A CLINICAL TRIAL OF BZ 55

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Two groups of German workers have recently reported the successful control of most elderly or middle-aged patients suffering from mild diabetes by BZ 55 (N-butyl-N'-sulphanilylurea) (Franke and Fuchs, 1955; Bertram *et al.*, 1955). It is, however, difficult to assess the therapeutic value of the drug from these reports because the data given are inadequate. When exact figures for diets are stated they seem unduly high by British standards. Certainly many of the patients in whom control was successfully achieved with BZ 55 appeared to have the type of diabetes which would usually have responded to dietary restriction alone, without the use of insulin or an insulin substitute (*British Medical Journal*, 1955).

It was therefore felt that further carefully planned and fully documented clinical trials were necessary to establish the place of these sulphonamide compounds in the management of diabetes.

Selection of Patients

We considered that orally administered BZ 55 would have its main practical use as a complete substitute for parenteral insulin. Since the German work emphasized that such a complete substitution was only rarely possible in the young diabetic, we limited this initial study to patients over the age of 45 suffering from mild diabetes who were not overweight by more than 10% of their ideal weight (Metropolitan Life Insurance Company, Statistical Bureau, 1943, quoted by Dunlop *et al.*, 1953), but who, on a fully restricted diet, continued to show significant hyperglycaemia and glycosuria, and to experience diabetic symptoms in the absence of insulin therapy.

From the diabetic out-patient clinic 65 active patients (5 male, 60 female) who appeared to be of this type were selected and observed as out-patients for periods varying from one to six weeks. None of these patients had any active focus of infection, although many had retinopathy and neuropathy of the diabetic type. Only five were not currently receiving insulin, but they were inadequately controlled by diet alone. Control in those receiving insulin was good or moderate.

At the first visit each patient was impressed with the necessity of adhering strictly to the diet which they were at that time supposed to be taking, and the administration of insulin was stopped. Thereafter each was seen once or twice weekly, when the blood-glucose concentration was estimated, 24-hour and fasting urine samples were tested for glucose and ketone bodies, and weight and symptoms were recorded.

It was possible to complete the trial of the drug in only 44 of the 65 patients initially selected. Of the 21 patients withdrawn from the trial, either in the out-patient adaptation period or after admission to hospital, seven developed severe ketosis consequent on the withdrawal of insulin, necessitating its further administration. One of these, previously well controlled on 24 units of insulin zinc suspension, was admitted to hospital almost comatose only three days after discontinuing insulin, while another became seriously ketotic on the second day, both of them emphasizing the possible dangers of stopping the administration of insulin even in cases of apparently mild diabetes. Three were rejected because their blood-glucose concentrations four hours after a meal consistently exceeded 480 mg. per 100 ml., and, on the other hand, 10 were discarded when it became clear that adequate control was achieved by dietary restriction alone. In another patient the development of a severe drug fever necessitated the prompt withdrawal of BZ 55 before data were complete.

It can be seen from Tables II and III that all the 44 patients finally included in the analysis required treatment with insulin or an insulin substitute in addition to dietary measures.

Methods

The first 22 patients were studied in hospital for twenty days, and constitute Group I. The remaining 22 patients were in hospital for eight days only, and form Group II.

On admission to hospital all patients were assessed for a control period of seven days in the case of Group I and three days in the case of Group II. BZ 55 was started on the eighth and the fourth day respectively, and the effect of continued dosage was studied for the remainder of the patients' stay in hospital.

The reduction in hospital stay for Group II was made, firstly, because it was clear from experience obtained with Group I that the patients had, with an occasional exception, adhered to their diets during the out-patient adaptation period, so that surprisingly steady levels of hyperglycaemia and glycosuria occurred in the control period in hospital (Figs. 1 to 6); and, secondly, because we were satisfied that the response to therapy could for clinical purposes be accurately assessed by the fifth day of treatment.

The design of the trial was to some extent governed by clinical considerations. Thus, although most factors were kept constant throughout for all patients, the diets were individually prescribed and the dosage of BZ 55 was adjusted according to the clinical response.

Each patient continued to receive the diet which had been taken as an out-patient. The total calculated daily calories, carbohydrate, fat, and protein were kept constant throughout the trial. The same meal each day contained a constant calculated quantity of these proximate principles.

All patients were ambulant, and daily activity was kept as unaltered as possible throughout the trial. Each patient was weighed at the same time daily in the same clothes.

Venous blood was withdrawn by one or other of us each day at 8.30 a.m. (patient fasting), at 4 p.m. (three and a half to four hours after lunch), and at 8.45 p.m. (two hours after the main evening meal). These times were chosen as being best fitted to demonstrate the daily profile and excursion of glycaemia. The specimen taken at 8.45 p.m. reflected the postprandial rise in blood glucose. The blood-glucose content was estimated by one of us (J. D. B.), using the Nelson (1944) modification of the Somogyi method.

24-hour urine collections were obtained daily (8.30 a.m.–8.30 a.m.). The glucose content was estimated by Benedict's quantitative method and nitrogen by the micro-Kjeldahl method by one person.

In the majority of patients, glucose tolerance was measured in the control period either by the standard oral procedure, using a loading dose of 50 g. of glucose (16 patients), or by the intravenous technique (14 patients) (Duncan, 1956). In patients whose response to BZ 55 was satisfactory the test was repeated after five to ten days of

treatment. Due allowance for the glucose given in these tests was made in the daily diet.

Haemoglobin, red blood cell count, white blood cell count, platelet counts, and differential white-cell counts were estimated in the first 22 patients. In the remainder it was possible to estimate only haemoglobin and white blood cell counts. In all, the following tests of liver function were made: plasma albumin and globulin, total serum cholesterol, thymol turbidity, colloidal gold flocculation, and serum bilirubin. Observations were also made on plasma electrolytes, non-protein nitrogen, and CO_2 combining power. In seven patients 24-hour urine A.S.F.S. (acid-stable formaldehydogenic steroids) were determined (Tompsett and Smith, 1954), and in six patients tracer doses of radio-iodine were given for assessment of thyroid activity. All these observations were repeated during treatment with BZ 55.

In the first 12 patients treatment with BZ 55 was started with 3 g. (six tablets) given by mouth before breakfast. In 32 patients the dose was 4.5 g., and in addition blood was withdrawn at hourly intervals for five hours thereafter and its glucose and BZ 55 content were determined. The patient remained in bed and food was withheld during the period of the test. It was hoped that the response to this single dose might be of value in predicting the patient's subsequent response to the continuous administration of BZ 55.

Further dosage was dependent upon the response of the patient. If it was satisfactory, the dose was gradually reduced over three or four days to 1.5 g. (Figs. 2 and 3), but when the response was inadequate it was continued at 4.5 g. daily for several days (Figs. 4 and 5).

The BZ 55 concentration in the blood was estimated by the method of Bratton and Marshall (1939), pure BZ 55 being used for the preparation of standards.

Patients whose response was considered to be clinically satisfactory were discharged on a daily maintenance dose of BZ 55 varying from 1 to 1.5 g. They are being seen

TABLE I.—*Clinical Data of the 44 Patients in Whom the Trial of the Drug was Completed*

	Group I Patients (22)				Group II Patients (22)			
	Responsive (16)		Unresponsive (6)		Responsive (19)		Unresponsive (3)	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Age at trial (years)	62·4	50–71	62·2	55–74	62·1	45–73	58·2	55–59
,, ,, diagnosis (years)	57·4	44–69	59·0	53–73	54·9	35–67	52·5	43–56
Duration of diabetes (years)	5	0–19	3·2	0–10	7·2	0–18	5·7	2–12
Ideal weight (kg.)	65·4	60–77	69·8	63·5–78	65·3	58–78	64·8	60–73
Weight at trial as percentage of ideal weight	90·2	79–104	85·3	83–95	92·3	76–104	87·2	75–106
Previous daily insulin requirement (units)	18·5	Nil–36	20·3	12–32	21·5	Nil–44	26·7	24–32
Diet: Calories	1,666	1,100–2,400	2,083	1,600–2,400	1,600	1,100–2,400	1,833	1,200–2,200
Diet: Carbohydrate (g.)	151·2	100–200	180·5	140–220	149·5	110–200	160	120–180

TABLE II.—*Group I Patients (22)*

	Responsive and Clinical Successes* (16)		Unresponsive and Clinical Failures* (6)		Responsive and Clinical Successes † (16)	
	Mean	Range	Mean	Range	Mean	Range
F.B.G. Control period	221	142–274	258	171–329	—	—
F.B.G. Treatment ,,	109	71–148	245	158–310	115	67–163
F.B.G. Difference	−112	−71/−157	−13	−30/+25	−106	−63/−158
Av.B.G. Control period	255	187–307	332	258–399	—	—
Av.B.G. Treatment ,,	142	92–185	320	231–366	151	86–198
Av.B.G. Difference	−113	−78/−151	−12	−33/+15	−104	−71/−157
Pp.B.G. Control period	312	220–388	421	304–495	—	—
Pp.B.G. Treatment ,,	204	113–259	406	274–464	214	117–260
Pp.B.G. Difference	−108	−74/−153	−15	−31/+16	−98	−65/−155
Difference F.B.G./Pp.B.G. Control	91	46–136	163	70–212	—	—
Difference F.B.G./Pp.B.G. Treatment	95	42–146	161	70–214	99	48–142
24-hr. urine glucose Control	49·2	22–124	100·8	49–157	—	—
24-hr. urine glucose Treatment	3·5	0–30	96·3	34–153	9·4	0–49
24-hr. urine nitrogen Control	13·7	10·5–17·8	14·9	8·6–19·8	—	—
24-hr. urine nitrogen Treatment	11·6	9·6–15·0	15·0	9·0–21·1	—	—

* Values for treatment period = mean from 5th to 12th day inclusive. † Values for treatment period = mean from third to fifth day inclusive.
F.B.G. = Fasting blood glucose (8.30 a.m. specimen). Av.B.G. = Average daily blood glucose (mean of 8.30 a.m., 4.30 p.m., and 8.45 p.m. specimens.)
Pp.B.G. = Postprandial blood glucose (8.45 p.m. specimen). Blood glucose in mg. 100 ml. Urine glucose and nitrogen in g.

TABLE III.—*Group II Patients (22)*

	Responsive (19)				Unresponsive (3)	
	Clinical Successes (16)		Clinical Failures (3)			
	Mean	Range	Mean	Range	Mean	Range
F.B.G. Control period	203	133-267	309	284–332	273	253–300
F.B.G. Treatment ,,	115	65–149	236	222–245	273	241–300
F.B.G. Difference	−88	−68/−146	−73	−62/−92	0	−12/+13
Av.B.G. Control period	234	190–281	331	324–337	319	302–342
Av.B.G. Treatment ,,	147	89–196	257	253–263	319	297–355
Av.B.G. Difference	−87	−62/−146	−74	−67/−80	0	−17/+13
Pp.B.G. Control period	297	225–362	374	333–401	426	385–448
Pp.B.G. Treatment ,,	215	126–257	299	266–339	429	388–463
Pp.B.G. Difference	−82	−66/−146	−75	−64/−96	+3	−7/+15
Difference F.B.G./Pp.B.G. Control	94	40–160	65	32–117	153	85–191
Difference F.B.G./Pp.B.G. Treatment	100	40–162	63	21–117	156	88–196
24-hr. urine glucose Control	37·8	20·0–76·0	71·8	65·5–76·0	75·3	67–84
24-hr. urine glucose Treatment	5·4	10·0–16·0	34·0	29–41	76·3	69·5–88

Values for treatment period = mean from third to fifth day inclusive. Blood glucose in mg./100 ml. Urine glucose and nitrogen in g.

regularly at intervals of one to two weeks at a special clinic by one or other of us. Each patient is weighed and brings a 24-hour urine collection, the glucose content of which is determined. A sample of blood is withdrawn and estimated for glucose and BZ 55 content, the patient having fasted since breakfast, taken at least four hours previously. Haematological examinations are done at intervals. Initially the patients were instructed to test fasting and evening urine specimens for a few weeks after discharge, but this practice was later discontinued and dummy tablets have been substituted in 12 patients to date. After a period on "dummy therapy," when it became clear that control of the diabetes was deteriorating, they were again given BZ 55. Both substitutions were made without the patients' knowledge. Many, however, were quick to recognize a return of diabetic symptoms while taking dummy tablets.

Comparison of Responsive and Unresponsive Patients

Clinical Features

The clinical data for both groups are presented in Table I. All our patients were over the age of 45 at the time of the trial, and within this middle-aged or elderly group age did not seem to have any bearing on the patient's response to BZ 55. Within the ranges observed in this series, the duration of clinical diabetes, the age of the patient when the diagnosis was made, the daily dose of insulin previously required, and the period of time over which it had been administered were unrelated to the result obtained with BZ 55. The presence of degenerative diabetic changes, or a family history of the disorder, were also without influence upon the result.

The total calorie and carbohydrate content of the daily diet was higher in the unresponsive group. This was due to the fact that on the whole these unresponsive patients were more underweight in relation to their ideal weight than the responsive group.

In seven of the nine unresponsive patients significant ketonuria had previously been recorded. Ketonuria had also been noted in 5 of the 35 responsive patients, but only at the time of diagnosis or in the presence of infection or considerable stress. We formed the strong impression that patients who are prone to develop ketonuria easily do not respond well to BZ 55.

Effect on Hyperglycaemia and Glycosuria

The summarized results for both groups of patients are presented in Tables II and III. From a consideration of the blood-glucose levels and degree of glycosuria found in each patient during the control period it is apparent that all these patients really required insulin. We were impressed by the fact that the level of fasting blood glucose was not a true expression of the impairment of glucose tolerance. Thus, in this series, relatively low fasting blood-glucose levels were combined with poor glucose tolerance, as indicated by a considerable postprandial hyperglycaemia and a relatively heavy glycosuria (Fig. 4). Conversely, high fasting levels were not infrequently associated with a surprisingly good glucose tolerance (Fig. 5; Fig. 6, Case 36). In some of the patients having high blood-glucose values, particularly when the disorder was of long standing, the renal threshold for glucose was elevated so that the small amount of glycosuria present was often misleading (Fig. 2).

Group I

Of the 22 patients in this group, 16 responded favourably to the drug. A fundamental observation on the character of the response was that the amount by which the blood-glucose values were reduced by treatment was virtually the same for each of the three daily determinations for any one patient. Thus there was no appreciable change in the difference between the fasting and postprandial blood-glucose levels before and during treatment (Figs. 1–6). (Mean difference in control period, 91 mg. per 100 ml.—range 46–136 mg.; during treatment, 95 mg. per 100 ml.—range 42–146 mg.) We were therefore unable to confirm the finding of Bertram *et al.* (1955) that the daily profile of glycaemia was narrowed. The mean absolute fall in fasting blood-glucose concentrations for the responsive patients was 112 mg. per 100 ml. (range 71–157 mg.). When the fall is expressed as a percentage of the fasting blood-glucose value, the mean was 50.6% (range 40–61%) (Fig. 8).

In this group all the responsive patients were adequately controlled clinically in that symptoms were abolished, blood-glucose levels were satisfactory, and glycosuria was reduced by at least 75% of the control values. It was considered that adequate control had been achieved when the fasting

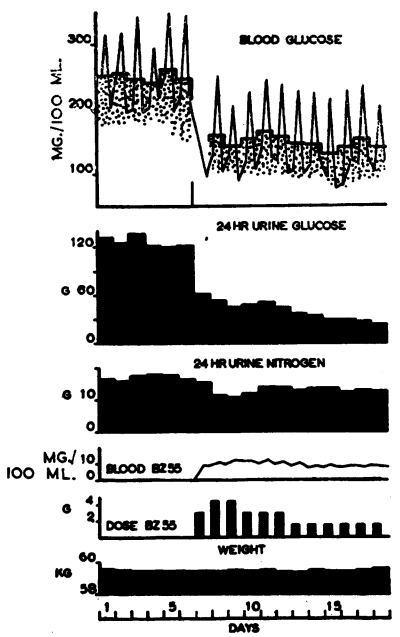

FIG. 1—Case 2: man aged 64. Note steady values of blood and urinary glucose during control period; immediate response to BZ 55 but no change in daily profile of glycaemia.

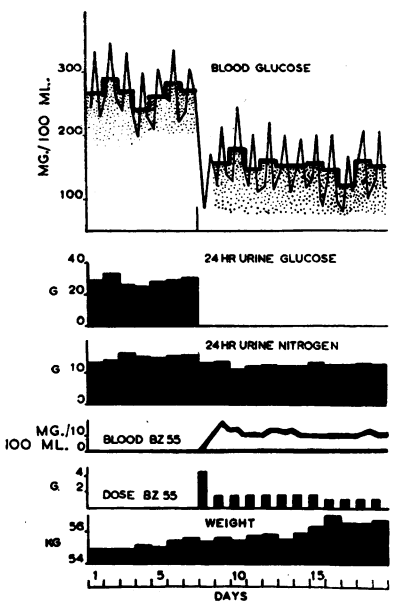

FIG. 2.—Case 15: woman aged 64. Note immediate response to BZ 55; glycosuria completely abolished because of higher renal threshold than Case 2; increase in weight mainly due to full diet not being taken as out-patient.

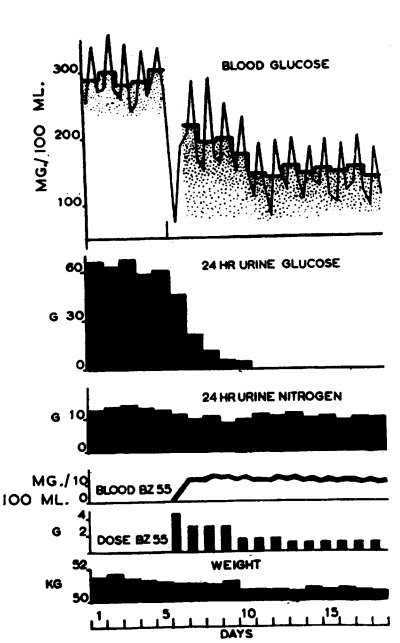

FIG. 3.—Case 20: woman aged 55. Note extreme response to single-dose test causing hypoglycaemia; slower response to continued treatment.

blood-glucose concentration did not exceed 150 mg. per 100 ml., the postprandial value was below 260 mg. per 100 ml., and the average daily blood-glucose level was less than 200 mg. per 100 ml. (Figs. 1–3). It will be seen that the mean values for the group as a whole were much lower than these limits. Some patients who had particularly high blood-glucose concentrations before treatment tended to have a high renal threshold for glucose. Thus glycosuria and symptoms were often abolished with treatment in spite of the persistence in a few cases of relatively high blood-glucose levels. Data for three of the patients successfully controlled by BZ 55 are shown in Figs. 1–3.

Six patients in this group were unresponsive to the drug. The mean absolute fall in their blood-glucose levels was only 13 mg. per 100 ml. (range −33 to +25 mg.). When expressed as a percentage of the fasting blood glucose the mean fall was 5% (−7.5 to +10%) (Fig. 8). All these patients continued to show blood-glucose values exceeding the limits defined for adequate clinical control. Data for two of the patients unresponsive to BZ 55 are shown in Figs. 4 and 5.

In Group I there was no difficulty in assessing the response of any one patient. In all cases it was quite obvious by the fifth day whether or not they were responsive to the drug. Analysis of the response at the fifth day shows that usually it was not significantly less than that at the twelfth day (Table II). The hypoglycaemic effect was therefore rapid and definite (Figs. 1 and 2). The response improved significantly after the fifth day in only three cases, but even in these the absolute fall in fasting blood-glucose levels was greater than 60 mg. per 100 ml. by the fifth day (Fig. 3). This contrasts with the experience of Bertram *et al.* (1955), who found that in 11 of their 28 patients a significant effect was delayed to between the fourth and thirteenth days.

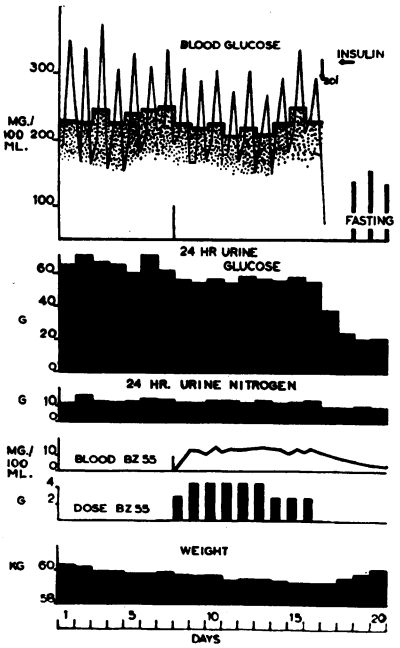

FIG. 4.—Case 12: woman aged 60. Note relatively low fasting glycaemia with marked postprandial hyperglycaemia; lack of response to BZ 55 but sensitivity to insulin; slow fall in blood BZ 55 concentration following cessation of treatment.

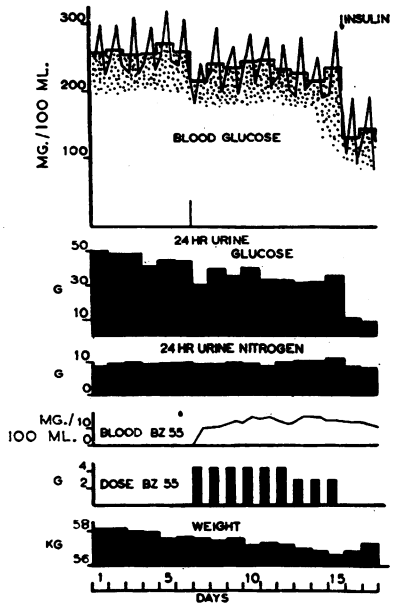

FIG. 5.—Case 8: woman aged 65. Note high fasting glycaemia but small postprandial effect; minimal response to BZ 55 but sensitivity to insulin.

Group II

The effect of BZ 55 on 16 of the 22 patients in this group was of the same character and magnitude as that seen in the responsive patients in Group I. The mean absolute fall in all blood-glucose values was greater than 60 mg. per 100 ml. (range 62–146 mg.). Expressed as a percentage of the control fasting blood-glucose concentration, the mean fall was 43.4% (range 38–55%) (Fig. 8). During treatment each of these patients showed a reduction in glycosuria of at least 75% of the control value, and all of them satisfied our criteria for adequate clinical control.

Three patients showed an absolute reduction in all blood-glucose levels greater than 60 mg. per 100 ml. (mean 74 mg.; range 62–96 mg.). However, their blood-glucose values during the control period were significantly higher than those of the previous 16 patients (Table III). Thus, if the reduction is expressed as a percentage of the control value, it is in all cases less than 30% (mean 23%; range 21–27%) (Fig. 8), and glycosuria was reduced by less than 75% (mean 47%; range 45–54%). These three patients obviously responded to the drug to some extent, but they could not be classed as clinical successes according to our criteria of adequate clinical control, in spite of high dosage with BZ 55. Data for two of these patients are shown in Fig. 6.

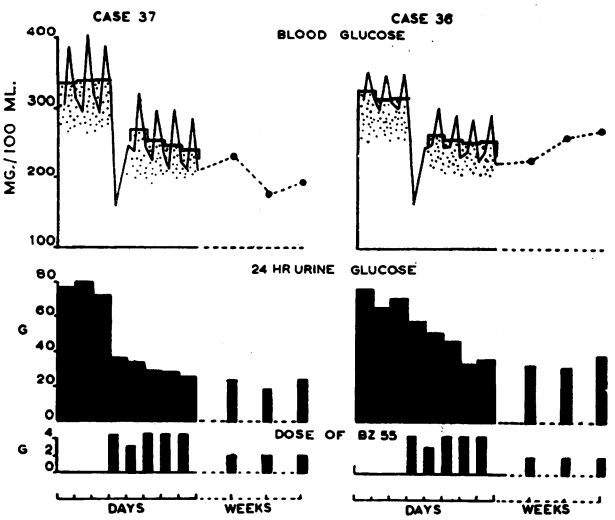

FIG. 6.—Case 37: woman aged 67. Case 36: woman aged 66. In spite of good response to single-dose test and significant response to continued high dosage with BZ 55, neither patient satisfied criteria of successful clinical control.

In three patients the drug was entirely ineffective although again BZ 55 was given in high dosage. The mean rise in their blood-glucose concentration was 1 mg. per 100 ml. (range −17 to +15 mg.) and glycosuria increased by 1 g. daily.

The seven patients who developed ketonuria are not included in this analysis. Four of them were admitted to hospital for the trial. Three developed ketonuria during the control period, and this continued in spite of high dosage with BZ 55, so that insulin had to be administered. When, as a result, hyperglycaemia was less severe and ketonuria absent the patients were subjected to a further trial of BZ 55, again without effect. The remaining patient developed severe ketonuria after five days of treatment with BZ 55, which was therefore replaced by insulin.

Blood-Glucose Values in the Control Period

It can be seen from Tables II and III that both the mean fasting blood-glucose values and the difference between the fasting and postprandial blood-glucose levels of the unresponsive group were considerably higher than those of the

responsive group. There is, however, no clear-cut distinction in this respect between the two groups, hence those values are of little use in predicting response or otherwise in the individual case.

Attempt to Predict Response

Of the 44 patients selected for their probable response, there were 35 who responded to continued dosage with BZ 55, but only 32 of these responded well enough to be classed as clinical successes. Owing to the difficulty of predicting therapeutic success clinically, an attempt was made to obtain this information by the response to the single dose of BZ 55 previously described.

Of the 32 clinical successes, 25 were tested in this way, and in them the mean fall in blood-glucose levels at five hours was 115 mg. per 100 ml. (range 68–185 mg.), and two developed classical symptoms of hypoglycaemia. When expressed as a percentage of the fasting level the mean fall was 53.2% (range 40–73%). The three responsive patients who were not clinical successes had a mean fall in blood-glucose levels at five hours of 148 mg. per 100 ml. (range 123–177 mg.). When expressed as a percentage of the fasting level the mean fall was 47.0% (range 44–51%).

Eight of the nine patients who did not respond to continued dosage with BZ 55 were tested. In this group the mean fall was 78 mg. per 100 ml. (range +1 to 135 mg.). When expressed as a percentage of the fasting blood-glucose level the mean fall was 30% (range 0–47%). Three of them had a fall of over 40%. During this test there was no difference between the blood sulphonamide levels reached by the responsive and unresponsive groups. Thus the value of the test in predicting an individual response is limited to the fact that no patient who showed a fall of less than 35% responded clinically to the drug in continued dosage. A fall of over 40%, on the other hand, did not necessarily mean clinical success. The degree of fall in the acute test was not directly related to that obtained with continuous dosage in any individual case.

Factors Affecting Response

Fasting Blood Glucose.—In responsive patients who were also clinical successes the fall in fasting blood glucose was roughly proportional to the fasting blood-glucose concentration in the control period. In the unresponsive group, however, there was no such relationship. The three responsive patients who were clinical failures occupied an intermediate position (Fig. 7). If the absolute fall is expressed as a percentage of the control fasting blood glucose, the patients group themselves in the same way (Fig. 8).

Difference between Fasting and Postprandial Blood Glucose.—The degree of fall in both groups bears no relation to this value.

Blood Sulphonamide Level.—The dosage of the drug was determined by its clinical effect upon the blood-glucose concentration, and varied widely from patient to patient. In any one patient following a known dose, the concentration of BZ 55 in the blood remained remarkably constant, but in different patients given the same dose considerable variation in the blood levels occurred. The levels produced in both the responsive and unresponsive groups were of the same order, although the latter received much larger quantities of the drug. For each responsive patient there seemed to be a minimal therapeutic blood level which again varied from patient to patient.

Other Observations

Urinary Nitrogen Excretion.—It was not practicable to undertake absolute nitrogen balances in such a number of patients. The daily urinary nitrogen excretion was, however, estimated in 22 patients over 20 days. Since the daily diet was kept constant and the number of observations was large, some significance may be attached to the results. From Table I it can be seen that in the 16 responsive patients in Group I the mean control 24-hour urinary nitrogen was 13.7 g., whereas the mean value from the fifth to the twelfth day of treatment was only 11.6 g. This change is statistically significant ($P=0.005$). In this connexion it may also be of interest to note that in the unresponsive patients there was no change in the urinary nitrogen excretion, the values being 14.9 g. for the control period and 15.0 g. for the period of treatment.

Glucose Tolerance.—Three measurements of glucose tolerance have been employed. (1) The difference between the fasting and postprandial blood-glucose concentration was used as a rough index of glucose tolerance. From Tables II and III it can be seen that there is no appreciable change in this value in the responsive or unresponsive groups as the result of treatment with BZ 55 (Figs. 1–6). (2) Oral glucose-tolerance tests before and during treatment were carried out on 10 of the successfully treated patients. At the time of the test the mean fasting blood glucose in the control period was 247.6 mg. per 100 ml., and during treatment 146.5 mg. per 100 ml. It can be seen from Fig. 9 that BZ 55 was without effect either on glucose tolerance or on the rate of its absorption. (3) Intravenous glucose-tolerance tests before and during treatment were performed on 11 of the successfully treated patients. At the time of the test the mean fasting blood-glucose concentration in the control period was 221.8 mg. per 100 ml., and during treatment 108.5 mg. per 100 ml. The mean increment index (Duncan, 1956) for the control test was 1.46 (S.D. 0.3) and during

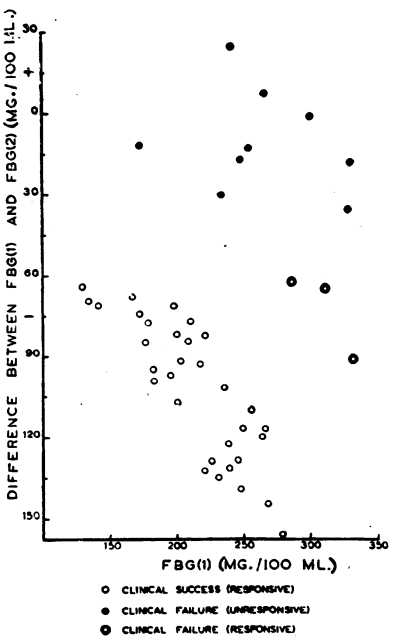

FIG. 7.—Graph relating fasting blood glucose to absolute reduction in fasting blood glucose obtained by treatment with BZ 55. F.B.G. (1)=Mean of values in control period. F.B.G. (2)=Mean of values during treatment.

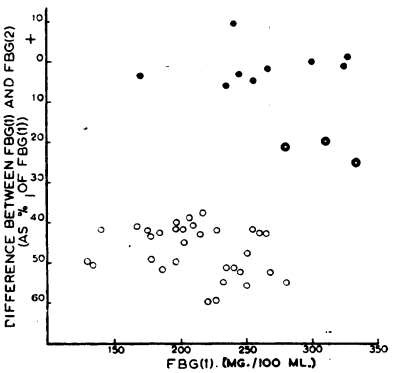

FIG. 8.—Graph relating fasting blood glucose (1) to reduction in F.B.G. obtained by treatment with BZ 55, the reduction being expressed as a percentage of F.B.G. (1). F.B.G. (1)=Mean of values in control period. F.B.G. (2)=Mean of values during treatment. (Symbols as for Fig. 7.)

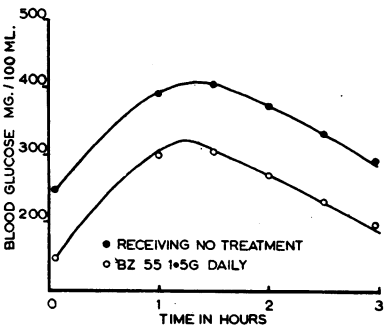

FIG. 9.—Mean of oral glucose-tolerance curves obtained in 10 responsive patients before and during treatment with BZ 55.

treatment 1.45 (S.D. 0.3). It is therefore clear that BZ 55 is without effect on glucose tolerance. We are reporting these observations in detail elsewhere.

Insulin Sensitivity.—We were unable to confirm that "unresponsive patients reacted poorly to insulin" (Franke and Fuchs, 1955). All our unresponsive patients were given a test dose of 20–30 units of soluble insulin in the fasting state, and all showed a profound drop in blood glucose, three becoming clinically hypoglycaemic (Fig. 4). All these patients are now very well controlled on small doses of insulin.

Weight.—While in hospital no very significant changes in weight were observed in the responsive patients.

Side-effects

A few patients complained of mild headache, malaise, and drowsiness when receiving the higher initial doses of the drug. When the dose was reduced to maintenance levels these symptoms disappeared.

In one patient a definite drug fever occurred on the fourth day, necessitating temporary withdrawal of the drug. The hypoglycaemic response had, however, been so good in this patient that after four weeks of out-patient observation, when no insulin was given, the administration of BZ 55 was once again cautiously started in daily doses of 0.5 g. No untoward effects occurred, and control has since been most satisfactory (Fig. 10, Case 45).

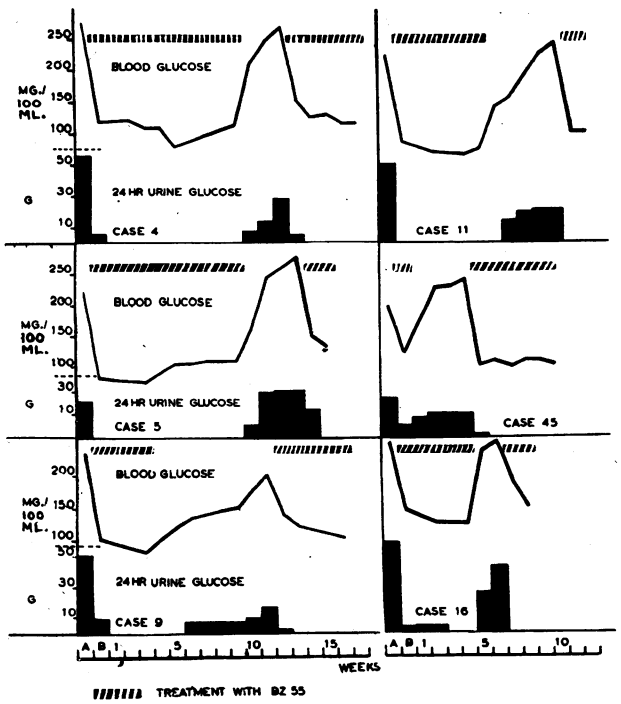

FIG. 10.—Data of six out-patients in whom courses of BZ 55 were interrupted with a return of hyperglycaemia and glycosuria. Values during periods A and B are the mean of those obtained in hospital during the control and treatment periods respectively. The blood-glucose concentrations refer to the fasting values.

In three patients a sulphonamide rash was seen, which, however, spontaneously regressed.

We have so far observed no alteration in the liver-function tests, serum electrolytes, or urinary A.S.F.S. as the result of treatment. There was some depression of iodine uptake by the thyroid in the six patients so tested during the initial two weeks of treatment, which, however, returned to normal during maintenance therapy (Kinsell *et al.*, 1956). One patient, who had for years been receiving 1 gr. (65 mg.) of thyroid daily for myxoedema, became increasingly hypothyroid after two months' treatment with BZ 55, but improved again when the dose of thyroid was doubled.

In the series as a whole there was a definite granulocytopenia in the initial two weeks of treatment. In the majority the count returned to normal despite continuance of BZ 55 in maintenance dosage, but in a few leucopenia has persisted. The lowest white-cell count recorded was 2,000 per c.mm.

A more disturbing feature has been the depression of the blood platelets. One patient reported with spontaneous purpura after only 10 days' treatment with BZ 55, and was found to have a platelet count of 60,000 per c.mm. The count returned to normal and the Hess test became negative within a week of discontinuing treatment. A test dose of 1.5 g. of the drug for two days resulted in a recurrence of thrombocytopenia and a positive Hess test. Another patient then presented with spontaneous purpura, and in this case a leucopenia was also present, the white-cell count being 2,300 per c.mm. This patient is at present being investigated in hospital.

Consequent on this experience platelet counts have been made on 30 out-patients, in none of whom the daily maintenance dose of BZ 55 had exceeded 1.5 g. The technique used was that of Oettle and Spriggs (1951), which gives a normal range of 250,000 to 350,000 per c.mm. Six of these 30 patients have been found to have counts under 180,000 per c.mm., the lowest value being 90,000 per c.mm., associated with strongly positive Hess tests, bringing the total of patients with thrombocytopenia to eight. Three of these had had platelet counts made during the control period before BZ 55 was given, all of which were at the lower limits of normal. Three other patients, although not thrombocytopenic, have shown a substantial fall in platelet counts in comparison with their control figures, and one of these has experienced severe menorrhagia. Among the patients who showed no reduction in platelets, four showed a slightly positive Hess test, a not unusual finding in elderly diabetics, particularly those with retinopathy (Beaser *et al.*, 1944).

Thus the haematological findings so far suggest that BZ 55 has a toxic action on the platelets, and, to a less extent, on the white blood cells. The red cells appear to be unaffected. A more detailed haematological investigation is at present being undertaken and will be fully reported at a later date.

Follow-up

Since discharge from hospital all the clinically responsive patients have been seen regularly. Five have been observed for 18 weeks, 2 for 16, 8 for 10, 4 for 8, 7 for 5, and 6 for 4 weeks. While receiving BZ 55 they have continued to be free of diabetic symptoms and have felt well. Blood-glucose levels and BZ 55 concentration in the blood have remained remarkably steady and satisfactory, and glycosuria has been absent or minimal. A slow but definite increase in weight has been recorded in most patients during this out-patient period of observation. Two patients on a maintenance daily dose of 1 g. of BZ 55 reported symptoms typical of hypoglycaemia which disappeared when dosage was reduced to 0.5 g. daily.

Dummy tablets have been substituted for BZ 55 in 12 patients. In all these the blood-glucose level and glycosuria started to increase within two weeks of stopping the drug, subsequently reaching the levels observed prior to treatment—10 within one month after stopping BZ 55 and 2 by the end of eight weeks. In most cases the hyperglycaemia and glycosuria were associated with a return of diabetic symptoms. The rate at which each of these patients became uncontrolled corresponded to the rate at which their diabetes became uncontrolled after withdrawal of insulin prior to the trial. At this point treatment with BZ 55 was reinstituted and good control was again achieved in all within one week (Fig. 10).

It was notable that an increase or a decrease in glycosuria lagged behind corresponding changes in blood-glucose concentration, which suggests that the drug may have some effect on the renal threshold for glucose. The three patients in Group II who showed a response to BZ 55 but were

classified as clinical failures were continued on 2 g. daily as out-patients and have been observed for three weeks. All three must continue to be classed as clinical failures, though in one there has been some diminution in glycaemia and glycosuria (Fig. 6).

Discussion

There can be no doubt that BZ 55 has a remarkable hypoglycaemic action in some diabetic patients. From our observations this would seem to be due to a reduction in the fasting blood-glucose value. Glucose tolerance is unchanged and there is no alteration in the daily profile of glycaemia, though the absolute values are set at a lower level and glycosuria is reduced or disappears. How this hypoglycaemic action is brought about remains unknown, and this preliminary clinical study was not designed to elucidate this point.

The number of patients likely to benefit from the administration of BZ 55 is limited. The evidence suggests that the drug is of little or no value in the treatment of the young type of diabetic and absolutely contraindicated for those with a marked tendency to develop ketosis. On the other hand, though the mild diabetes of obese patients may well respond satisfactorily to the drug, there should be no substitute for dietetic restriction in the control of such patients. There remains a limited group of middle-aged or elderly non-obese patients suffering from comparatively mild diabetes who, in spite of dietetic treatment, require small or moderate doses of insulin, and for these BZ 55 may provide a welcome alternative. From a group of 55 patients of this type only 33 were adequately controlled by the drug. This is a smaller proportion of successful cases than has been claimed by other workers (Franke and Fuchs, 1955), who, however, may well have used BZ 55 as a substitute for dietary restriction.

When our clinical failures are considered, some are found to have been completely refractory to the drug; in some the response was insignificant; and in a few, although a good response occurred as evidenced by a fall of 60 to 90 mg. per 100 ml. in the blood-glucose concentration, this was insufficient to establish clinical control owing to the very high initial blood-glucose levels. Patients who readily became ketotic proved unsuitable subjects for this treatment. They seldom responded to it, and the drug itself was without effect on diabetic ketosis.

In those patients in whom treatment with BZ 55 resulted in satisfactory clinical control the reduction in glycaemia was of the order of 100 mg. per 100 ml. (range 65–160 mg.). Besides having their blood-glucose levels reduced to satisfactory figures and their glycosuria abolished or greatly reduced, these patients were rendered free from diabetic symptoms. They felt well and put on weight, and there seemed little doubt that some improvement in nitrogen balance occurred. When dummy tablets were substituted for BZ 55 deterioration began to take place within a short space of time, so that in these patients there did not seem to be any place for intermittent treatment, which has been suggested by Franke and Fuchs (1955).

A high incidence of toxic effects was observed in this series—skin reactions, drug fever, slight granulocytopenia, and particularly thrombocytopenia, associated in two cases with spontaneous purpura.

It may well be questioned whether convenience alone justifies the replacement of a well-tried and safe parenteral preparation by an oral substitute in the case of a small percentage of diabetics, especially when its toxic potentialities are considered and when the dangers of its misuse in unsuitable cases are appreciated. Even in patients who might seem to be suitable for such treatment selection is possible only by trial and error, and in those who prove unresponsive ketosis may develop rapidly on withdrawing insulin. Further, in patients who are ordinarily well controlled by BZ 55 an intermittent infection may produce dangerous ketosis which is unaffected by the drug.

BZ 55 will almost certainly prove to be a valuable research weapon which may help to elucidate some of the obscure problems of diabetic metabolism. Nevertheless, we believe that it would be premature at the present time to make it generally available for therapeutic use. This should await the results of further study in special centres to establish the pharmacological action of the drug, to assess its long-term toxicity, and to crystallize more completely the indications and contraindications for its use in any individual patient.

Summary

BZ 55 proved to be an effective substitute for insulin in 33 of 55 middle-aged or elderly diabetic patients.

The drug was without effect on ketosis or on those patients who readily developed ketosis.

The difficulties in selecting the responsive patient and the dangers of withdrawing insulin in the unresponsive patient are emphasized.

The character of the hypoglycaemic response has been analysed with particular reference to the daily profile of glycaemia, glucose tolerance, and its relationship to fasting blood-glucose values.

From follow-up studies it is concluded that maintenance treatment with BZ 55 requires to be continuous and not intermittent.

Minor toxic effects were encountered in several patients, and there appears to be a possibility that thrombocytopenia may occur with alarming frequency.

BZ 55 should not be given as a substitute for dietary restriction. If this principle is observed the number of patients in whom it can replace insulin is more limited than reports to date have suggested.

We are indebted to many people for nursing, dietetic, biochemical, and medical assistance, and particularly to our patients, whose co-operation enabled the study to be undertaken. Our thanks are due to the British Insulin Manufacturers for supplies of BZ 55

REFERENCES

Beaser, S. B., Rudy, A., and Seligman, A. M. (1944). *Arch. intern. Med.*, **73**, 18.
Bertram, F., Bendfeldt, E., and Otto, H. (1955). *Dtsch. med. Wschr.*, **80**, 1455.
Bratton, A. C., and Marshall, E. K. (1939). *J. biol. Chem.*, **128**, 537.
British Medical Journal, 1955, **2**, 1435.
Duncan, L. J. P. (1956). *Quart. J. exp. Physiol.*, **41**, 85.
Dunlop, D. M., Davidson, L. S. P., and McNee, J. W. (1953). *Textbook of Medical Treatment*, 6th ed., p. 385. Edinburgh.
Franke, H., and Fuchs, J. (1955). *Dtsch. med. Wschr.*, **80**, 1449.
Kinsell, L. W., Brown, F. R., Friskey, R. W., and Michaels, G. D. (1956). *J. clin. Endocr.*, **16**, 821.
Nelson, N. (1944). *J. biol. Chem.*, **153**. 375.
Oettle, A. H., and Spriggs, A. I. (1951). In *Recent Advances in Clinical Pathology*, edited by S. C. Dyke, 2nd ed., p. 406.
Tompsett, S. L., and Smith, D. C. (1954). *J. clin. Endocr.*, **14**, 922.

The work of the department of obstetrics in Adeyo Hospital, Nigeria, which serves three-quarters of a million people, is described in the "Clinical Report" of the department of obstetrics, University College, Ibadan, for the period April 1, 1953, to December 31, 1954. The report is by Drs. J. B. Lawson and U. G. Lister and contains 25 tables analysing the work of the department. Ibadan is the largest city in tropical Africa; more than half the population are Mohammedans, and the majority are polygamous. The diet is grossly deficient in proteins needed for a pregnant woman, and anaemia of pregnancy is the most serious complication encountered. The patients themselves are suspicious of scientific medicine; native medicines are often the cause of major disorders. Of a total of 5,985 patients, 5,582 were delivered in hospital. There were 76 maternal deaths (only 3 of which were considered to be not ultimately preventable), 409 stillbirths, and 333 neonatal deaths. The department's facilities were "at an appallingly low level," but a mile away a new hospital has been built where there will soon be 110 obstetric beds.