has become our practice not to administer the drug without first carrying out a four-hour response test following the procedure listed below:

1. In patients requiring insulin, either omit insulin or give only crystalline insulin in the forty-eight hours preceding the test.
2. Omit insulin and breakfast on the day of the test.
3. Determine the blood sugar in the fasting state.
4. Give 3.0 gm. of BZ-55 orally.
5. Determine the blood sugar four hours after giving the drug.

In many patients the blood sugar was determined also at two, six and eight hours after the administration of BZ-55, but experience has shown that the four-hour value is the most helpful. In interpreting the results we have regarded a fall in blood sugar of more than 20 per cent as a good response. A decrease of 20 per cent or less has been rated as unsatisfactory. In general the results of the response tests have served a good, although by no means infallible, guide as to whether satisfactory control of blood sugar might be anticipated with maintenance of the patient on the preparation. As may be seen in table 1, of forty-eight patients with a good response test, forty-one achieved good, and five fair, control of blood sugar and glycosuria in long-term maintenance studies. On the other hand, of thirteen patients with a poor response test, nine had poor control in maintenance trials. It must be admitted that occasionally patients are encountered who achieve good control in maintenance studies despite a poor outcome during a response test. Furthermore, some patients who show little or no benefit from the drug at first may, after a period of time, experience good control of blood sugar and glycosuria, particularly if some complication such as an infection, has been overcome.

MAINTENANCE STUDIES

Methods. The maintenance studies were initiated both with patients in the hospital and with those seen as outpatients. Insulin was almost invariably stopped although in certain cases reduction in dosage was carried out gradually. In only seven patients was insulin given regularly in reduced dosage along with BZ-55. The usual sequence of study was as follows: (a) if the patient had

been treated with a depot insulin, this variety was discontinued and either no insulin or only crystalline insulin was given for two to five days; (b) a response test was performed; (c) if this was positive, then an attempt was made to control hyperglycemia and glycosuria with BZ-55 alone. The dosage of BZ-55 usually was 3 gm. daily for two or three days and finally 0.5 to 1.5 gm. daily thereafter. Attempt was made to keep the amount down to 0.5 to 1.0 gm. daily. Usually the entire dosage was given before breakfast. The diet was kept at a constant level throughout the period of study; in the adult patients, this consisted usually of 150 to 190 gm. of carbohydrate, 70 to 90 gm. of protein and 60 to 80 gm. of fat, yielding from 1500 to 1900 calories daily.

In hospitalized patients the amount of sugar excreted in the urine in twenty-four hours was determined daily and qualitative tests made before each meal. Frequent determinations of the blood sugar were made before each of the three meals.

With outpatients living at home, attempts were made to have the urine tested qualitatively before each meal although complete cooperation in this regard often was not secured. Patients were seen at intervals of one to two weeks at first, and later at monthly intervals so that determinations of the blood sugar could be made and the physical status of the patient evaluated.

The degree of control obtained during maintenance studies was classified as "good," "fair," or "poor" according to the standards outlined in table 2. In practice, the most commonly used criteria were as follows: If in a given case, 70 per cent of blood sugar ("true glucose") values were 110 mg. per 100 ml. or below either in the fasting state or three hours after a meal, and if the twenty-four-hour specimen of urine contained 2 gm. or less of sugar, then "good" control was judged to have been secured. If the corresponding values were 130 mg. per 100 ml. and 5 gm. for blood sugar and urine sugar, respectively, then the degree of control was classed as "fair."

Results. Using the standards outlined in table 2, the results of maintenance studies in the 150 patients were classified as shown in table 3. It must be pointed out that, with seven exceptions, patients were maintained *on BZ-55 alone, without the use of insulin.*

It is evident that in 86, or 57 per cent, good control and in 18 patients, or 12 per cent, fair control, was obtained. In 41 patients, 31 per cent of the total, poor results followed the use of BZ-55.

After satisfactory control of hyperglycemia and glycosuria had been secured for two months or more, in twenty-six cases BZ-55 was discontinued and studies carried on as before in order to determine whether or not the beneficial effect had been due simply to long-continued dietary control alone. It was found that in 16 of the 26 cases, it was necessary to resume BZ-55 because of rising blood sugar values and return of glycosuria.

In ninety-three patients white blood counts were done *at various times during the administration of BZ-55; no instance of leucopenia was encountered. Eosinophilia* occurred in one patient. In seventeen patients red blood counts, in forty-six cases blood hemoglobin determinations and in thirty-five cases blood platelet counts were carried out; the results were uniformly normal except in one patient who developed a well-marked anemia.

In eighty-seven patients the blood level of BZ-55 (expressed as sulfanilamide) was determined. In patients

TABLE 1

Comparison of response test with results of treatment up to nine months

BZ-55 response test		Clinical control		
Results	Patients (no.)	Good	Fair	Poor
Good	48	41	5	2
Poor	13	1	3	9
	61	42	8	11

TABLE 2

Standards of control*

	Degree of control†				
	Good		Fair		Poor
Relation to food	Blood sugar‡ mg./100 ml.	Urine sugar per cent	Blood sugar‡ mg./100 ml.	Urine sugar per cent	All other cases
Fasting	110	Trace	130	0.1	
1 hr. P.C.	150	0.3	180	0.5	
2 hr. P.C.	130	0.1	150	0.3	
3 hr. P.C.	110	Trace	130	0.1	
Urine sugar in 24 hr.	2 gm. or less		5 gm. or less		

* For purpose of classification as to degree of control, 70 per cent or more of values must conform with standards listed in the table.

† These standard values are the highest acceptable.

‡ Glucose as determined by the Somogyi-Nelson procedure.

TABLE 3

Degree of control of diabetes obtained with BZ-55

Control	Patients	
	Number	Per cent
Good	86	57
Fair	18	12
Poor	46	31
	150	100

responsive to the drug as regards blood sugar, blood sulfanilamide levels in the range of 8 to 12 mg. per 100 ml. were found effective. However, similar blood levels were obtained in individuals not responsive to BZ-55.

SEQUELAE

In 26 or 9.2 per cent of 279 patients receiving BZ-55 (380 patients less 101 children who had a response test only), untoward effects or sequelae were observed. These are listed in table 4.

TABLE 4

Sequelae in 279 patients on BZ-55 (excludes 101 children with response test only)

Skin rash	15	Diarrhea	2
Jaundice	4	Disorientation	1
Hypoglycemia	2	Cer. vasc. accid.	2
Anemia	1	Par. auric. tach.	1
Nausea with or without vomiting	5	Total	33

33 sequelae in 26 patients or 9.2 per cent

A skin eruption occurred in fifteen patients. The most common form was a measles-like rash affecting particularly the body but occasionally the face. In some instances only a generalized erythema was seen, but often the eruption was elevated. The rash was in some cases accompanied by fever as high as 103° F. In only a few patients did itching occur. In two patients, enlargement of lymph nodes preceded the onset of fever and skin eruption. With these symptoms general malaise and nausea often were present. Unfortunately, in almost every patient who developed a skin eruption, it was found that the patient was also receiving other medication, including multivitamin preparations and, in some cases, barbiturates and antibiotics. Antihistaminics were, in general, ineffective in treatment of the rash.

Jaundice occurred in four patients. In two it was mild and of short duration. In one of these patients, carcinoma of the prostate was under treatment. In these two cases, possibly the jaundice had no relation to the drug. In the third case of jaundice, BZ-55 had been taken for two weeks. When the patient returned for observation he had fever and a generalized skin eruption together with jaundice. He had been given by other physicians Terramycin®, methamphetamine, Chlor-Trimeton®, ascorbic acid, salicilamide and Coricidin Forte®. The jaundice persisted and only after two months was the urine found free of bile. In this case a biopsy of the liver revealed areas of necrosis of the central type with marked bile stasis. In the fourth case, a woman aged fifty-eight years with mild diabetes of some ten years' duration, BZ-55 was begun at her own request. Loss of appetite, weakness and jaundice appeared in the fourth week and she noted swollen cervical nodes at the onset of the illness. In her case as in the third case of jaundice, a high serum alkaline phosphatase level, with little alteration in the cephalin flocculation and other liver function tests, was observed. She had no fever and her progress seemed satisfactory until suddenly she became comatose; a severe hemolytic anemia developed, although no anemia had been present on admission to the hospital several days previously. Death occurred suddenly. The post-mortem examination, which was complete and included the brain, showed two important findings. The liver presented general hepatitis without any cholangitis. The hepatitis was characterized by multiple areas of necrosis with marked bile stasis. The kidneys showed a typical bilirubin nephrosis of such degree that in the opinion of the pathologist, kidney failure might well have been the chief cause of death. In addition there was a mild degree of chronic vascular nephritis.

Severe *hypoglycemia* occurred twice. In one man, despite persistence for forty-eight hours, recovery took place. Another man who had received BZ-55 in dosage of 3 gm. for the first six days and 2 gm. on the last day, developed hypoglycemia with a blood sugar as low as 38 mg. per 100 ml. Following omission of the drug for two days, the blood sugar rose to 246 mg. per 100 ml. BZ-55 was then resumed and good control was obtained with 2.0 gm. daily. On the twelfth day severe diarrhea began. On the fourteenth day a blood sugar of 46 mg. per 100 ml. was observed. The drug was then omitted again although only 1.0 gm. per day was being given at this time. The next day the blood sugar reached levels of 164 and 171 mg. per 100 ml. but two days later the patient died, probably because of myocardial failure. Permission for autopsy was not obtained.

In one patient a severe *anemia* was observed together with malaise and grippe-like symptoms. Recovery was uneventful. *Nausea* with or without *vomiting* occurred in five cases and *diarrhea* in two. In one elderly woman, eighty years of age, a period of *disorientation* was observed when the blood sulfanilamide level reached 21 mg. per cent.

Certain complications occurring in patients receiving BZ-55 were most likely not related to the administration of the drug. Thus, in two cases *cerebrovascular accidents* occurred; recovery was rapid in one, but the second patient was an elderly woman with hypertension of

long duration and death followed what seemed a typical cerebral hemorrhage. In one patient *paroxysmal auricular tachycardia* occurred with good recovery.

SUMMARY

1. From December 1955 through August 1956, BZ-55 was administered to a total of 380 patients. Of this number, 150 patients were maintained on the drug for periods ranging from a few days to nine months.

2. The results of the response of the blood sugar to a single dose of BZ-55 have served as a good guide as to whether satisfactory control of hyperglycemia and glycosuria might be anticipated in maintenance studies.

3. According to arbitrarily chosen standards of control, 57 per cent of the 150 patients achieved "good," and 12 per cent "fair" control of hyperglycemia and glycosuria. In 31 per cent of cases, "poor" control was obtained and the drug discontinued.

4. In 26 or 9.2 per cent of 279 patients, untoward effects or sequelae were noted. These included skin eruptions in fifteen patients, jaundice in four, severe hypoglycemia in two, anemia in one, nausea with or without vomiting in five, diarrhea in two and disorientation in one patient. In addition, two patients developed cerebrovascular accidents and one paroxysmal auricular tachycardia while receiving BZ-55. In two of the four cases with jaundice, severe liver damage occurred with one fatality.

Clinical Experience and Experimental Studies with Tolbutamide

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This conference affords evidence of the intense interest and the thoughtful investigations which have been stimulated by the recent introduction of two sulfonylurea compounds, carbutamide and tolbutamide. A careful study of the effects of these compounds on patients with diabetes mellitus of varying types and etiologies should aid in the assessment of their clinical usefulness and might yield information about their blood sugar lowering mechanism. Such a study will be described in this paper. Detailed descriptions of some of our results have been published previously[1, 2] and will be only summarized here.

CLINICAL STUDIES

All of the patients were hospitalized and maintained on a constant dietary intake during the period of study. When insulin was employed it was given as regular insulin twice daily, except in the case of the patient with lipoatrophic diabetes who received 500 units of insulin each day in a single dose. Tolbutamide* was the sulfonylurea compound used for these studies.

The first three patients had diabetes mellitus of undetermined etiology but varied in their clinical characteristics. Each one represented a different type of R. D. Lawrence's three types of idiopathic diabetes mellitus.[3] As previously reported, in a patient with stable or lipoplethoric diabetes, who had required 45 units of NPH insulin daily, the fasting blood glucose concentration and twenty-four-hour glucose excretion were well controlled without insulin by 2 gm. of tolbutamide daily. It is interesting that surgery on this patient was associated with a temporary marked rise in the blood concentration and urinary excretion of glucose in spite of the continued administration of tolbutamide. This patient has now received the drug, 2 gm. daily for ten months, with no apparent decrease in its effectiveness and without toxic manifestations. The results in a patient with labile or insulin deficient diabetes were in sharp contrast to those just described. During the period of study this patient received 70 units of insulin daily instead of her usual dose of 90 units to ensure a persistent hyperglycemia and glycosuria. The administration of 2 gm. of tolbutamide daily in addition to 70 units of insulin produced no significant alteration in the blood glucose concentration or the glucose excretion. The third patient had lipoatrophic diabetes mellitus and required 2,000 units of insulin daily to control her hyperglycemia. Two grams of tolbutamide daily produced a significant lowering of the fasting blood glucose concentration and twenty-four-hour glucose excretion in the absence of exogenous insulin, but adequate clinical control was not obtained with this drug alone. The effect

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