FURTHER EXPERIENCES IN THE USE OF TOLBUTAMIDE (D 860) IN DIABETES MELLITUS

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Since 1955 a great deal of interest has been stimulated in the treatment of diabetes mellitus by the introduction of oral substitutes for insulin.[1-3] The original substance used was N-sulphanilyl-N′-butyl-carbamide, also known as carbutamide, BZ 55, or Nadisan. It soon became evident that, although certain diabetics could be controlled with carbutamide, toxic effects constituted a hazard. Kirtley[4] reported on 8 deaths in 7,193 cases treated. These toxic effects consisted of generalized sulphonamide sensitivity, agranulocytosis, thrombocytopenia, and hepatic and myocardial changes. The use of carbutamide has therefore been discontinued and it has been superseded by a new substance N-(4-methyl-benzenesulphonyl)-N′-butyl-urea, known as tolbutamide, D 860, Rastinon, Orinase or Artosin.

Tolbutamide has been the subject of clinical trials by many workers in different countries, and it is estimated that 150,000 patients have been treated. The hypoglycaemic effect is similar to that of carbutamide but the toxic effects are minimal. Allergic skin rashes, gastro-intestinal symptoms, leucopenia and thrombocytopenia[5, 6] have been reported, but these have not been severe. The results of numerous clinical trials have revealed that tolbutamide is successful in controlling the hyperglycaemia of a highly selected group of diabetic patients. Dunlop[7] has described as follows the type of diabetic most likely to respond:

1. They should have developed the disorder over the age of 40 years.
2. They should have shown no previous tendency to develop ketosis easily.
3. Their daily insulin requirements should not exceed 40 units.
4. Their fasting blood glucose when receiving no insulin should not exceed 300 mg. per 100 ml.

Not all patients conforming to these criteria respond to

tolbutamide and the most recent British results show adequate control in only 52% of these cases.[8]

Although these substances have been used for about 2 years, their exact mechanism of action has not been elucidated. It has been shown that they are effective only if some insulin is being produced by the patient and that they usually fail in the insulin-deficient patient.[9] They do not simulate insulin by increasing peripheral utilization of glucose.[10] As they have no effect on the depancreatized subject it has been suggested that they act by stimulating the production of insulin by the B-cells of the islets of Langerhans.[11] Other workers[12] have shown that they prevent the output of glucose from the liver by interfering with enzyme systems.

A most important aspect, which will be answered only after several years of observation, is the effect of tolbutamide in preventing, postponing or controlling the late manifestations of diabetes. At the moment we know that it lowers the blood sugar in certain patients, but we are ignorant of its effect on other metabolic processes in the diabetic. Elucidation of this problem will determine whether tolbutamide has a place in the long-term treatment of diabetes.

Two of the present authors reported on their early experiences with carbutamide and tolbutamide in a previous publication.[13] The object of this paper is to report further on our experiences with tolbutamide.

SUBJECTS AND METHODS

105 patients attending the Diabetic Clinic of the Johannesburg General Hospital were selected for tolbutamide therapy. The consisted of 17 males and 88 females between the age of 43 and 84 years. The duration of diabetes varied from 2 months to 30 years, and the age of onset from 36 to 75 years.

During the course of the investigation these patients have attended the clinic regularly for periods of up to 1 year. They were seen at frequent intervals by at least one of the authors and were instructed to test their urines for sugar with Benedict's solution 4 times daily (before each meal and at bedtime). They were told to report immediately if any untoward symptoms occurred (sore throat, rash or temperature) or if urine tests were unsatisfactory. All side-effects were carefully observed whenever they appeared.

The dosage of tolbutamide did not exceed 3 g. daily. A dose of 3 g. was employed on the first day, and this was decreased by 0·5 g. per day until a maintenance dose of 1·0 - 1·5 g. daily was reached. Initially the total daily dose was given before breakfast each morning but, as several patients experienced hypoglycaemic symptoms of giddiness and headache during the morning, the plan adopted was to administer the drug in 3 equal doses either before or after meals.

Where the previous dose of insulin did not exceed 20 units, insulin was discontinued on the day that tolbutamide therapy was instituted. Where the dosage exceeded this amount, insulin was gradually withdrawn by reducing the dose by 5-10 units per day. If symptoms and signs of ketosis appeared during this regime, tolbutamide was discontinued and the patient re-stabilized on insulin.

Blood counts, prothrombin indices, liver function tests and blood-urea estimations were carried out at frequent intervals. Protein-bound iodine and serum-inorganic-phosphorus estimations were performed on about half the patients.

The true blood sugar was determined by the method of King and Garner,[14] the serum cholesterol by the method of Pearson *et al.*,[15] the serum protein-bound iodine by the method of Meyer *et al.*,[16] the serum inorganic phosphorus by the method of Briggs,[17] and the serum potassium with an Eel flame photometer as described by Varley.[18]

The efficacy of treatment has been assessed according to our previous criteria[13] and the cases have been classified into 'good', 'fair' and 'poor' categories. The 'good' category consists of those cases in whom (*a*) insulin where used has been discontinued, (*b*) urine examinations at home and at the clinic have proved satisfactory, (*c*) blood sugars have been maintained at normal or near normal levels, and (*d*) the patients are feeling well and there are no side-effects. The 'fair' category consists of those patients in whom (*a*) insulin where used has been discontinued, (*b*) urine examinations at home and at the clinic have shown 0 to ++ glycosuria, (*c*) the blood sugar has not been maintained at normal levels but has been reduced appreciably, and (*d*) the patients are feeling well and there are no side-effects. The 'poor' category contains those cases who have shown little or no response.

RESULTS

'Good' Category. Control was good in 45 of the 105 cases (8 males and 37 females). The ages of this group varied between 43 and 77 years (average 61·9 years). The diabetes had been present from 3 months to 20 years (average 6·4 years); 13 of these 45 cases had been diabetic for 10 or more years. The age of onset of diabetes varied from 36 to 72 years. The group comprised 5 thin, 20 medium and 20 fat individuals. Patients with and without late manifestations of diabetes were included in this group. Of the 45 patients, 20 (44%) had been treated previously with insulin and the largest daily dose replaced by tolbutamide was 60 units (PZI 30 units + soluble insulin 30 units).

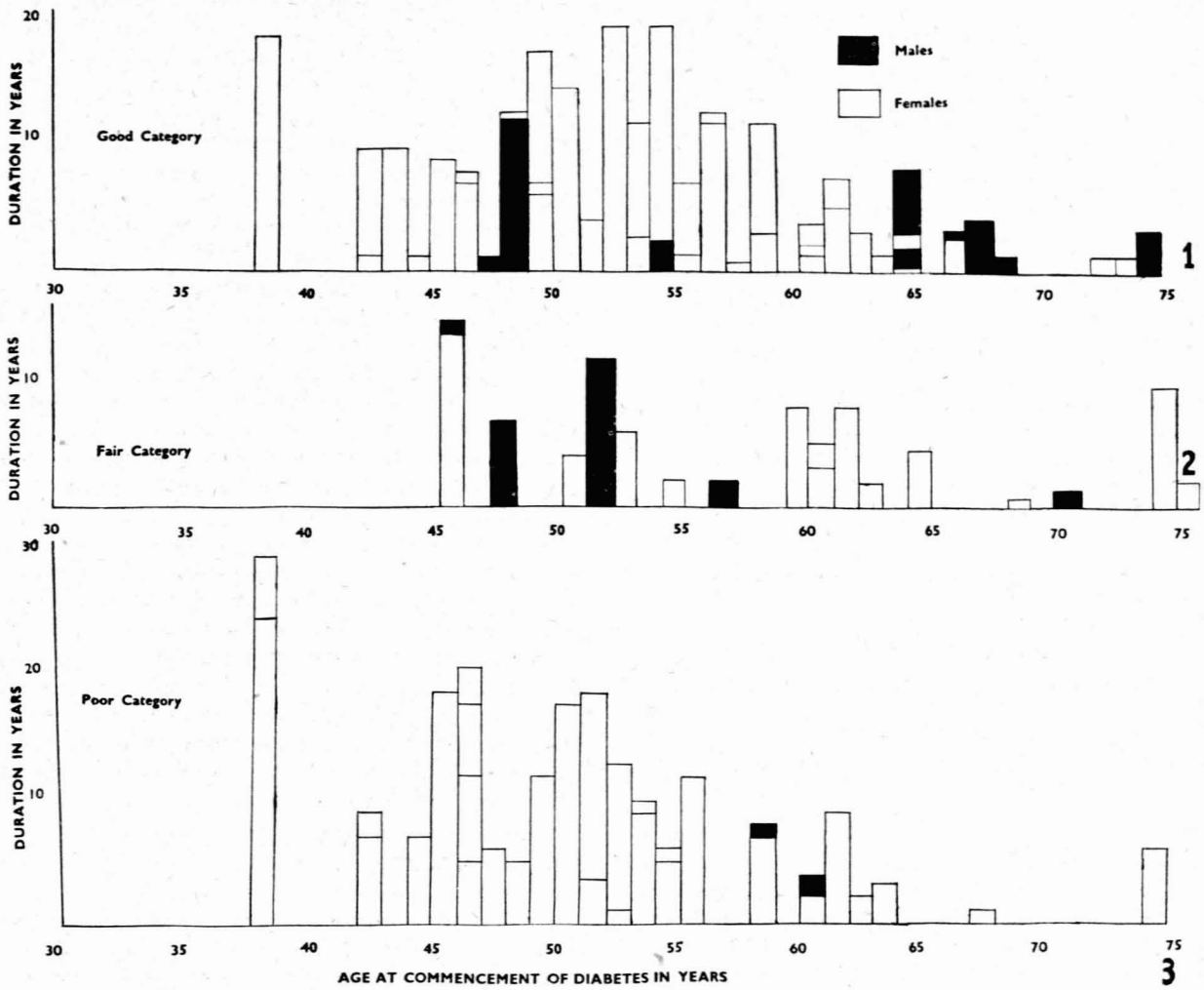
'Fair' Category. Fair control was obtained in 25 cases (6 males and 19 females). In this group the age ranged between 54 and 84 years (average 63·9 years), and the duration of diabetes from 2 months to 15 years (average 5·4 years). Body build was again variable, 4 patients being thin, 8 medium and 8 obese, and cases with and without late manifestations of diabetes were included. Of the 25 patients, 9 (36%) had been treated previously with insulin and the largest daily dose replaced by tolbutamide was 70 units of NPH insulin.

'Poor' Category. The control was poor in 35 cases (3 males and 32 females). The ages varied between 49 and 80 years (average 61·9 years) and the duration from 7 months to 30 years (average 9·8 years). Variation in body build was again noted, 6 patients being thin, 9 medium and 17 obese. Late manifestations of diabetes were present in some of the patients. Of the 35 patients, 23 (66%) had been treated previously with insulin. The age of onset varied from 38 to 74 years. Insulin dosage ranged from 0 to 60 units.

These results are demonstrated in Figs. 1, 2 and 3.

Change in Control

A change in control has occurred in 8 cases, all of whom were included in the series previously reported. Of 7 in the 'good' category, 5 have deteriorated to 'fair' control, and 2 to the 'poor' category, while 1 case under 'fair' control has now regressed to the 'poor' category. There have been several cases in our series who have felt so well while taking tolbuta-



Figs. 1; 2 and 3.

mide despite poor diabetic control that they have refused to discontinue the drug. Insulin has therefore been added to improve the control, but the dose has usually been less than that previously required.

Laboratory Investigations

The laboratory investigations did not reveal any gross abnormalities. The main haematological change noted was a frequent reversal of the neutrophil/lymphocyte ratio. This was not a permanent feature; all cases reverted to normality while still on treatment. The cause of this interesting phenomenon has not been ascertained.

In one case, a leucopenia of 2,900 per c.mm. (neutrophils 37% and lymphocytes 63%) occurred after a period of normal counts. Treatment with tolbutamide was continued and within 1 month the count had increased to 6,800 per c.mm. (neutrophils 44% and leucocytes 42%). The blood picture has remained normal during the past 4 months.

Alteration in liver function tests occurred in 2 patients during treatment. In one normal tests became markedly abnormal but no clinical change was evident; in the other an aggravation of previously abnormal tests occurred after an interval of 8 months.

Prothrombin indices were not affected.

The determinations of inorganic phosphorus, potassium, cholesterol and protein-bound iodine which were performed during treatment are shown in Table I. The phosphorus and potassium results showed no abnormality, except in one case where the potassium was raised. No cause for this was ascertained. There was little correlation between the cholesterol level and the degree of diabetic control. The serum protein-bound iodine values varied widely. A low serum protein-bound iodine result of 3·2 micrograms per 100 ml. was observed in one case and high values of 10·2, 14·0 and 16·0 μg./100 ml. in 3 patients. The high results may have been due to the ingestion of iodine-containing medicines. We were unable to demonstrate any depression of thyroid activity resulting from tolbutamide therapy.

TABLE I

Serum	*Mean*	*Range*	*Normal Values*
Inorganic phosphate	3·3 mg./100 ml.	1·8—4·4	2·0—4·0
Potassium ..	4·9 mEq./l.	4·1—6·4	4·4—5·1
Cholesterol ..	284 mg./100 ml.	170—450	120—250
PBI	6·2 μg./100 ml.	3·2—16·0	3·5—8·0

Side-effects

Side-effects were minimal. Two patients were unable to tolerate the drug because of nausea which supervened. Another case developed moderate angioneurotic swelling of the face.

A patient who had suffered a vitreous haemorrhage in the right eye while on 35 units of lente insulin, developed another haemorrhage in the left eye while on tolbutamide therapy.

A patient who was receiving 120 units of soluble insulin per day in 2 divided doses developed ketosis when the insulin was reduced and tolbutamide added. For a period of 1 week, while further attempts to control him were persevered with, he varied between hypo- and hyperglycaemia, and only returned to his normal control when the use of tolbutamide was abandoned. His previous dose of insulin was well able to control him and he has remained under good control since. This case emphasized the danger of using tolbutamide in patients requiring large doses of insulin.

DISCUSSION

Analysis of tolbutamide therapy in 105 diabetic cases reveals good control in 42·9% of cases, fair control in 23·8%, and poor control in 33·3%. Our results are in accord with the findings quoted by the workers of 3 leading British hospitals at the 11th Banting Memorial Meeting in July 1957,[19,20] who reported satisfactory control in 52% of their cases. The proportion of successful cases published by other authors varies enormously and is dependent to a large extent on the choice of patients and the criteria adopted for assessing adequate control.

The patients selected for treatment were all over the age of 43 years and the majority over 60. Previous workers have shown that this age-group responds most satisfactorily to tolbutamide and that the drug usually fails in the younger insulin-deficient diabetic. However, it must be noted that the youngest age at onset in the 'good' category was 36 years, and that 29% of these cases had been diabetic for 10-20 years.

Most of our patients were between medium and obese and only 14% could be classified as thin. The majority of workers in this field are agreed that obese diabetic patients should be treated with dietary restriction only, as this measure will achieve adequate control in a large percentage of cases.[21] However, tolbutamide has a definite advantage in the treatment of those obese patients in whom dietary restriction fails. It must be emphasized that these patients should be warned not to become careless over their diet. Such negligence will lead to further gain in weight and deleterious effects on the patient's health. In contrast, tolbutamide may be of great value in the treatment of elderly thin diabetics who are unable to regain their normal weight. We have found that tolbutamide will maintain good control when these patients partake of a more liberal diet.

The usual maintenance dose of tolbutamide has been 1·0 - 1·5 g. per day. Where control has not been adequate this has been increased up to 3 g. per day with slight improvement in a few cases.

Some workers have suggested that nausea is less likely to occur if the drug is administered after meals. In this series, however, no difference has been noted whether the drug was given before or after meals.

Although effective control is often achieved within the first week of administration, it is advisable to persist for at least 3 weeks, because the optimal effect may be delayed.

No serious toxic effects have been noted during tolbutamide administration, in contrast to the fatalities reported during the treatment with carbutamide. Moreover, side-effects have been minimal. Two of our patients were compelled to discontinue the drug on account of nausea, and one patient as a result of angioneurotic oedema. Similar side-effects have been reported by other workers.[22-24]

We have been particularly concerned with blood changes which might occur during treatment. The most constant change found was that of a reversal of the neutrophil/lymphocyte ratio. This change was always temporary and occurred in 9 of the 'good', 20 of the 'fair', and 8 of the 'poor' cases. No explanation for this has been found, and it will be necessary to do a similar series of blood counts on a control group before it can be associated with the administration of tolbutamide.

Severe leucopenia developed in 1 case in our series (2,900 leucocytes per c.ml.), but this disappeared in spite of continuing the tolbutamide in unchanged dosage. Stötter[24] found a reduction of leucocytes in some cases of tolbutamide-treated diabetics, but found similar reduction in cases treated with insulin.

The alteration in liver function tests found in several of our cases during treatment cannot be considered as having special significance in view of the common occurrence of abnormalities in liver function tests during the course of diabetes.[25]

Clinically no symptoms or signs were noted to suggest any liver dysfunction during the course of tolbutamide administration.

Protein-bound iodine estimations have not revealed any alterations in thyroid function.

Infections, injuries and operations may disorganize diabetic control and it has been found that tolbutamide, even in increased dosage, is unable to control the resulting hyperglycaemia and ketosis. Insulin is then required as an emergency measure. Several of our patients in the 'good' category have been successfully controlled while undergoing cataract operations under local anaesthesia; the tolbutamide has maintained adequate control during the operative and post-operative period.

The presence of ketosis constitutes a definite contra-indication to the use of tolbutamide and it must be emphasized that it is dangerous to continue with the drug in its presence.

Amongst our cases who were originally reasonably well controlled, 8 have now deteriorated and stabilization is unsatisfactory. Other workers have reported similar experiences.[8, 24] The cause of this phenomenon has not been elucidated. It is possible that the therapeutic effect of the drug may diminish after a period. However, a more likely explanation is that the patients adhere less strictly to the prescribed diet; we have noted that gain in weight has often accompanied deterioration in control.

We have used a combination of tolbutamide and insulin in a few patients who did not respond to tolbutamide alone. These patients have required a smaller dose of insulin, but it is

doubtful whether the addition of tolbutamide has any advantage over routine insulin therapy.

It is premature to speculate on the effect of tolbutamide in preventing the late manifestations of diabetes. This will require careful follow-up studies over many years and comparison with insulin-treated cases.

SUMMARY

1. 105 diabetic out-patients with an average of 61 years were treated with tolbutamide.

2. Good control was obtained in 42·9%, fair control in 23·8% and poor control in 33·3%.

3. No toxic and only minimal side-effects were encountered.

4. A temporary reversal of the neutrophil/lymphocyte ratio was found in 37 cases.

5. Deterioration in control has occurred in 8 patients after several months of tolbutamide therapy.

6. The long-term effect of tolbutamide cannot be assessed at this stage.

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