LONG-TERM RESULTS IN TREATMENT OF DIABETES MELLITUS WITH THE SULPHONYLUREAS

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There is no general agreement about the mode of the hypoglycaemic action of the sulphonylurea compounds. The experimental results have been so diversely interpreted as to indicate either a depression of hepatic glycogenolysis (Anderson *et al.*, 1956; Stowers *et al.*, 1958) or an increased peripheral utilization of glucose (Goetz *et al.*, 1956; Lundbaek *et al.*, 1958). However, there has been unanimity that the type of diabetes suitable for treatment with these drugs is the mild form in a middle-aged or elderly patient who is not liable to ketosis; if the patient is already being treated with insulin the dose should be less than 40 units daily.

At the Diabetes Clinic, Royal Victoria Hospital, Belfast, 291 patients have been treated with tolbutamide (36 of these were initially treated with carbutamide) for periods between 6 months and 2½ years (April, 1956, to October, 1958). The distribution in terms of time since the beginning of treatment is as follows: longer than 24 months, 39 cases; 18 to 24 months, 55 cases; 12 to 18 months, 100 cases; 6 to 12 months, 97 cases. The results have been studied to find how correct is the general concept of the type of patient suitable for treatment, particularly with regard to the long-term results. Since the site of action of tolbutamide is unknown, the problem has arisen whether the basic diabetic state is influenced by its use. We have therefore tried to assess changes in carbohydrate tolerance in some of these patients after a period of prolonged treatment.

The Patients

Of the 291 patients, 60 had previously received treatment with insulin. The remaining 231 had been attending the clinic for periods between a few months and 20 years. An attempt to control the diabetes by a reduction of the amount of carbohydrate in the diet had been made in all instances. The patients with a prolonged period of previous dietetic treatment had been well controlled until recent visits to the clinic, when it had been discovered that the hyperglycaemia and glycosuria were increasing despite adherence to the diet. Control of the diabetes was assessed by means of the estimation of the fasting (post-absorptive) blood glucose by the Herbert and Bourne (1930) modification of the Folin and Wu method. Venous blood for this was drawn at 7.30 a.m., 11 a.m., 4.30 p.m., and 10 p.m., no food having been taken in each instance during the previous three hours. The amount of sugar in the urine, as assessed by "clintest," was used only as a rough guide to the state of control, except in cases where the total 24-hour excretion of sugar was estimated. Assessment of the severity of the diabetes and of changes in carbohydrate tolerance was done on the results of an

intravenous glucose-tolerance test and the calculation of the glucose assimilation coefficient "K" as described by Conard *et al.* (1953).

Results

The response to sulphonylurea treatment of the 231 patients who had not been treated previously with insulin is shown in Table I.

TABLE I.—Response to Sulphonylurea Treatment of 231 Diabetic Patients Not Previously Treated with Insulin

	Success		Failure	
	Males	Females	Males	Females
No.	46	141	20	24
Average age (years)	63	65½	56½	66
Duration of diabetes (years)	1½	3½	3½	3½
Average weight (lb.; kg.)	154; 69.9	139; 63	131; 59.4	129; 58.5
Average fasting blood glucose:				
Before treatment (mg./100 ml.)	199	233	294	276
After* treatment (mg./100 ml.)	107	123	243	225
Average fasting blood glucose now	103	117	—	—

All blood-glucose values are the mean of four tests. * Taken 10-14 days after start of treatment.

Sex and Age

There is a 2.5 to 1 ratio of females to males in the entire series, but this is not an unexpected finding in a group of diabetic patients over 40 years of age. In the female group the proportion of initial failures to treatment was 15%, whereas in the males it was 30%. When the occurrence of failure among the females and males was compared in a $2 \times 2\chi^2$ table, it was seen that the incidence of failure in the males was significantly higher ($0.02 > P > 0.01$). However, though the males were all over 40 years old, their average age was lower than that of the females, and this finding was more pronounced in the failure group than in the success group. The effect of age by decades on the response

FIG. 1.—Effect of age on response to treatment.

to treatment is shown in Fig. 1. The higher incidence of failure below the age of 50 was associated with the large number of males in this group. Over the age of 80 a high incidence of failure (in both sexes) was also noted.

Duration of Diabetes

The male "successes" had a shorter average duration of previous diabetes (1 year 8 months) than either the male "failures" or the female group as a whole (3 years 6 months). In Fig. 2 it will be seen that, whereas the duration of previous diabetes had little effect on the response in the females, in the males there was a difference between a short and a long duration of the diabetes.

Severity of Diabetes

The average initial fasting blood glucose in the successful cases was lower than in the failures, and this was most pronounced in the male group (Table I). This finding is further illustrated in that 44% of the failures had average initial blood sugars greater than

FIG. 2.—Effect of the duration of previous diabetes on response to treatment.

300 mg./100 ml., whereas only 3% of the successes had average initial figures in excess of this. The average initial amount of glucose excreted in 24 hours by a group (eight patients) with a successful response was 22.6 g., whereas a similar group of failures had an average excretion of 67.5 g. in 24 hours. In the successful cases glycosuria ceased or was greatly decreased; the highest excretion after treatment was 9.5 g. in 24 hours. Ketone bodies could not be detected by "acetest" tablets in the urine of any patient responding to treatment, but were present in the urine of one-third of the patients who did not respond. Even among those who did not respond to treatment a further difference in behaviour can be seen. During the initial 10 days of treatment the patients without ketosis showed an average fall of 66 mg./100 ml. in the fasting blood-glucose levels. The patients with ketosis had practically no alteration in the fasting blood-glucose (an average fall of 16 mg./100 ml.) on tolbutamide treatment. It was found that an initial period of insulin therapy resulted in the development of partial responsiveness to tolbutamide in some of these patients, and in three cases the response was sufficient to permit long-term oral treatment.

The fasting blood glucose in the successful cases at 10–12 days after treatment illustrates the response that can be achieved by tolbutamide. In some patients satisfactory blood-glucose levels were obtained as early as the third or fourth day of treatment, but usually we have found it advisable to await the results of the second week before finally deciding the nature of the response. However, 7% of the successful group had only partially successful results at the end of the second week of treatment (average fasting blood glucose 160–

200 mg./100 ml.) but later tests at one to two months showed that satisfactory levels had been attained (<160 mg./100 ml.).

Secondary Failures

Eight patients (3%) have developed "secondary failure" after a period of treatment—that is, an initial successful response has been followed by a deterioration in diabetic control. All were females, their average age was 67 years, and the previous duration of diabetes averaged 4½ years. In none of these patients had the initial fasting blood sugars been greater than 300 mg./100 ml., but their average initial response to treatment had been less than the general average (average fasting blood sugar at 10 days was 133 mg./100 ml.). Failure had become established in each case between the sixth and twelfth months of treatment, though a gradual prior deterioration in the state of control had occurred for two to three months.

Weight

The patients were divided into three groups—obese, normal, and thin—on the basis of their initial weight. The thin patients did not appear to respond as well to treatment as either the normal or the obese patients (Fig. 3), but this difference was not significant at the 5% level, owing possibly to the small number (22) of thin patients in the group.

During the period of treatment there was no significant change in the average weight of the females (139 lb.—63 kg.) or of the males (154 lb.—69.9 kg.) successfully treated. In the entire group of successfully treated patients 48% gained weight, 47% lost weight, and in 5% the weight was unaltered. No correlation could be detected between the progress of the patients and their changes in weight, except that in the secondary-failure group seven of the eight patients gained weight, but in only two of these was the gain greater than 10 lb. (4.5 kg.).

FIG. 3.—Response to treatment in relation to patients' weight.

Diet

The patients had been placed under dietary control (carbohydrate portion of the diet weighed) before starting tolbutamide treatment. The average calorie content of the diet was 1,400, with a range of 1,000 to 2,200 calories; however, the majority of the diets were below 1,700 calories. In order to study what effect the limitation of carbohydrate and calorie intake had on the degree of response to treatment, a group of 30 patients were given a 400-calorie (70 g. of this being carbohydrate) increase in their diet. At the end of the two months the average fasting blood sugar of the group as a whole showed little change—107.5 to 106 mg./100 ml., but their average weight had increased by 3 lb. (1.4 kg.). Eight patients had a gain in weight greater than 5 lb. (2.3 kg.). The study was discontinued, as it was felt that, while strictness of the dietary control did not affect the blood-glucose levels, the rise in body weight was undesirable. One of the 30 patients became a secondary failure during this two-months period.

Changes in Carbohydrate Tolerance

At the onset of treatment intravenous glucose-tolerance tests were carried out in 62 patients. Control studies on normal subjects with the glucose method of estimation used by us gave a K value between 1.5 and 2. In diabetic subjects K ranges from 1.5 to 0, the lowest values indicating the more severe degrees of reduced carbohydrate tolerance.

The glucose assimilation coefficient K at the beginning of treatment had an average value of 0.77 in 50 successful cases. This test was then repeated in these same patients at periods varying between six months and one year after the onset of treatment. The average value of the second test was $K=0.97$. When these values were compared by Fisher's t test the difference was not significant— $0.10>P>0.05$. In 12 patients of the failure group the initial average K value was 0.41. Only two of the patients in this group had a K value greater than 0.6. Five of the patients who eventually became secondary failures had initial intravenous glucose-tolerance tests performed, the average being $K=0.53$.

Value of an Acute Test

It has been proposed by various workers that cases suitable for treatment with the sulphonylureas can be selected by their response to a single oral dose of these compounds. A fall of 30% in the blood sugar from the fasting level at three to four hours is regarded as indicating suitability for long-term treatment. An initial acute test was done in 51 patients: the results are shown in Table II.

TABLE II.—Results of An Acute Response Test to Tolbutamide in 51 Patients. Percentage Fall at 3 Hours in Fasting Blood Sugar After Ingestion of 3 g. of Tolbutamide

Fall	Long-term Successful Patients	Long-term Failure Patients
10%	2	9
10-20%	2	4
20-30%	4	5
30-40%	5	3
>40%	13	4

It will be seen that while the results of this test give a useful indication of the type of long-term response there are too many exceptions for it to be reliable.

Cases Previously Treated with Insulin

Sixty patients have been transferred from insulin treatment. This number is rather a small proportion of the total cases treated, and there are still some patients attending the clinic on treatment with insulin who would be suitable for transfer to oral treatment. It is probably ideal but not essential that cases should be transferred from insulin to oral treatment as in-patients; it is for this reason that the numbers in this group are small. We have details of three patients who developed moderate-to-severe diabetic ketosis (requiring intravenous fluids for correction) when transfer from insulin to tolbutamide was attempted on an out-patient basis. On the other hand, an intelligent patient able to test his own urine for sugar and ketones is usually at no great risk when transfer as an out-patient is made.

The average age of the 60 patients successfully transferred was 68 years and the average previous dose of insulin was 22 units daily. The largest previous insulin dose was 68 units daily, and seven patients had daily insulin doses in excess of 40 units. The effect of previous insulin dose on the response in adult onset

diabetes indicated that all the patients receiving under 10 units daily responded, that two-thirds responded if the previous insulin dose was 10-30 units, and that one-third responded if the dose was greater than 30 units. Two patients had been on insulin treatment for 22 years, and a third of the patients had been so treated for longer than 10 years.

Treatment

Dose of Drug.—Tolbutamide was given after meals two, three, or four times daily. The present distribution of the successfully treated patients according to daily dose is 1 g., 17%; 1.5 g., 22%; 2 g., 40%; 3 g., 21%. During the period of treatment it was found possible to decrease the original maintenance dose in some patients. Patients showing progressively less satisfactory blood-sugar results had the dose of tolbutamide increased to the maximum of 3 g. All the patients who developed a secondary failure required the larger doses (either 2 or 3 g.) from the beginning of their treatment.

Toxic Effects.—The toxic effects observed in the whole series of patients over 2½ years were few. In three patients treatment had to be stopped because of nausea and vomiting. One of these had a previous history of peptic-ulcer and dyspepsia. In two other patients treatment was persisted with despite some nausea, and it was found that this symptom soon ceased. In three patients (one had a previous history of eczema) an itchy papular skin rash occurred. One patient complained of generalized aching muscular pain, which ceased on stopping treatment.

Cessation of Treatment.—Oral treatment has been completely stopped in five patients. In three of these relapse occurred and treatment was started again at one, two, and six months after the original course was stopped. The other two have remained in good control for two and five months respectively.

Control During Infections.—Three patients have become mildly ketotic during acute pulmonary infections and were changed temporarily to insulin treatment. On the other hand, some were acutely ill with influenza during the autumn of 1957 without loss of "diabetic control."

Discussion

This study summarizes our clinical experience with the oral treatment of diabetes over a period of 2½ years. The results do nothing to explain the mechanism by which the sulphonylureas exert their hypoglycaemic action, except that, even within a group of relatively mild adult cases of onset diabetes, those not responding to treatment have a more severe form of the disease than those who respond. In non-responsive as opposed to responsive patients, the fasting blood glucose and the 24-hour urinary excretion of glucose were higher, the excretion of urinary ketone bodies was more common, and the intravenous glucose-tolerance test showed less ability to utilize glucose. These findings support the concept that patients responding to the sulphonylureas have some endogenous insulin secretion. The dependence for success of these drugs on endogenous insulin has led to the hypothesis that they act either by augmenting the circulating insulin or by rendering it more effective. As against this, the experimental work has failed to demonstrate the concomita of an increased peripheral insulin effect, such as the fall in the serum phosphate, the rise in pyruvic-acid level, and the increase

in the arteriovenous glucose difference (Moorhouse and Kark, 1956; Purnell *et al.*, 1956).

In a previous study we were unable to demonstrate by the rat-diaphragm technique any increase in the insulin-like activity of the serum in diabetic patients on tolbutamide treatment (Weaver *et al.*, 1958). However, should the hypoglycaemic properties of sulphonylureas be due entirely to a depression of hepatic glycogenolysis, such an effect is probably manifest only if it is associated with some peripheral utilization of glucose, and hence the dependence on insulin.

The finding that males are less likely to respond than females might be expected from the results of Wrenshall and Hamilton (1957) on the levels of insulin extractable at post-mortem examination from the pancreas of diabetic subjects. Their study showed that, at an equivalent age and duration of diabetes, males had a lower content of pancreatic insulin. The greater incidence of failure in patients over 80 years may be related to the observation of Joslin *et al.* (1952) that diabetes at this age resembles more the juvenile than the average adult onset type. Changes in weight in relation to the degree of diabetic control (as judged by the blood-sugar levels) have been relatively unimportant during the period of study, except that some control of the diet is necessary to prevent these patients gaining weight rapidly. Neither the duration of previous diabetes nor the duration of previous insulin treatment seemed to be of any importance in determining the type of response in the female. The duration of previous diabetes may be of some importance in the male.

As regards the severity of the diabetes, the findings of Dunlop (1957) that a patient with a fasting blood sugar greater than 300 mg./100 ml. is unlikely to respond seems to be an important differential criteria. The presence of ketones in the urine even in "trace" quantities, lessened (or almost excluded) the chance of a successful response. An acute test for selecting responsive patients is of limited value only. The previous dose of insulin seems to be important, and the chance of failure increases greatly when the total daily dose is more than 30 units. On the other hand, the duration of insulin treatment does not seem to influence the result. In patients already on insulin treatment the best criteria for the selection of suitable cases for the trial of oral treatment are a history of an original mild onset of the diabetes, original fasting blood-glucose values less than 300 mg./100 ml., and absence of ketones from the urine. The patient's progress on treatment with insulin should have been relatively uncomplicated, particularly in regard to an absence of sudden fluctuations in the degree of diabetic control. During prolonged treatment the difficulties encountered are few, toxic effects are slight, and secondary failure is rare. During acute infections, the patient should be watched carefully for signs of ketosis.

The most significant observation in this study is that prolonged treatment with tolbutamide does not appear to lead to a deterioration in the diabetes. The intravenous glucose-tolerance tests performed at the onset and after prolonged treatment indicate that this drug has not adversely affected the disposal rate of sugar in these patients. The possibility of eventual " β -cell exhaustion" has been mentioned in earlier reports, but these results on the assimilation rate of intravenously administered glucose appear to exclude this, at least in terms of treatment for up to one year.

Summary

The results of oral therapy with tolbutamide in 291 diabetic patients treated for periods up to 2½ years have been studied.

The findings with regard to the type of patient suitable for this treatment are largely in agreement with the previous studies of other workers.

A difference not previously reported in responsiveness of males and females was noted.

Studies on the assimilation of glucose administered intravenously indicated that the ability to utilize carbohydrate had not been adversely influenced by prolonged tolbutamide treatment.

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XANTHINURIA

BY

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In 1954 Dent and Philpot published an account of a patient with "xanthinuria." The only symptoms were urinary, and proved to be due to xanthine stones in the urinary tract. Chromatography of the urine showed a constant biochemical abnormality, in that xanthine and not uric acid was the predominant purine present, no other purines being found in detectable amounts. No purines at all could be demonstrated in the plasma by the chromatographic methods used, but these were not sensitive enough to detect concentrations of less than 1 mg./100 ml. Chemical analysis by the non-specific method of Folin and Trimble (1924) seemed to show that small amounts of uric acid were present both in plasma and in urine.

Dent and Philpot proposed two possible explanations for their results. The enzyme xanthine oxidase normally catalyses the oxidation of xanthine to uric acid; and this enzyme could have been absent or defective. Alternatively, the disorder could be explained by a very high selective renal excretion of xanthine—