TRIAL OF AN ORAL HYPOGLYCAEMIC AGENT IN DIABETES

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During an investigation in man of the chemotherapeutic properties of some new sulphonamides, Franke and Fuchs (1955) reported that one, N-butyl-N'-sulphanilyl-urea (BZ 55), produced hypoglycaemia. Following this observation the compound was examined clinically in diabetics by Franke and Fuchs and by Bertram, Bendfeldt, and Otto (1955). Pharmacological observations were described by Achelis and Hardebeck (1955).

Subsequently, another hypoglycaemic agent, N-(4-methyl-benzosulphonyl)-N'-butyl-urea (D 860) was discovered, on which joint clinical and pharmacological studies were described by Bänder *et al.* (1956). This preparation is not a sulphonamide and has no bacteriostatic activity, but its hypoglycaemic properties are similar to those of BZ 55.

It was evident from German data that these compounds successfully controlled hyperglycaemia and glycosuria in some diabetics, many of whom were overweight. This latter fact suggested to us that in this country some of their successful cases might have been treated by diet alone.

In view of this we decided to undertake a detailed in-patient study on a group of 45 diabetics, from which we attempted to obtain information on the effect of stopping insulin under conditions of constant diet. If hyperglycaemia and glycosuria persisted BZ 55 was administered orally to ascertain its value as a substitute for injected insulin. In addition, information was sought on the possibility of establishing a short-term test which might enable us to predict the usefulness of this drug in long-term therapy.

Studies of free and conjugated sulphonamides in blood and urine were undertaken in an attempt to find correlation between these levels and therapeutic activity.

Methods

Selection of Cases.—Although an attempt was made to get a representative cross-section of the diabetics attending the hospital clinic, numbering just over a thousand, the necessity of spending two weeks in the wards meant a preponderance of middle-aged or elderly female diabetics in those who were admitted. The majority (34) were out-patients already receiving insulin, the need for which had previously been established. Eleven others had not been receiving insulin. Seven of these were newly diagnosed diabetics who would normally have received insulin. Four others have had diabetes for several years, controlled by diet alone; but increasing glycosuria, hyperglycaemia, and loss of weight had latterly suggested their need for insulin. A group of six

young and brittle diabetics were admitted for a few days only and took part in a short-term test.

Design of Trial.—On admission each patient was given a diet suitable for his or her physique and metabolic needs, prepared in a diet kitchen. For out-patients of long standing this was a continuation of the diet to which they were accustomed. These diets have been maintained since the patients were discharged. Apart from the group of young diabetics, patients were kept under observation in the wards for at least two weeks, and were then followed up twice weekly in a special out-patient clinic. For the first five days after admission patients were maintained without insulin on diet alone. Once the initial control period had been completed, a two-day test was performed. On these two days no breakfast was given, but on the second day BZ 55, in a dose of 50 mg./kg. body weight, was administered by mouth. This sequence enabled us to assess the effect simply of the omission of breakfast. In a first group of 12 patients, blood and urine sugar and sulphonamides were estimated hourly for six hours, while in subsequent tests samples were obtained every three hours under the same conditions. The patients were kept in hospital and maintained on BZ 55 for at least a further five days. If there was evidence that hyperglycaemia and glycosuria were diminishing, the diabetics were continued to be maintained on BZ 55 as out-patients for at least two weeks. In those who failed to respond even to an increased dosage, insulin therapy was resumed.

Dosage.—The initial dose was 50 mg./kg. body weight for each case—that is, 2.5 to 3.5 g. a patient—and was given in the morning. Except for the young and brittle cases, patients received a dose of 2 g. on the following morning, followed by 1 g. daily for at least five days as in-patients, and then as out-patients. Where control was poor, 3 g. daily was begun on the eighth day and continued for five days. In some, rapid loss of weight and ketosis necessitated an earlier resumption of insulin therapy, which also eventually became necessary in those patients in whom trebling of dose had been attempted.

Body Weight.—Patients were weighed daily; this was continued when they attended as out-patients.

Laboratory Tests.—On admission of patients the following examinations were performed to exclude relevant disease and for later reference: urine tests for albumin and casts; haemoglobin estimation, white-cell count and differential; and serum bilirubin, thymol turbidity, and alkaline phosphatase.

Urine Sugars and Sulphonamides.—Each day 24-hour specimens of urine were collected, the volume was measured, and the total sugar was estimated by Benedict's quantitative method (King, 1951). When BZ 55 was given, the amounts of free and conjugated sulphonamides were estimated by the method of Bratton and Marshall (1939). Urine was also tested four-hourly for sugar and acetone and charted in the usual way.

Blood Sugar and Sulphonamides.—Samples of venous blood were obtained at least three times daily, including a fasting, pre-lunch, and post-lunch specimen, and the sugar was estimated by the method of Hagedorn and Jensen (1923). When BZ 55 was administered the levels of free and conjugated sulphonamides were also estimated by the method of Bratton and Marshall. All estimations were continued on out-patients whenever they attended, bringing with them a 24-hour specimen of urine in a winchester provided.

Results

The patients were divided into two groups, successes and failures, depending upon their response to BZ 55. The blood-sugar levels of those in the successful group fell to within normoglycaemic limits following the administration of the drug, either whilst the patients were in hospital or during the subsequent follow-up as out-patients, and glycosuria almost or completely disappeared during the corresponding period of observation. Within the group of failures

the blood-sugar levels either were not reduced following the administration of BZ 55 or were reduced, but not to within the normoglycaemic range, and the amount of glycosuria was still significant.

Within these two classifications the data were studied statistically under the following headings: (1) Previous history of diabetes. (2) The mean change in blood sugar, glycosuria, volume of urine excreted, body weight, and sulphonamide levels during up to five days in hospital after treatment with BZ 55 compared with the corresponding period in hospital before treatment, during which the patient received no insulin. (3) The two-day test referred to under "Methods," in which the patient received BZ 55 for the first time.

In all the analyses which follow, the maximum amount of data available has been used. For example, it was obviously impossible to continue the administration of BZ 55 to the young and brittle diabetics beyond the first dose in the two-day test because of ketosis and the consequent risk of coma. In such instances the results can be included only when considering data from the two-day test or from previous history of diabetes.

Sex, Present Age, and Duration of Diabetes.—Table I shows the results from 45 cases. An analysis of variance revealed neither regression of age on the duration of dia-

TABLE I.—*Distribution of Sex, Present Age, and Duration of Diabetes*

Present Age (Years)	Successes (19)		Failures (26)	
	Males (3)	Females (16)	Males (10)	Females (16)
21-40	0	0	4	2
41-60	1	3	3	6
61-80	2	13	3	8
Mean age and range (years)	65 (51 to 77)		55 (22 to 80)	
Duration of Diabetes (Months)	Successes		Failures	
0-12	9		6	
13-60	6		5	
61-120	1		6	
121-240	3		7	
>240	0		2	
Mean duration and range (months)	50 (0 to 192)		104 (0 to 324)	

betes nor any significant difference in the duration of the disease in successes and failures. This is not surprising in view of the wide range of the duration of diabetes within each group. In the successful cases the mean age is slightly higher ($P < 0.05$) than in the failures. Since the majority of patients in this study were elderly female diabetics the significance of the age factor would probably have been increased if a larger number of young diabetics could have been included, since none of the young brittle diabetics responded at all to BZ 55.

Family History and Complications.—There was evidence of diabetes in the families of 3 out of 16 successful cases and in 3 out of 25 of the failures. The complications are shown in Table II. These data are collected from too small

TABLE II.—*Number of Cases Showing Complications*

	Successes	Failures
Retinopathy	4	5
Nephritis	1	1
Claudication	0	2

a number of patients for a significant statistical assessment, but there does not appear to be any difference in the distribution of complications between the two groups.

Insulin Requirements.—Table III shows the mean daily dose of insulin given to patients in both the successful and unsuccessful groups at the time when the present study was

started, and the mean change in insulin requirements from the time when the disease was first diagnosed.

TABLE III.—*Correlation Between the Daily Requirements of Insulin Just Prior to the Test with BZ 55 and the Amount of Insulin Required When the Diabetes was First Diagnosed*

	Daily Dose of Insulin Just Prior to the Test with BZ 55		Change* in Daily Dose of Insulin from Time when Diabetes was First Diagnosed until Just Prior to Test with BZ 55		No. of Cases
	Mean (Units)	Range (Units)	Mean (Units)	Range (Units)	
Successes ..	13.3	0 to 32	-9.8	-54 to +6	16
Failures ..	40.8	0 .. 120	+10.7	-24 .. +90	25

* -, Decrease in insulin requirements. +, Increase in insulin requirements.

A statistical analysis revealed that the insulin requirements of those patients in the group of failures were significantly greater ($P = 0.001$) than the requirements of those in the successful group prior to the administration of BZ 55, and the successful patients needed slightly less insulin at this time and the unsuccessful patients slightly more ($P = 0.05$) than they did when the diabetes was first diagnosed.

Present Age, Duration of Diabetes, and Deviation from Ideal Body Weight.—The ideal body weights of 38 patients were determined, using the table of Kemsley (1951-2), and are shown in Table IV. There was no significant difference

TABLE IV.—*Deviation of Actual Body Weight from the Ideal Body Weight*

	Deviation* from Ideal Body Weight (lb. and kg.)		No. of Cases
	Mean	Range	
Successes ..	-3 (-1.36 kg.)	-44 to +42 (-19.96 to +19.05 kg.)	15
Failures ..	-11 (-4.99 kg.)	-46 to +16 (-20.86 to +7.26 kg.)	23

* -, Underweight. +, Overweight.

between the mean deviations in body weight for the two groups, nor was there any correlation between the deviation from ideal body weight and the duration of diabetes or present age when the data in Table I were analysed with those of Table IV.

Deviation from Ideal Body Weight Before Administration of BZ 55 and the Change in Body Weight Whilst in Hospital following its Administration.—One possible action of BZ 55, if it restores a normal metabolism, would be its effect on the body weight of the patient where an obese patient might be expected to show a decrease in weight and a thin patient an increase. The data from 37 cases were available in which daily observations on body weight were made carefully in the period before and after the administration of BZ 55 while the patients were in hospital. Table V shows

TABLE V.—*Deviation from Ideal Body Weight Prior to BZ 55 Administration and Change in Body Weight Following its Administration*

	Deviation from Ideal Body Weight lb. (kg.)	Change in Body Weight oz. (g.)	No. of Cases.
Successes { Mean	-3 (-1.36 kg.)	-14 (-397 g.)	15
Range	-44 to +42 (-19.96 to +19.05 kg.)	-13 to +54 (-368 to +1,531 g.)	
Failures { Mean	-16 (7.26 kg.)	-7 (-198 g.)	12
Range	-49 to +16 (-22.25 to +7.26 kg.)	-88 to +44 (-2,495 to +1,247 g.)	

the results obtained. There was no correlation between the change in body weight after BZ 55 and the deviation from the ideal body weight for either group, nor was there any significant difference between the two groups in either change in body weight or deviation from ideal weight. The lack of significance, however, could be due to too small a

number of cases or too short a period of observation of body weight after BZ 55.

Effect of BZ 55 on Fasting (6 a.m.) Blood-sugar Levels.—The results of the mean 6 a.m. level of blood sugar for the group of successes and failures, averaged over five days without insulin, together with the mean reduction in blood-sugar level averaged over the five days following the administration of BZ 55, are summarized in Table VI, and

TABLE VI.—Effect of BZ 55 on Fasting (6 a.m.) Blood-sugar Levels

	6 a.m. Blood-sugar Level Before BZ 55 (mg./100 ml.)		Reduction in Blood-sugar Level After BZ 55 (mg./100 ml.)		No. of Cases
	Mean	Range	Mean	Range	
Successes	215	132 to 275	73	15 to 132	16
Failures	267	123 to 421	29	-60* to 150	18

*—, Increase in blood-sugar level.

FIG. 1.—Effect of BZ 55 on fasting blood-sugar level.

expressed graphically in Fig. 1. The correlation between the 6 a.m. mean blood-sugar level before treatment and its reduction after treatment is statistically significant ($P < 0.01$), and the mean 6 a.m. blood-sugar level is higher among the group of failures than among the group of successes ($P < 0.05$). When the regression on initial blood-sugar level is allowed for, the fall in the 6 a.m. blood-sugar level after BZ 55 is significantly greater ($P < 0.01$) in successes than in failures.

There is therefore, in general, a fall in the resting blood-sugar level of the failures after BZ 55 administration, but it is less pronounced than that observed in the successes, and, in view of the higher mean initial levels in the former, their blood sugar levels are not reduced to within the normoglycaemic range.

Effect of BZ 55 on the Postprandial (2 p.m.) Blood-sugar Levels.—The results of the mean 2 p.m. level of blood sugar for the two groups of patients averaged over five days without insulin, together with the mean reduction in blood-sugar level averaged over the five days following BZ 55 administration, are summarized in Table VII. An analysis of variance revealed no correlation between the fall in blood sugar after BZ 55 and the mean level before administration, which is in contradistinction to the results for fasting (6 a.m.) levels. The average blood-sugar level at

TABLE VII.—Change in Postprandial Blood-sugar Levels (2 p.m.) After Administration of BZ 55

		2 p.m. Blood-sugar Level Before BZ 55 (mg./100 ml.)	Reduction in Blood-sugar Level After BZ 55 (at 2 p.m.) (mg./100 ml.)	No. of Cases
		Mean	Range	
Successes	Mean	272	87	15
	Range	165 to 376	171 to 37	
Failures	Mean	354	-182*	18
	Range	176 to 474	197 to -182	

*—, Increase in blood-sugar level.

2 p.m. before treatment is lower for the successful group than for the failures ($P = 0.01$), and the reduction in blood sugar is greater in the former group than in the latter ($P = 0.01$).

Mean Rise in Blood-sugar Levels from 6 a.m. to 2 p.m. Before and After Administration of BZ 55.—This analysis was undertaken to determine the effect of BZ 55 in controlling the postprandial rise in blood-sugar levels. The average of the mean initial blood-sugar levels at 6 a.m. before and after treatment, and the corresponding average of the mean difference between the 2 p.m. and 6 a.m. blood-sugar levels are shown in Table VIII. There is no regression

TABLE VIII.—Mean Rise in Blood-sugar Levels from 6 a.m. to 2 p.m. Before and After the Administration of BZ 55

		6 a.m. Blood-sugar Level (mg./100 ml.)		Increase in Blood-sugar Level at 2 p.m. (mg./100 ml.)		No. of Cases
		Before BZ 55	After BZ 55	Before BZ 55	After BZ 55	
Successes	Mean	211	140	55	46	15
	Range	132 to 298	89 to 197	0 to 164	3 to 107	
Failures	Mean	267	238	83	118	18
	Range	123 to 421	119 to 396	-3* to 162	-140* to 408	

*—, Decrease in blood-sugar level.

of the postprandial rise in blood-sugar level on the 6 a.m. level; the mean 6 a.m. level is lower after BZ 55 administration (successes, $P = 0.001$; failures, $P = 0.05$); the mean blood-sugar level of the failures is higher at 6 a.m. than that of the successes ($P = 0.001$). The most important finding, however, is the lack of a significant difference between the postprandial rise before and after treatment with BZ 55 and the fact that this rise is greater in the group of failures than in the group of successes ($P = 0.01$). Furthermore, the postprandial rise is more variable in the group of failures after treatment with BZ 55 than before ($P < 0.002$). These findings suggest that BZ 55 exerts no action on the utilization of exogenous glucose and that it therefore may control the mechanisms of gluconeogenesis, glycolysis, or glycogenolysis.

Acute Effect of BZ 55 on Blood-sugar Levels of Overnight Fasted Patients whose Fasting is Continued from 6 a.m. to Midday.—The methods previously outlined for the two-day test were used and the mean 6 a.m. level of blood sugar following the administration of BZ 55 is recorded in Table IX. There is a positive regression of the reduction of blood sugar after BZ 55 on the initial 6 a.m. level, which is shown in Fig. 2. When the reduction in blood-sugar level is corrected for the initial 6 a.m. level it is greater in the successful group than in the failures ($P = 0.001$).

In addition the reduction in blood-sugar levels in the two-day test—that is, from 6 a.m. to midday—is greater than the mean reduction in fasting blood-sugar levels in the five days after administration of BZ 55 for the same patients.

TABLE IX.—Acute Effect of BZ 55 on Blood-sugar Levels of Fasted Patients from 6 a.m. to Midday

	6 a.m. Fasting Blood-sugar Level on Day BZ 55 was given (mg./100 ml.)		Amount by which Blood-sugar Level was Reduced 6 Hours after Administration of BZ 55 (Midday) (mg./100 ml.)		No. of Cases
	Mean	Range	Mean	Range	
Successes ..	224	129 to 303	*116	49 to 197	15
Failures ..	290	119 to 450	123	-15 to 249	14

Effect of BZ 55 on Glycosuria.—The mean of the amounts of glucose in 24-hour samples of urine (6 a.m. to 6 a.m.) for the five days prior to the administration of BZ 55, and the amount by which the glucose excretion is reduced in a corresponding period after treatment with BZ 55, are summarized in Table X. There is a positive regression of the reduction of glycosuria on the mean level before treatment

FIG. 2.—Effect of BZ 55 on 6 a.m. blood-sugar level. (Two-day test.)

with BZ 55 ($P=0.001$), and when the reduction of glycosuria is corrected for the mean initial level it is more pronounced in successful cases than in unsuccessful cases ($P=0.01$). The regression is shown in Fig. 3, and the high degree of correlation for the successful group is clearly evident. In nearly every instance there is virtually no glycosuria in the successful group following treatment with BZ 55.

TABLE X.—Effect of BZ 55 on Glycosuria

	Amount of Glucose Excreted in 24-hour Samples of Urine before BZ 55 Administration (g.)		Reduction in Amount of Glucose Excreted in 24-hour Samples of Urine after BZ 55 Administration (g.)		No. of Cases
	Mean	Range	Mean	Range	
Successes ..	30.4	1.3 to 82.6	23.8	1.3 to 77.0	15
Failures ..	61.3	26.8 to 116.3	19.8	16.5* to 57.1	15

*—, Increase in amount excreted.

FIG. 3.—Effect of BZ 55 on glycosuria.

Change in Volume of Urine Excreted and in Glycosuria Following Administration of BZ 55.—There is a reduction in the mean volume of urine excreted in both the successes and the failures which is not statistically significant (see Table XI). This is not surprising in view of the wide range in the volumes of urine excreted. There is no correlation between the change in urine volume and reduction in glycosuria in the successful group, but there is a significant correlation in the group of failures ($P=0.001$). These differences in correlation are evident in Fig. 4. In the group of failures, therefore, the smaller the volume of urine excreted in 24 hours after BZ 55 the less sugar will that sample

contain. The lack of correlation in the group of successful cases may be due to too small a number tested and a narrower range in quantity of urine excreted.

TABLE XI.—Change in Volume of Urine Excreted and in Glycosuria Following Administration of BZ 55

	Change in Volume of Urine Excreted after BZ 55 (ml.)		Reduction in Glucose Content of Urine after BZ 55 (g.)		No. of Cases
	Mean	Range	Mean	Range	
Successes ..	—199	—943 to 350	21.4	1.3 to 77.0	15
Failures ..	—248*	—1,080 to +463	12.8	—38.6† to 57.1	13

*—, Decrease in volume. †—, Increase in amount (g.).

FIG. 4.—Relationship between the change in volume of urine excreted and glycosuria after BZ 55.

Blood and Urine Sulphonamide Levels.—On the first group of 12 patients the blood sulphonamide levels on the day of the two-day test were estimated at hourly intervals after the dose of BZ 55; they showed a steady rise up to six hours in each patient. The blood sulphonamide levels at one hour and six hours after the treatment with BZ 55 are shown in Table XII. It can be seen that there are no differences between the levels of the successful cases and those of the failures. On all the other patients the blood sulphonamide levels were estimated on the day of the two-day test at six hours after the dose of BZ 55. The average level for free sulphonamide at this time was 11.9 mg. per 100 ml. for successes and 11.4 mg. per 100 ml. for failures, whilst the corresponding levels for conjugated sulphonamide were 0.8 mg. and 0.9 mg. per 100 ml. respectively. There was

TABLE XII.—Blood Sulphonamide Levels on the Day of the Two-day Test

Time		6 Successful Cases		6 Failures	
		Blood Sulphonamide (mg./100 ml.)		Blood Sulphonamide (mg./100 ml.)	
		Free	Conjugated	Free	Conjugated
1 hr. after BZ 55	Range	5–10	Nil	5.2–8.7	Nil
	Mean	6.9		7.0	
6 hrs. after BZ 55	Range	9.5–11.7	0.8–2.5	9.5–11.7	0.8–2.3
	Mean	10.65	1.48	10.6	1.56

TABLE XIII.—Excretion of Total Free and Conjugated Sulphonamide in 24-Hour Specimens of Urine in Patients Receiving a Maintenance Dose of 1 g. BZ 55 Daily

	Mg. of Sulphonamide Excreted 24 Hours		Ratio Free: Conjugated	No. of Cases
	Free	Conjugated		
Successes ..	468	180	2.60	13
Failures ..	325	348	0.93	10

no significant difference between the levels in either group. On maintenance doses of BZ 55 the blood sulphonamide levels six hours after 1 g. of BZ 55 ranged from 7.7 to 12.5 mg. per 100 ml. (mean 11.7 mg.), and eight hours after, from 8.7 to 23 mg. per 100 ml. (mean 13.6 mg.).

The total amount of free and conjugated sulphonamide excreted in 24-hour specimens of urine was also estimated

FIG. 5.—Excretion of free and conjugated BZ 55 in 24-hour specimens of urine when patients are receiving a maintenance dose of 1 g. of BZ 55 daily.

for patients during the in-patient period when they were receiving a maintenance dose of 1 g. of BZ 55 each day. On analysis, the results, presented in Table XIII, show that there is a significant positive correlation between the amount of free and conjugated sulphonamide excreted ($P=0.01$); the excretion of conjugated sulphonamide is higher in failures than in successes ($P<0.01$) and the difference between the excretion of free sulphonamide in either group is not significant. The evidence for the regression is shown in Fig. 5.

Complications of Treatment

Skin reactions occurred in 5 out of 45 cases. In four cases BZ 55 was then replaced by N-(4-methyl-benzosulphonyl)-N'-butyl-urea (D 860), and the rash, a typical maculopapular sulphonamide rash, in each case gradually disappeared. No other complications have occurred in our series so far.

Examples of Successful and Failed Cases

Case A.—A woman, aged 72. Diabetes was first diagnosed in November, 1955, following gradual onset of thirst, polyuria, lassitude, and loss of weight. On 20 units of insulin zinc suspension her urine was sugar-free. During the trial period in the ward without insulin her urine showed heavy glycosuria; her fasting blood sugars were over 200 mg. per 100 ml. and her postprandial blood sugars over 300 mg. per 100 ml. She was, however, symptom-free and had no acetonuria. The test dose of BZ 55 led to a marked drop in the blood sugar, and subsequently a maintenance dose of 1 g. daily cleared the urine of sugar and lowered her blood-sugar levels. This was an example of a successful replacement of insulin by BZ 55 as shown in Fig. 6.

Case B.—A woman aged 57. Diabetes was diagnosed six years previously, following a history of thirst and polyuria. Her diabetes had been controlled on 30 units of protamine zinc insulin daily. She was admitted to the ward and her insulin discontinued for five days. During this period she showed heavy glycosuria and acetonuria. BZ 55 was administered and caused some fall in the blood sugar the first day, but after that blood and urine sugars rose

steadily on 1 g. a day. Trebling of dose to 3 g. daily did not reverse this trend; she began to complain of thirst and polyuria. Insulin was reinstituted, with rapid improvement. This was an example of failure to replace insulin by BZ 55 as shown in Fig. 7.

Discussion

The fasting blood-sugar level would appear to be an important factor in assessing the effect of BZ 55. In none of our successful cases was this more than 275 mg. per 100 ml. While these patients were in the ward, on a measured diet but without insulin, they showed raised blood sugars and considerable glycosuria.

There was, however, no acetonuria; thirst and polyuria were slight. They might thus be described as mild diabetics, and a maintenance dose of 1 g. daily was successful during the period of observation in keeping their blood level normoglycaemic and the urine free of sugar.

BZ 55 proved ineffective in the control of diabetics who easily developed acetonuria. The fasting blood sugars ranged from 123 to 421 mg. per 100 ml. In some patients substitution of the morning dose of insulin by BZ 55 had led by the afternoon to rising blood sugars, acetone in the urine, and symptoms of thirst, necessitating administration of insulin. These were young diabetics normally difficult to control. In the remainder of the failed cases the test dose of BZ 55 caused a significant drop from the fasting blood-sugar level, but subsequent maintenance therapy failed to prevent hyperglycaemia and glycosuria, and in some there was gradual onset of thirst, polyuria, and loss of weight. Trebling the dose of BZ 55 did not reverse this trend.

Failure to control these severe or moderately severe diabetics on oral therapy alone does not exclude the possibility

FIG. 6.—Details of Case A, a woman aged 72. (Success.)

FIG. 7.—Details of Case B, a woman aged 57. (Failure.)

that BZ 55 given in conjunction with insulin might reduce the amount of insulin required or might lead to an easier control in unstable patients; these problems were not investigated.

The response of patients to BZ 55 was not related to the duration of their diabetes or to the incidence of complications. In the group of successes, however, there was generally a history of diminishing insulin requirements, while in the failures the need for insulin was greater, and had, if anything, increased with the progression of the disease. It may be that in the successful cases with mild diabetes BZ 55 acted either by stimulating the secretion of endogenous insulin or by preventing its destruction, while in the failed cases there was insufficient endogenous insulin.

In 39 cases the initial dose of BZ 55 produced hypoglycaemia which was greater than that produced by any subsequent dose. This suggests that following the initial dose the available insulin, or the mechanism regulating its use, was quickly exhausted in those diabetics who subsequently failed to respond.

BZ 55 exerted no control in either group over the post-prandial rise in blood sugar. Its action is therefore probably on the mechanism controlling the utilization of endogenous glucose. With that in view, in all patients maintained on BZ 55 stress has been laid on the importance of adhering to the dietary regime.

German workers have indicated that BZ 55 and D 860 are most likely to be successful in obese diabetics. The present study showed the mean deviation in body weight in the group of successful cases to be slightly lower than the ideal weight, with only one case of gross obesity. This indicates that the drug can act as successfully in underweight patients as in those who are normal or overweight. During their period as in-patients, body weight did not alter significantly once BZ 55 therapy had begun.

Kinsell *et al.* (1956) found in two severe diabetics that the greater part of the sulphonamide excreted in the urine was conjugated in the patient treated successfully by BZ 55, whereas the greater part of the urinary sulphonamide was in the free state in the patient who failed to respond. The present investigations were at variance with this, since it was found that the excretion of conjugated sulphonamides was higher in the failed cases than in the successes.

Skin reactions occurred in 11% of the cases, but gradually disappeared when the patients were transferred to D 860. In view of these toxic manifestations, and the possibility of other adverse effects which may appear, particularly in the blood or liver, caution must be exercised before deciding to treat a patient with these drugs. Finally, it must be stated that the mode of action of BZ 55 remains unknown, as does its influence on the complications in the vessels, kidneys, and eyes which occur in long-term diabetes.

For these reasons BZ 55 must not be regarded as having reached therapeutic status in the management of the diabetic patient.

Summary

The response to the administration by mouth of BZ 55 tablets was studied in a group of 45 diabetics normally requiring insulin. These studies were undertaken under conditions of controlled diet on in-patients.

Diabetics in whom the drug was successful often had a history of diminishing insulin requirements. In no instance was the fasting blood-sugar level greater than 275 mg. per 100 ml., and the fasting range was from 123 to 275 mg. per 100 ml.

Diabetics in whom the drug failed tended to have a higher insulin requirement than the previous group. The fasting blood sugars ranged from 123 to 421 mg. per 100 ml. and there was a tendency to acetonuria.

BZ 55 does not exert any influence over the post-prandial rise in blood sugars, either in the group of successes or in the failures.

There is no difference in levels between free and conjugated sulphonamides in the blood between successes and failures. In the urine there is more excretion of conjugated sulphonamides in the failed cases than in the successful ones.

Five patients (11%) developed skin reactions due to the drug.

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REFERENCES

- Achelis, J. D., and Hardebeck, K. (1955). *Dtsch. med. Wschr.*, **80**, 1452.
Bänder, A., *et al.* (1956). *Ibid.*, **81**, 823.
Bertram, F., Bendfeldt, E., and Otto, H. (1955). *Ibid.*, **80**, 1455.
Bratton, A. C., and Marshall, E. K. (1939). *J. biol. Chem.*, **128**, 537.
Franke, H., and Fuchs, J. (1955). *Dtsch. med. Wschr.*, **80**, 1449.
Hagedorn, H. C., and Jensen, B. N. (1923). *Biochem. Z.*, **135**, 46.
Kemsley, W. F. F. (1951-2). *Ann. Eugen.*, **16**, 316.
King, E. J. (1951). *Micro-analysis in Medical Biochemistry*, 2nd ed. London.
Kinsell, L. W., Brown, F. R., jun., Friskey, R. W., and Michaels, G. D. (1956). *Science*, **123**, 585.

CLINICAL TRIAL OF THE NEW ORAL HYPOGLYCAEMIC AGENT BZ 55

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The discovery of the hypoglycaemic action of certain sulphonamide preparations, and their use in the treatment of diabetes, has recently been the subject of a number of publications on the Continent, notably in Germany (Bertram *et al.*, 1955; Franke and Fuchs, 1955; Loubatières, 1955; Quilley, 1955). The drug most commonly used has been N-butyl-N'-sulphanilylurea (BZ 55, "nadisan," "carbutamide"), and the preliminary results obtained in a clinical trial of this substance in the Diabetic Department at King's College Hospital are briefly described.

In the absence of reliable information on the clinical type of diabetes and on the influence of diet in the cases treated in Germany and elsewhere, it was decided first to give BZ 55 to a small series of representative diabetics, with the object of correlating such broad clinical distinctions as age, severity, insulin requirement, and duration of the diabetes with responsiveness to the drug. From the results so obtained it was hoped that a group or groups of patients could be selected for treatment in the out-patient department; this policy was largely dictated by lack of beds.

Clinical Material

Representative Group.—A group of 21 patients were selected to cover a wide range of age, weight, and severity and duration of diabetes for the purpose outlined above; eight of these were in-patients.

Selected Group.—A group of 17 patients were treated in the out-patient department, the criteria for selection being based on results obtained in the representative group.