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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REFERENCES

- Bornstein, J., and Lawrence, R. D. (1951). *British Medical Journal*, 1, 732.
Fajans, S. S., Louis, L. H., Seltzer, H. S., Gittler, R. D., Hennes, A. R.,
Wajchenberg, B. L., Ackerman, I. P., and Conn, J. W. (1956).
Metabolism, 5, 820.
Franke, H., and Fuchs, J. (1955). *Dtsch. med. Wschr.*, 80, 1449.
Kemsley, W. F. F. (1951-2). *Ann. Eugen. (Lond.)*, 16, 316.
Kirtley, W. R. (1957). *Diabetes*, 6, 72.
Walker, G., Leese, W. L. B., and Nabarro, J. D. N. (1956). *British Medical Journal*, 2, 451.
Wrenshall, G. A., and Best, C. H. (1956). *Canad. med. Ass. J.*, 74, 968.

TOLBUTAMIDE IN TREATMENT OF DIABETES MELLITUS

BY

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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.

It will be appreciated that tolbutamide is likely to be successful in those patients who in the past have been controlled by diet, either alone or with small doses of insulin. By control we mean that the patient's blood sugar two to two and a half hours after lunch is less than 180 mg. per 100 ml., and that the urine tests performed four times a day before meals show no more than an average of one green ($\frac{1}{2}\%$) result each day. Some of these patients will hear of and request the oral form of therapy, but we do not recommend the doctor to change over to tolbutamide if diet and insulin are satisfactory. However, there are some cases in which such a regime of diet and insulin is impracticable, inconvenient, or ineffective, even with the ancillary services available to a hospital clinic.

Thus some patients cannot follow a diet because they are unwilling to curb their appetite. Other patients are not mentally or physically capable of carrying out the necessary manipulations for measuring and injecting the insulin, so that continuous and close supervision by the district nurse or some responsible relative is required to maintain control. Still other diabetics are so haphazard in measuring insulin and arranging their diet that the danger of hypoglycaemic reactions is always present. Though they are not numerous, these patients are a source of concern, especially if they drive a car or live alone. Oral therapy offers an attractive method for smooth control of their hyperglycaemia.

We have not found tolbutamide of value in the management of so-called "brittle" diabetics—that is, young patients whose hyperglycaemia is inadequately controlled by large doses of insulin (over 80 units a day) but who on such doses run the risk of frequent hypoglycaemic attacks. However, in older patients who cannot be controlled successfully, or who have hypoglycaemic symptoms, tolbutamide may be tried even if the patient does not satisfy all the criteria given above.

Trial and Maintenance of Tolbutamide Treatment

We know of no single test to distinguish which patients will ultimately be satisfactorily controlled by tolbutamide. Under these circumstances a therapeutic trial is necessary for each patient. It is advisable to defer the trial if the patient is temporarily out of control through infection or at the time of an operation. There are no reports of patients being treated with tolbutamide during pregnancy, and we have no experience of this clinical problem.

Arrangements for a preliminary period of observations of one to two weeks should be made. The patient's diet and insulin should be fixed, and instructions given for the urine to be tested for glycosuria four times a day; if sugar is present the urine is also tested for acetone. If definite acetonuria is found at any time during this preliminary period the patient must report immediately to his doctor for prompt treatment with insulin. Ketosis indicates that treatment with tolbutamide alone is likely to be unsuccessful.

After the preliminary observation period of one to two weeks the patient's diabetic status and the need to start tolbutamide are assessed as follows:

Patients on Diet but No Insulin.—A proportion of these cases lose their glycosuria during the control period. The explanation seems to be that the procedures encourage the careless patient to pay attention to his diet so that no tolbutamide is needed. If the patient shows glycosuria despite the dietary regime, trial of tolbutamide is not difficult to manage. The patient should be seen each evening for assessment, at least during the first week of tolbutamide therapy. Tolbutamide is begun in doses of 2 to 3 g. a day. On the first day two 0.5-g. tablets are taken with breakfast, two tablets with the midday meal, and one to two tablets with the evening meal. Thereafter the dose is one to two tablets three times a day. It is reduced as the hyperglycaemia lessens. Glycosuria usually disappears within the first week, whereupon the dose should be fixed at the minimum which gives adequate control. If glycosuria is not less by the end of the fourth day the dose of tolbutamide may be increased to 1.5 g. three times a day and the trial continued for as long as three weeks.

Patients Controlled on Insulin.—It is advisable to extend the observation period in these patients so that the effect of reducing the dose of insulin can be tested. For those controlled by up to 20 units of insulin a day the dose may be reduced by 4 units a day until mild glycosuria occurs, provided the situation is reviewed each week. In some of these cases it has been found possible to discontinue insulin. For those receiving 20–40 units of insulin a day the dose must be reduced with more caution. These patients are less likely to benefit from tolbutamide therapy, so it is less justifiable to risk loss of control of the diabetic state. The patient should therefore be seen at least twice a week and the dose of insulin reduced by not more than 4 units a day at each visit. If the patient finds more than 1% of sugar in his urine (a yellow or orange Benedict or "clinitest") he should test his urine for acetone, report to his doctor, and return to his previous insulin dosage. Patients receiving over 40 units of insulin a day should be admitted to hospital for the change over to tolbutamide. When the insulin has been reduced so that mild glycosuria occurs regularly, treatment with tolbutamide may be started. The dose given is the same as in those patients not receiving insulin, and the degree of glycosuria from day to day serves as a guide to the effect of treatment. In patients who respond it is usually possible to reduce the insulin by about one-fourth on the second and subsequent days, till by the end of the fifth day insulin is no longer required. If there is no reduction of glycosuria after three to four days the dose of tolbutamide may be increased to 1.5 g. thrice daily.

Patients Uncontrolled on Insulin Therapy.—If the patient is known not to be controlled by insulin therapy, tolbutamide may be started after he has undergone sufficient preliminary observation to ensure that any subsequent effect of tolbutamide, or lack of effect, will be clearly recognizable.

Response to Tolbutamide

The rapidity of response to tolbutamide varies in different patients, so that a therapeutic trial should last for three weeks and be cut short only if there is evidence that the diabetes is getting out of control. This is shown in Fig. 1,

FIG. 1.—Mean results from 10 diabetics whose hyperglycaemia has been controlled subsequently by tolbutamide for up to one year. Two of these had recently shown mild acetonuria. The rise of mean blood sugar on days 4, 5, and 6 cannot be attributed to reducing the insulin dosage, since it also occurs in patients not on insulin.

which refers to a group of patients who were ultimately controlled for periods of up to a year. It will be seen that in some patients the hyperglycaemia and glycosuria were not finally brought under control until the end of the first week and in others not until during the second or third week. A reduction of glycosuria and hyperglycaemia on the second or third day of treatment does not necessarily indicate that control will be maintained, as is illustrated in Fig. 2.

During the period of substitution of insulin by tolbutamide we have followed the above routine and have been worried

neither by loss of control of the patients' diabetic state nor by the occurrence of hypoglycaemic attacks. Tolbutamide is less likely than insulin to produce a hypoglycaemic attack because its full effect takes place about four hours after administration, by which time the next meal is due.

Maintenance.—If satisfactory control is achieved the patient may be maintained indefinitely on up to 3 g. of tolbutamide daily. Such control should not be allowed to encourage any relaxation of the dietary restrictions.

FIG. 2.—Mean results from 12 diabetics who showed a temporary response to tolbutamide but could not be maintained on it. Five of these patients had recently shown heavy acetoneuria.

Side-effects.—In very few instances so far has tolbutamide had to be discontinued because of side-effects. Skin rashes appear to be the most common complication. They clear within a few days of discontinuing the drug, but antihistamine therapy may be indicated if the patient complains of much irritation. Early reports from the Continent suggested that a gain in weight was to be expected by patients maintained on the drug, but the average weight of our patients on tolbutamide has not increased during nine months or more. Blood dyscrasias, which were the major drawback to treatment with the sulphonamide carbutamide, are rarely seen with tolbutamide, which is not a sulphonamide. Renal damage has not been encountered, but it should be noted that tolbutamide is excreted in the urine as an oxidation compound which, under certain circumstances, gives a coarse flaky precipitate with sulphosalicylic acid and thus might be confused with albumin.

Long-term Treatment

Since clinical trials of tolbutamide were begun by the Hoechst Laboratories in Germany in August, 1955, some 150,000 patients have been treated with the drug in this country, in Germany, and in the U.S.A. for periods of up to two years. Though no one can be certain of the long-term effects of the drug, few other drugs can have had more extensive trials to ensure their safety.

We should guard against the mistake of believing that control of hyperglycaemia and glycosuria indicates cure of diabetes. The main therapeutic problem in the type of diabetes in which tolbutamide is successful is to prevent the progress of such complications as arterial disease, retinitis, neuritis, and renal disease. Insulin probably has some effect in preventing or reducing these complications, though it certainly has not eradicated them. It will be some years before we can assess the value of tolbutamide in the prevention of complications. So far it seems unlikely that it will be more effective than insulin. It will not prevent ketosis or the exacerbation of the diabetic state associated with infection or trauma. In one of our patients the rapid progress

of retinitis and neuritis was not halted during a period of three months, during which time tolbutamide produced satisfactory control of the hyperglycaemia and glycosuria. It is necessary, therefore, to end on a note of uncertainty. Though tolbutamide may effectively control the hyperglycaemia of diabetes mellitus, we have yet to learn its effects on the progress of the underlying diabetic state and the development of diabetic complications.

Summary

Tolbutamide has proved an effective and apparently safe compound for controlling blood-sugar levels in some diabetics, especially the older stable type of patient, but there are no means of deciding which patients will respond satisfactorily short of an actual trial.

Criteria for selecting patients are given together with the details of a scheme which we have found useful in testing the patients' response to tolbutamide.

REFERENCES

- British Medical Journal*, 1956, 2, 431 *et seq.*
Canad. med. Ass. J., 1956, 74, 957 *et seq.*
Dtsch. med. Wschr., 1956, 81, 823, 887 *et seq.*
Metabolism 1956, 5, 721 *et seq.*

TOLBUTAMIDE IN DIABETES

SOME CLINICAL AND BIOCHEMICAL STUDIES

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Previous experience (Bertram *et al.*, 1955; Duncan *et al.*, 1956; Wolff *et al.*, 1956) has demonstrated that the sulphonylurea carbutamide (BZ 55) when given by mouth is capable of controlling the diabetic state in some patients. However, carbutamide was shown to have occasional toxic effects (Duncan *et al.*, 1956; Phemister, 1957), and in view of this fact another sulphonylurea, tolbutamide, is now being tried. Tolbutamide differs from carbutamide in that a methyl group replaces the *p*-amino group. Unlike carbutamide, it is therefore not a sulphonamide.

The present study has been undertaken with the following aims: (1) to assess the value of oral tolbutamide therapy in controlling diabetes, particularly in newly diagnosed cases; and in those patients successfully controlled by the drug, to see whether relapse occurred when this therapy was discontinued. (2) To determine whether tolbutamide behaved as insulin does in lowering plasma amino-acid nitrogen and inorganic phosphorus. (3) To correlate blood tolbutamide levels with the control of sugar in the blood and urine, with particular reference to the administration of tolbutamide as a single dose and in divided doses.