# CLINICAL EXPERIENCE WITH TOLBUTAMIDE

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In 1955 Franke and Fuchs, in Germany, discovered that a sulphonamide, *carbutamide* (1-butyl-3-sulphanilylurea; BZ 55), reduces the blood sugar in normal subjects and in many patients with "mild" diabetes. This type of diabetes usually appears in middle-aged or elderly patients who are or have been overweight, who are relatively resistant to insulin, and who even when untreated rarely become ketotic. The drug is of no value in the treatment of "severe" or "juvenile" diabetes, for which insulin is essential. It frequently causes rashes and neutropenia, and deaths from agranulocytosis, and sulphonamide sensitization with myocarditis and granulomatosis, have been reported from America (Kirtley, 1957). Carbutamide has now been superseded by a similar compound, *tolbutamide* (1-butyl-3*p*-tolylsulphonylurea ("rastinon," "orinase," "artosin," D 860), which is equally effective and apparently much less toxic.

We present here the results of a trial of tolbutamide in 72 patients observed for up to one year. The response of some of them to carbutamide has already been reported (Walker *et al.*, 1956).

## Method

The trial was conducted on an out-patient basis. Patients were selected who were not grossly obese and had "mild" diabetes (as defined above) that could not be satisfactorily controlled by calorie and carbohydrate restriction alone. All our patients who were taking carbutamide and a few who were having insulin were transferred to tolbutamide. Those transferred from carbutamide were initially given the same dose of tolbutamide. Those who had been taking insulin were given reduced doses for a few days; the injections were then stopped and tolbutamide was started the next day. Patients who had had neither carbutamide nor insulin were observed on a strict low-carbohydrate diet for at least a month, and if their mid-morning blood sugar remained above 200 mg. per 100 ml. they were given tolbutamide. The starting dose for these patients and for those transferred from insulin was 0.5 g. two or three times daily, taken with the main meals. The dose was subsequently adjusted to a maximum of 4 g. daily, according to the blood-sugar response.

Patients transferred from insulin were seen daily during the withdrawal period and for the first week of tolbutamide treatment. Special attention was paid to ketonuria, which was regarded as an indication for stopping the drug and resuming insulin treatment. Subsequently these and the other patients were seen weekly for the first month and then at least once monthly. At each visit a record was made of symptoms, weight, urine, and blood sugar, and the presence or absence of ketonuria and proteinuria. White blood cell and platelet counts were made monthly, and liver-function tests (serum proteins and electrophoresis, serum bilirubin and alkaline phosphatase, thymol turbidity, colloidal gold, and zinc sulphate flocculation tests) were performed when treatment began and subsequently every two or three months.

## The Patients

Of the 72 patients, 41 had previously been treated by diet alone, 19 were transferred from carbutamide (dose 0.5 to 2 g., mean 1.1 g. daily), and 12 were transferred from insulin (dose 12 to 60 units, mean 26 units daily); 12 other patients, including four in the carbutamide group, had taken insulin at some time.

The age at diagnosis varied betweeen 22 and 78, mean 53 years, and the duration of the diabetes between 1 and 30, mean 6.6 years. Thirty-five of the patients were within 10% of their "expected" weight when treatment was started, 20 were more than 10% overweight, and 17 were more than 10% underweight. Seven patients are known to have been mildly ketotic at some time and five had diabetic retinopathy.

The necessity of following a strict diet was stressed, and the diets prescribed varied from 1,000 calories with 80 g. carbohydrate, to 2,200 calories with 220 g. carbohydrate, depending on the weight and activity of the patient.

## Results

*Duration of Treatment.*—The trial started in July, 1956. Details of the period of observation of patients who are still taking or have stopped taking the drug are as follows:

| Treatment in Weeks: | | < 14 | 14–26 | 27–39 | 40–52 |
|---|---|---|---|---|---|
| Still on drug | Transfers .. | 0 | 1 | 4 | 7 |
| | New cases.. | 15 | 12 | 10 | 4 |
| Stopped drug | Transfers .. | 4 | 0 | 2 | 1 |
| | New cases.. | 10 | 2 | 0 | 0 |

*Dosage.*—The number of patients receiving different dose levels as a maximum dose and for maintenance in those still on tolbutamide is as follows:

| Dose in Grammes Daily | 0·5 | 1 | 1·5 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|
| Maximum .. | — | 19 | 35 | 10 | 7 | 1 |
| Maintenance .. | 1 | 15 | 29 | 7 | 1 | — |

*Withdrawals.*—Nineteen patients stopped treatment for the following reasons: Resistance (requiring insulin), 2; failure to respond, 6; rash, 2; abdominal symptoms, 4; not required, 1; irregular attendance, 2; returned to insulin at own request, 2.

*Blood-sugar Response.*—The overall effect of tolbutamide on the blood-sugar levels of the 72 patients is shown in Fig. 1.

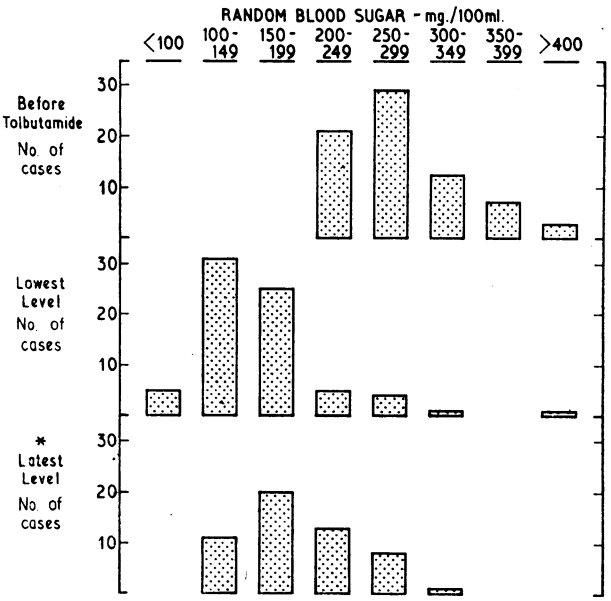


FIG. 1.—Overall effect of tolbutamide on the blood-sugar levels of the 72 patients treated. *The latest level is shown only for the patients still receiving tolbutamide.

Of the 53 patients who had not been treated with carbutamide, 7 showed no response, 33 showed an "immediate" response, the blood sugar falling during the first week of treatment, and 13 showed a "delayed" response, the blood sugar falling to a minimum over 12 to 16 weeks, irrespective of changes in weight. Twenty patients (61%) who showed the "immediate" response and 9 (69%) who showed the "delayed" response appear to be satisfactorily controlled by tolbutamide. Examples of the two types of response are shown in Figs. 2 and 3. All patients who had responded to carbutamide did so to tolbutamide, but one (Fig. 4) became resistant to it.

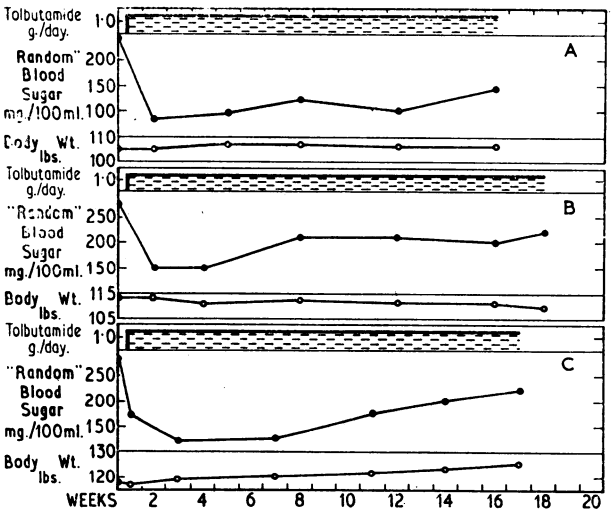


FIG. 2.—"Immediate" type of response to tolbutamide. A. Woman aged 56. Diabetes 4 years. No insulin. Expected weight 131 lb. (59.4 kg.). B. Woman aged 73. Diabetes 26 years. Transfer from P.Z.I. 16 units. Expected weight 127 lb. (57.6 kg.). C. Woman aged 62. Diabetes 4 years. Previous insulin. Expected weight 130 lb. (59 kg.).

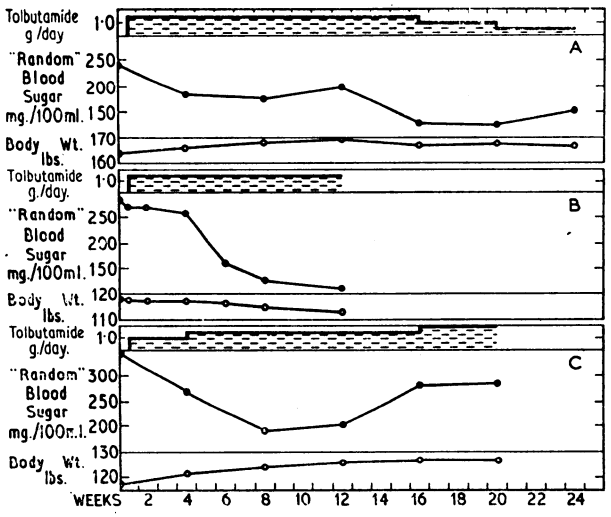


FIG. 3.—"Delayed" type of response. A. Man aged 81. Diabetes 30 years. No insulin. Expected weight 145 lb. (65.8 kg.). B. Woman aged 67. Diabetes 1 year. No insulin. Expected weight 119 lb. (54 kg.). Woman aged 76. Diabetes 2 years. No insulin. Expected weight 130 lb. (59 kg.).

*Relief of Symptoms.*—Twenty-six patients complained of diabetic symptoms (thirst 13, polyuria 20, and pruritus vulvae 6). Of these, 23 responded to tolbutamide, and their symptoms were relieved as the blood sugar fell.

*Side-effects* encountered were: Rash, 2 cases—tolbutamide stopped in each; abdominal pain, 4 cases—tolbutamide stopped in 2; vomiting, 1 case—tolbutamide stopped; activation of duodenal ulcer with melaena, 1 case—tolbutamide stopped. Details of the last case are as follows.

A married man, aged 66, was found to be diabetic in 1951 and was treated with a 1,250-calorie 125-g. carbohydrate diet and intermittently with small doses of insulin (6–12 units daily). He was admitted to hospital in March, 1957, with an infected foot; at that time he was known to have diabetic retinopathy, cataracts, peripheral neuropathy, and arterial disease. His diabetes was well controlled with a 1,250-calorie 125-g. carbohydrate diet and soluble insulin 6–8 units twice daily. He was transferred to tolbutamide, 0.5 g. thrice daily, but 11 days later he complained of abdominal pain and had a melaena for which blood transfusion was required. The pain was closely related to taking the tablets; it disappeared when the dose was reduced to 0.25 g. twice daily, and returned when it was put up to 0.5 g. twice daily. Tolbutamide was then stopped and the pain ceased altogether. A barium-meal examination showed a small hiatus hernia and a chronic duodenal ulcer. The patient denied previous dyspepsia or melaena.

There was no effect on the white-cell and platelet counts or on the liver-function tests.

*Resistance.*—Two patients who showed a good initial response failed to maintain a satisfactory blood-sugar level despite increasing doses of tolbutamide, strict adherence to a suitable diet, and failure to gain weight. They were both transferred to insulin treatment. It seems that four other patients are also becoming resistant to the drug.

A married man aged 64 was found to be diabetic in 1955. His symptoms were mild and were relieved by a 1,750-calorie 125-g. carbohydrate diet, but random mid-morning blood sugars remained above 200 mg. per 100 ml. and he was started on carbutamide, 0.5 g. twice daily, in May, 1956. He responded satisfactorily and was transferred to tolbutamide, 0.5 g. thrice daily, in August. After an initial response the blood sugar began to rise and continued to do so despite increasing doses of tolbutamide (Fig. 4). He was admitted to hospital two weeks after

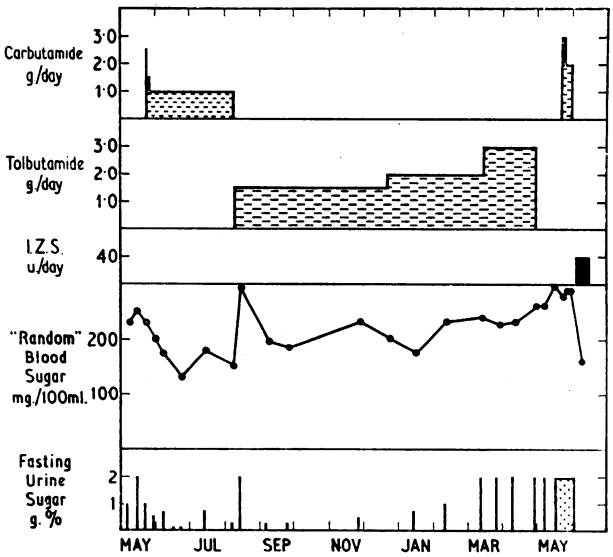


FIG. 4.—Development of resistance to tolbutamide. Case report in text.

stopping the drug and given carbutamide, 1 g. twice daily for 10 days, without any effect on his blood-sugar level. He became mildly ketotic and was eventually stabilized on a 2,250-calorie 225-g. carbohydrate diet with I.Z.S. 44 units daily. His weight was virtually constant throughout.

*Failures.*—Seven patients showed unequivocal failure to respond to tolbutamide. These include two who had been transferred from insulin treatment and four of the seven who were known to have been mildly ketotic at some time.

*Effect on Weight.*—Most responsive patients showed an increase in weight, and this was sometimes associated with decreased effectiveness of the drug. The overall effect on weight is shown below:

| No. of Patients | Before Treatment: Weight as % of "Expected" (Kemsley, 1951–2) | During Treatment: Gained | Unchanged | Lost |
|---|---|---|---|---|
| 20 | More than 10% overweight .. | 8 (0) | 7 (1) | 5 (0) |
| 35 | Within 10% of "expected" weight | 20 (0) | 10 (3) | 5 (2) |
| 17 | More than 10% underweight .. | 10 (0) | 2 (1) | 5 (0) |

The figures in parentheses give the number of patients in each group who failed to show any response to the drug.

*Present Assessment.*—In 22 of the 53 patients still taking tolbutamide control is unsatisfactory as judged by a mid-morning blood sugar which is persistently more than 200 mg. per 100 ml. The reasons appear to be: failure to follow diet, 11 cases; response decreasing as weight increases but still not overweight, 6 cases; probable failure to respond, 1 case; probable resistance, 4 cases.

### Discussion

The hypoglycaemic sulphonylureas (including carbutamide and tolbutamide) cannot act without physiologically active endogenous insulin (Fajans *et al.*, 1956), and are effective in the treatment of "mild" diabetes only. Patients with "mild" diabetes have demonstrable insulin activity in their plasma (Bornstein and Lawrence, 1951) and pancreas (Wrenshall and Best, 1956), while those with "severe" or "juvenile" diabetes do not.

Ketosis is a feature of "severe" but not of "mild" diabetes. Seven of our patients, although in all other respects "mild" diabetics, are known to have been mildly ketotic at some time, and four of these failed to respond to tolbutamide. Of the 12 patients who were taking insulin until transferred to tolbutamide, two did not respond. We suggest that lack of response is due to inadequate endogenous insulin activity.

The "immediate" and "delayed" types of responses seen in patients not previously treated with carbutamide do not appear to have been reported hitherto. We cannot explain them. So far as can be told from observation of a small number of patients for a relatively short time, there does not appear to be any difference in the ultimate behaviour of the two groups.

The effectiveness of the sulphonylureas (and insulin) decreases as weight increases, but we have confined the term "resistance" to describe an escape from control in patients who continue to follow a suitable diet, who do not gain weight, and who are given increasing doses of tolbutamide. We suppose that it is due to decreasing endogenous insulin production, but do not think that the phenomenon necessarily supports the hypothesis that the sulphonylureas stimulate insulin secretion, as a similar rise of blood sugar is sometimes seen in patients treated by diet alone. Both patients who developed resistance became mildly ketotic, suggesting reduced endogenous insulin activity.

Side-effects are less common and less serious with tolbutamide than with carbutamide. In particular we found no effect on the white-cell and platelet counts and only two patients developed a rash. Both had had a rash with carbutamide and the drug was stopped in each. Tolbutamide has a greater tendency to cause abdominal symptoms than carbutamide. Four patients complained of upper abdominal pain unaffected by meals and antacids, and the drug was stopped in two of them. Treatment was also stopped because of vomiting in one case and because of activation of duodenal ulcer in another.

It is not yet possible to judge whether controlling the blood sugar with tolbutamide will modify the incidence or severity of diabetic "degenerative" complications (retinopathy, cataracts, arterial disease, neuropathy, and nephropathy).

### Conclusion and Summary

A study of 72 patients treated with tolbutamide for up to one year suggests that about 50% of patients with "mild" diabetes that cannot be controlled by diet alone will benefit from it.

We feel that, as it is a relatively new drug and its mode of action and possible long-term ill effects are not yet known, tolbutamide should be used cautiously and that patients treated with it should be selected and supervised carefully. It should be given only to adults who are not excessively overweight, whose diabetes cannot be controlled by diet alone, and who do not become ketotic even when untreated. The response may be evident immediately or only after several weeks.

Patients who respond usually gain weight and must follow a diet restricted in calories and carbohydrates. Increasing weight is often associated with decreasing effectiveness of the drug, but two patients who did not gain weight became truly resistant.

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# TOLBUTAMIDE IN TREATMENT OF DIABETES MELLITUS

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There is no doubt that the oral antidiabetic drugs, the sulphonylureas, reduce the hyperglycaemia of certain diabetic patients, and it is now certain that tolbutamide (D 860, "rastinon," "orinase," "artosin") causes far fewer toxic effects than its forerunner carbutamide (BZ 55, "invenol," "nadisan"). These statements are substantiated by many papers which have appeared in several medical journals (see references). In consequence this drug is likely to be more widely used. The following remarks are intended to assist doctors in deciding which patients are suitable for oral therapy. The scheme we give for administration of tolbutamide is based on our experience during the past 18 months.

### Selection of Cases

Those patients in whom glycosuria is discovered in middle life are most likely to prove suitable. The chances of successful treatment with tolbutamide appear to be greatest if the patient is over 40 years of age, is obese or thick-set, has not previously received insulin therapy or is adequately controlled by less than 40 units of insulin a day, and has no previous history of diabetic coma or ketosis. We now know that some patients not fulfilling all these criteria may respond, but the following rules are recommended in general practice. Tolbutamide should not be used in children, in patients receiving over 40 units of insulin a day, or in patients who are prone to acetonuria.