given in addition to their normal daily dose of insulin. It follows that, when insulin is a vital necessity in treatment, any attempt to replace it by BZ 55 is almost certain to result in a serious relapse. It is of interest that no response was obtained in a child of 9 with diabetes of five months' duration who had never had insulin and whose urine contained no ketone bodies.

On the negative side no constant relationship could be demonstrated between the response to BZ 55 and the age of the patient, the duration of the diabetes, or the duration of insulin therapy. It seemed to be immaterial that in some of those who responded there had in the past been episodes of severe ketosis, associated with infection or other general conditions, the treatment of which required large doses of insulin.

The factors in the representative series of 21 patients most consistently related to responsiveness to BZ 55 were the age of onset of diabetes, over 40 years in all cases, and absence of more than minimal ketonuria while on dietary control without insulin. The second series of 17 patients was therefore selected on these criteria. All the patients in this group were treated in the out-patient department and all showed some response to BZ 55. This would seem to indicate that the criteria used for selection were, in a limited sense, reasonably correct, and lend support to the findings of others who have carried out more extensive therapeutic trials with BZ 55 (Symposium 1956a, 1956b).

Our thanks are due to Professor G. Gray, the late Dr. H. Whittaker, Dr. J. A. Robertson, and other members of the staff of the Diabetic Department who co-operated in this trial, and also to Eli Lilly and Co. and Boots Pure Drug Co. for supplies of BZ 55.

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BZ 55 IN DIABETES

BY

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This paper gives an account of the administration of BZ 55 (N-butyl-N'-sulphanilylurea) under controlled conditions to 20 diabetic patients. They were a carefully selected group of diabetics, 16 of whom came into the category of those who could not be satisfactorily controlled by diet alone but did not require large quantities of insulin and had never shown ketosis. Four required insulin to avoid ketosis. More extensive clinical studies on the effect of BZ 55 in severe diabetics and other investigations designed to shed light on the mode of action of this and other hypoglycaemic agents are at present in progress. These will be published later.

Methods

The patients given BZ 55 were in various groups. In Group 1 there were 10 in-patients who had blood-sugar estimations carried out thrice daily (fasting, at 4 p.m.—that is, four hours after lunch but before tea—and at 8 p.m.,

TABLE I.—Summary of Clinical Data

Case No.	I.P. O.P.	Sex and Age	Age of Onset of D.M. (Yr.)	% of Av. Wt.	Insulin (Units)	Diet (Cals.)	Family History	Response to BZ 55
1	I.P.	M 68	36	82	16-32	2,000	—	+
2	I.P.	F 62	61	80	20	2,000	—	+
3	I.P.	M 73	70	(Amputation)	20	1,900	—	+
4	I.P.	M 82	82	89	24	1,800	—	+
5	I.P.	F 56	52	89	Nil	1,500	—	+
6	I.P.	F 45	45	103	20	2,000	—	+
7	I.P.	F 51	51	120	Nil	1,200	—	+
8	I.P.	F 55	50	113	16	2,000	—	+
9	I.P.	F 68	63	111	16	2,000	—	+
10	I.P.	F 55	ca 48	110	52	1,000	—	+
11	O.P.	M 62	51	68	20	2,000	+	+
12	O.P.	M 71	66	105	Nil	2,000	—	+
13	O.P.	F 54	53	104	16	1,600	—	—
14	I.P.	M 54	ca 36	96	80	1,850	—	—
15	I.P.	F 40	34	96	44	2,000	—	—
16	I.P.	M 25	25	86	64	2,500	+	—
17	I.P.	F 58	56	75	Nil	1,500	—	+
18	O.P.	F 47	44	125	16	1,000	—	—
19	O.P.	F 55	41	87	128	2,000	—	+
20	O.P.	F 63	56	91	16	1,800	—	+

two hours after the evening meal) (Table I). The 24-hour urinary output of sugar was measured, and thrice daily a semi-quantitative test of urine for sugar ("clinitest") and for ketones ("acetest") was carried out. The patients' weights were measured at the same time each morning, with the patient fasting and having emptied bowel and bladder.

Diet was constant throughout the period of each trial and no insulin was given. When it was judged that no further improvement was being obtained by the dietary restrictions alone, or hyperglycaemia was increasing, BZ 55 was given. This initial period varied from two to ten days. A high "loading" dose of BZ 55 was given over the first three days, and then a dose of 0.5 g. twelve-hourly was maintained. Daily measurement of BZ 55 blood level was carried out on a specimen obtained before the morning dose of the drug was given. The length of time over which the response to BZ 55 was observed varied with several factors, in particular the patient's willingness to remain in hospital. In three cases the effect of withdrawal and subsequent readministration of BZ 55 was studied.

The response of three out-patients (Group 2) was similarly observed (Nos. 11-13, Table I), the criteria in these cases being 24-hour urinary sugar outputs three or four times a week, with blood sugars measured three or four times a week on specimens taken at the same time each day. These patients tested their urine for sugar by clinitest regularly at home and their weight was measured on each visit to hospital. A control period of two weeks was established when, unknown to the patients, dummy tablets identical in appearance with BZ 55 tablets were administered. A minimum period of two weeks was studied to learn the effect of the drug.

An attempt was made to determine the efficacy of BZ 55 in a third group of three patients (Nos. 14-16, Table I) in whom previous study had shown that they undoubtedly required insulin to remain free from ketosis. In these cases BZ 55 was given in addition to a constant dose of insulin. With this exception observations were carried out as in Group 1. A minimum of five days' steady control was obtained before adding BZ 55 to the regime of diet and insulin.

Finally, in Group 4, consisting of one in-patient and three out-patients (Nos. 17-20, Table I), BZ 55 was used simply as a "therapeutic" agent, the response being judged by three daily semi-quantitative urine tests for sugar by clinitest. Of the three out-patients one was ill-controlled on diet alone, having sporadically in the past been given up to 16 units of insulin a day; the second was an insulin-resistant diabetic on 128 units of insulin a day (and this dose remained constant); and the third, an obese (125% of average weight) 47-year-old diabetic with heavy glycosuria despite an advised

diet of 1,000 calories. The in-patient was an elderly mild diabetic requiring insulin during the stress of a leg amputation for diabetic gangrene.

With Cases 14, 15, 16, and 19 the insulin dosage quoted is that given at the same time as BZ 55. With the remainder the dose of insulin is that on which the patient was controlled prior to the trial.

In all these cases the blood sugar was measured by the Hagedorn-Jensen method, urinary sugar by the quantitative Benedict method, and blood BZ 55 by the method adapted by King (1951) from the procedure of Bratton and Marshall (1939).

In addition to the procedures outlined above, the effect of BZ 55 on the arteriovenous difference in blood sugar was investigated. Six patients were studied, one on two occasions. In these instances the sugar estimations were done in duplicate by the Somogyi-Nelson method. Capillary blood was used as equivalent to arterial blood in glucose content, and venous blood was drawn from the dependent arm without stasis being induced by a tourniquet.

Results

In each of the first 16 patients (Table I) the mean blood-sugar level (usually the fasting level, unless otherwise stated) before and during treatment with BZ 55 was calculated and the significance of the fall in blood sugar determined. Only Group 1, with 10 patients, however, was large enough for further analysis. The mean fasting blood sugars of this group are shown in Fig. 1. In all but the last patient, the fall in fasting blood sugar on BZ 55 treatment was highly significant, as was also the mean fall for the whole group, shown in the final pair of columns.

A superficial inspection of these data suggests that, within the limits of the blood-sugar levels involved, the fall in blood sugar is greater when the initial level is high. On plotting the values for the fall in each patient against the initial level (Fig. 2, upper graph) there was, in fact, found to be a highly significant correlation ($P < 0.01$) between fall in blood sugar and the initial blood-sugar level. On the other hand, there was not a significant correlation ($P = 0.1$) between the mean fasting blood-sugar levels before and during BZ 55 treatment (Fig. 2, lower graph). These two facts together indicate that, in the mild diabetic at any rate, BZ 55, in the dose used, lowers the fasting blood sugar from its initial level down to a level approximating the normal.

The effect of BZ 55 on the blood sugars of the three out-patients studied in detail (Cases 11-13) was statistically analysed in each case. In Cases 11 and 12 there was a clear-cut positive response to the drug. Case 13 did not respond. The fluctuation in blood-sugar estimations obtained made it clear that study of the effect of BZ 55 on out-patients was unrewarding.

FIG. 1.—Effect of BZ 55 on diabetics maintained on diet alone (Cases 1-10).

FIG. 2.—Correlation between (upper graph) mean fall in fasting blood-sugar on BZ 55 and initial fasting blood sugar, and (lower graph) mean fasting blood sugar on BZ 55 and initial fasting blood sugar.

Of the three patients (Cases 1, 7, and 10) in whom the effect of withdrawal of BZ 55 was studied, one (Case 1) relapsed in less than 72 hours, when there was still a BZ 55 blood level of 4.3 mg./100 ml. (Fig. 3). The other two took 9 and 15 days respectively before blood-sugar levels tended to rise.

The fasting blood sugars in Case 3 are recorded in Fig. 4 and compared with the BZ 55 blood level. With this patient a better response was noted when the large initial dose of BZ 55 was given than when the maintenance level was reached. Subsequently the maintenance dose was doubled to 1 g. twice daily, with the described effect.

One patient (Case 7) was readmitted six weeks after her initial trial of BZ 55. A mild diabetic, she had a good response and was discharged taking 0.5 g. twice daily. Gradually her diabetic symptoms, especially pruritus vulvae, returned. On readmission there was some improvement on the more exact in-patient 1,200-calorie diet. Satisfactory control, however, was obtained only on doubling the maintenance dose to 1 g. twice daily.

A statistical analysis of the fasting blood sugars of Cases 14, 15, and 16 is shown in Table II, in which the figures obtained when the patients were on insulin alone are compared with those obtained when BZ 55 was given in addition to the same or smaller dose of insulin. It will be seen that two of the three patients had very high initial blood sugars, which were reduced only to the 180-200 mg./100 ml. level by BZ 55. In this group, too, it will be seen that, although

the fall in blood sugar on BZ 55 is of the same order as in the first group, in no case is it significant. This is due to a greater fluctuation in blood-sugar levels in the insulin-treated group. Further analysis of this group is, of course, impossible until the numbers have been increased.

Case 15 is of interest. This patient was reasonably well controlled on 44 units insulin zinc suspension (I.Z.S.) daily. The reduction of this to 36 units resulted in ketosis developing within 24 hours. After she had been on 44 units of I.Z.S., with BZ 55 in addition, insulin dosage was reduced once more to 36 units. The patient was seven days on this regime without ketosis developing. The stoppage of BZ 55 on the eighth day was followed by ketosis on the ninth day, when the BZ 55 blood level was 4.6 mg. per 100 ml.

With the therapeutic use of BZ 55 in Cases 17-20, glycosuria was cleared in Cases 17 and 20 and, subjectively

and by urine tests, control was better in Case 19. There was no apparent response to the administration of BZ 55 in Case 18.

No constant effect of BZ 55 on the arteriovenous difference of blood sugar was found. A decrease in the difference occurred as often as an increase.

No change in weight was noted in spite of improvement in control.

Toxic Effects.—Two widespread and fairly typical sulphonamide skin rashes occurred. One cleared with the administration of antihistamines, and the other with the cessation of the drug. Two patients were mildly nauseated on high dosage.

Discussion

Statistical analysis of the data derived from the 10 patients in group 1 would lead to the following conclusions. BZ 55 would appear to have a "normalizing" effect on the blood-sugar levels of these mild diabetics, and the higher the initial fasting blood-sugar levels found the greater the effect. The effect does not seem to be due to an increased sensitivity to insulin.

The study of the effect of BZ 55 on the arteriovenous difference of blood sugar, and other unpublished observations we have made on serum inorganic phosphorus levels, would support this conclusion. In the more severe diabetics the fall in fasting blood sugar on BZ 55 was not statistically significant, and a larger group will have to be studied.

We can deduce no evidence in support of the contention that the drug is active only in overweight diabetics. The duration of the diabetic state has no correlation with the responsiveness of the patient. It is already evident from our limited experience of the drug that, although a satisfactory fall of blood-sugar and urine-sugar levels will occur in hospital on a carefully controlled diet, patients can relapse on a more liberal outpatient regime. In three of our patients it is now evident that 2 g. of BZ 55 is required daily to maintain a satisfactory clinical response. We have as yet no definite proof of the development of tolerance.

The fact that BZ 55 has already been shown to have toxic effects (Duncan, Baird, and Dunlop, 1956), and that it is also of course an antibacterial substance, is a challenge to the synthetic chemist to produce something better. Whether this compound proves ultimately to have a place in therapeutics or not, a laboratory tool of great importance is now available, and already new vistas in the intermediate metabolism of carbohydrate are appearing.

Summary

Results are reported of a clinical trial of BZ 55 on 20 diabetic patients, 14 of whom were in hospital. Ten mild diabetics, not satisfactorily controlled by diet alone, were studied under basal conditions and then on BZ 55 therapy and the same diet. Detailed measurements of blood and urine sugar were made, as well as of the blood level of BZ 55 and the daily weight. Three out-patients were studied similarly but in less detail. A further three patients who required insulin to prevent ketosis were studied in hospital when taking insulin and when taking BZ 55 in addition, the diet remaining constant. A fourth group of four patients were given BZ 55 simply as a therapeutic agent, in one case in addition to 128 units of insulin, and the effects were judged by the relief of symptoms and the results of qualitative tests for urinary sugar.

Statistical analysis of the data of the first group of 10 mild diabetics showed that the BZ 55 had a normalizing

TABLE II.—Effect of BZ 55 on Insulin-maintained Diabetics

Case No.	Treatment		Mean F.B.S.	n	t	P	Significance
	BZ	Insulin					
14	Before	80 u. I.Z.S.	136	6	1.94	0.08	—
	On	80 u. I.Z.S.	90	6			
15	Before	44 u. I.Z.S.	320	5	1.70	0.1	—
	On	36 u. I.Z.S.	211	8			
16	Before	84 u. I.Z.S.	274	6	1.54	0.15	—
	On	64 u. I.Z.S.	181	7

FIG. 3.—Case 1. Height 63 in. (160 cm.), weight 118 lb. (53.5 kg.). Effect on fasting blood sugar of stoppage and subsequent readministration of BZ 55, with concurrent BZ 55 blood levels.

FIG. 4.—Case 3. Effect on fasting blood sugar of doubling the dose of BZ 55, with concurrent BZ 55 blood levels.

effect on the fasting blood-sugar levels. The higher the initial fasting blood sugar the greater was the hypoglycaemic effect obtained. The four patients receiving BZ 55 in addition to insulin had better control than when receiving insulin only, but the series is too small to achieve significance. Studies of arteriovenous blood-sugar differences and of the changes in serum inorganic phosphorus levels provided no evidence that BZ 55 increased the effectiveness of the peripheral action of insulin.

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HYPOGLYCAEMIC SULPHONAMIDES IN TREATMENT OF DIABETES

BY

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Recent reports from Germany (Bertram *et al.*, 1955) have suggested that certain relatively non-toxic sulphonamides with a hypoglycaemic action may be of value in the treatment of diabetes mellitus. Because of the interest which has been aroused by these reports, the following preliminary account is being published. It deals with experience in a diabetic clinic where 24 patients have been treated with N-butyl-N'-sulphanilylurea (BZ 55, "carbutamide") for periods up to seven months.

The German workers found that this compound was most effective in middle-aged "stable" diabetics: stable, in this context, meaning that if patients were not receiving insulin although they were hyperglycaemic they did not develop ketosis, and if they were using insulin it could be stopped without any immediate rise of blood sugar or the development of ketosis. Diabetics of this type are often obese, and, believing obesity to be undesirable in diabetics, it is the practice in this clinic to endeavour to control the condition with a low-calorie diet with less than the usual proportion of carbohydrate. In most cases if the diet is followed for a few weeks weight is lost, the blood sugar falls, and symptoms and glycosuria disappear. In a few, although the weight comes down, hyperglycaemia, glycosuria, and occasionally some symptoms persist. In the past it has been necessary to use insulin to achieve normoglycaemia in these patients; recently we have been assessing the possible use of oral BZ 55 as an alternative.

Selection of Patients

Patients were selected for trial with BZ 55 on the lines indicated above. Of the 24 patients, nine were men. Ages ranged from 38 to 82 years (mean, 63), and the diabetes had been recognized for from 1 to 42 years (mean, 10). Nine patients had developed their diabetes before they were 45 years of age. Ten had received insulin at some time, and in six of these it was being taken in doses of 10 to 84 units a day up to the time of the trial of BZ 55. All except two of the patients had glycosuria when BZ 55 was started, six had mild diabetic symptoms, most commonly polyuria, and five had diabetic retinitis. No patient had at any time

had any significant degree of ketosis, although mild ketonuria had previously been observed in two. Thirteen patients were underweight when treatment was started; the majority of the others were only slightly overweight. Prior to treatment, three blood-sugar estimations were made on consecutive weeks ("random blood sugar"—that is, taken during the clinic between 10.30 a.m. and 12 noon after a normal breakfast—method of Kingsley and Reinhold (1949) modified). The means of these pre-treatment blood sugars are shown in Fig. 1. Patients who were on insulin had this stopped and were put on a low-calorie and restricted carbohydrate diet. BZ 55 was not started until the blood sugar exceeded 200 mg. per 100 ml.

Technique of Treatment

In most cases treatment was started with 2.5 g. the first day, 1.5 g. the next day, and 1 g. a day subsequently. In a number of cases BZ 55 was preceded by two weeks on inert tablets. During the control period and first few weeks of treatment the patients were on a low-calorie and restricted carbohydrate diet (1,250 calories, 100 g. of carbohydrate, in 12 patients; 1,500 calories, 125 g. of carbohydrate, 5 patients; 1,750 calories, 150 g. of carbohydrate, 7 patients). When it

FIG. 1.—Mean pre-treatment and most recent "random blood-sugar" levels in each patient and maintenance dose of sulphonamide.

FIG. 2.—Man aged 56. Diabetes 12 years. No insulin. Diet 1,250 calories (92 g. carbohydrate). High renal threshold. Diabetic retinitis. Response to BZ 55 and effect of substituting dummy tablets for two weeks.

Results

Diabetic symptoms when present have been relieved and many of the patients claim to have felt better as their blood sugars have come down. No alteration has been observed in the retinitis. The reduction of blood sugar is shown in Fig. 1; with two exceptions the level is now satisfactory. In one of these the dose of BZ 55 (0.5 g. a day) is probably too low; the other patient has a blood sugar of 238 mg. per 100 ml. although she is taking 2 g. of sulphonamide daily. Lack of control in this case is thought to be due to unsatisfactory dieting. Only two patients continue to have glycosuria—one the uncontrolled patient just mentioned, and the other on account of a low renal threshold. BZ 55 was discontinued temporarily in six