TOLBUTAMIDE (ARTOSIN, RASTINON, D 860) IN DIABETES *

CLINICAL TRIALS CONTINUED

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We have previously reported our preliminary findings with tolbutamide based on a short-term trial in 73 patients,[1] some of which have been modified and extended by further experience. For discussion of the chemical aspects of the substance and of its mode of action the reader is referred elsewhere. The object of this paper is simply to record our results up to the end of June 1957 and to make certain recommendations based upon them. I shall try particularly to indicate where our approach or findings differed from previous reports.

THE PATIENTS

We have records of 250 patients who have been treated with D 860 (tolbutamide), some in the wards and some in the diabetic clinic. In the latter the patients have been seen as far as possible at weekly intervals and have had regular blood-sugar estimations then performed (usually fasting). All blood sugars were determined by a modified Hagedorn-Jensen method. Weekly 24-hour urine collections have been analysed for sugar in some cases; in others a note has been made by the patient of his own tests throughout the week; in a few, repeated glucose tolerance tests have been carried out.

The dosage of D 860 in most cases has been 1 g. (2 tablets) daily; in several the maintenance has been higher, up to 3 g. Only in special cases in hospital have higher doses been tried.

* Presented at the South African Medical Congress, Durban, September 1957.

It is not feasible to analyse our results separately into different dosage groups, but there is certainly very little difference between the effects of 1 g. and of 3 g. If a patient does not respond at all to 1 g. he is very unlikely to respond to 3 g., though he may respond somewhat better to the larger dose.

Incidentally tolbutamide is less cumulative than carbutamide (BZ 55) and should be given in divided doses, 2 or 3 times daily.[2] It is perhaps best to take the drug after meals so as to prevent the nausea which it occasionally produces.

The change-over from insulin to D 860 seems to us very important for a scientific assessment of response. Whenever possible, where no risk was thought to be involved, insulin was stopped completely for some time before D 860 was started. In this way a real base-line control could be established. In a surprisingly large number of cases where insulin had been stopped, the patient remained as well controlled as before, or even better, so that D 860 was unnecessary. Had it been used either with or immediately replacing insulin it would have got the credit for this improvement quite erroneously and the patients would have continued getting unnecessary treatment. Several patients were found to be much better controlled after insulin had been stopped than they had been before they had originally started insulin—clearly suggesting a real 'curative' or at least alleviating effect of insulin! This finding further suggests that a review of all 'mild' diabetics on insulin, with a view to omitting this drug where possible, might prove most salutory and rewarding, quite apart from the use of D 860

Case F.F. A Coloured female of 69, with mild diabetes of 2 years' duration had been taking 20-24 units of lente insulin daily. Her urine always contained sugar (+ to +++) and our last record of her blood sugar was 163 mg. per 100 ml. fasting and 255 mid-morning. Insulin was stopped, her urine became sugar-free, and mid-morning blood-sugar readings of 130, 151 and 195 have been obtained.

Certainly, however, this method of change-over should not be used in the 'severe' or doubtful diabetic where, if D 860 is to be tried at all, it must first be added to insulin or the latter slowly decreased. We have made one error in this connexion!

Case M.W. A 50-year-old non-obese European female who had been diabetic for 2 years was taking 28 units of lente insulin daily. After omitting insulin she was admitted to hospital 4 days later in severe ketosis. This is the only instance in which any serious difficulty has arisen in the trial.

Since it is well known that the severe ('growth-onset', ketosis-prone, insulin-requiring) diabetic is most unlikely to respond to D 860 at all, such cases will be considered separately from the older, mild ('maturity-onset', frequently obese) group.* We have also separated an 'intermediate' group, members of which were in the older age-group but developed severe diabetic symptoms with marked loss of weight when deprived of insulin. It must be realized that some older people may actually have the severe, 'young' type of diabetes (e.g. case M.W. above).

RESULTS

The response to D 860 is graded as excellent, partial or negligible. 'Excellent' indicates that an absence of glycosuria, and blood sugars within the normal range, were obtained—in many of the 'partial' responses control of the diabetes could be considered adequate.

Type of diabetes (Table I)

As expected, of 15 'severe' diabetics in whom D 860 was tried in doses up to 12 g. a day, none responded well. In one there was a partial, but very incomplete, response while in 3 the control was at least temporarily improved by D 860 used in conjunction with insulin. Of the 14 'intermediate' diabetics, 3 responded extremely well. There were 200 'mild' cases, of which 21% had an excellent response, while 29·5% failed to respond.

TABLE I. TYPE OF DIABETES AND CONTROL WITH D 860

	Excellent Control	*Partial Control*	*Negligible Control*	*Total*
Severe	0	4*	11	15
Intermediate ..	3	1	10	14
Mild	42 (21%)	99 (49·5%)	59 (29·5%)	200
'Steroid' Diabetes ..	1	0	1	2
Chronic Pancreatitis	0	2	4	6
Insufficient data for classification ..	—	—	—	13
				250

* In combination with insulin in 3 cases.

There were 2 cases of steroid diabetes, one of which responded very well to D 860 (much better than to 80 units of insulin), while one failed completely to respond to 6 g. a day. In both cases the diabetes became latent after the corticosteroid therapy was stopped. (This variability of response presumably accounts for the discrepancies in the literature on the subject of D 860 in steroid-induced diabetes.)

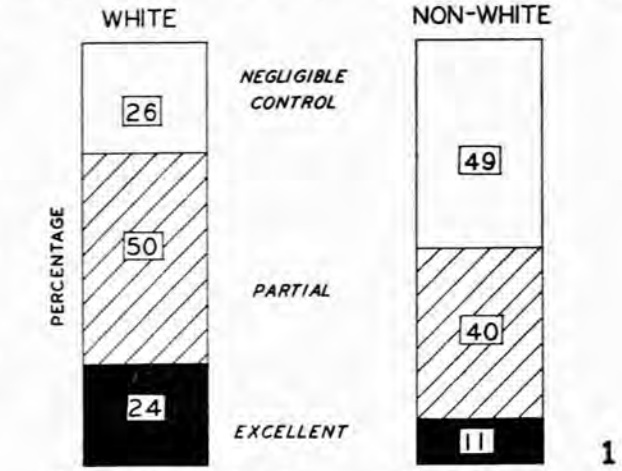
Of the 6 cases of proven chronic pancreatitis, 4 had the typically severe diabetic syndrome, and D 860 was of no value even in large doses; 2 had much milder and more recently developed diabetes, and in them D 860 achieved partial control.

Sex, Race and Age

The following further analyses refer solely to the 200 'mild' diabetic patients:

Sex. There were only 45 males, as opposed to 155 females, in the series. No significant difference in response was found between the sexes.

Race (Fig. 1). There were 45 Coloured and African patients among the 200, and it was surprising that they did distinctly



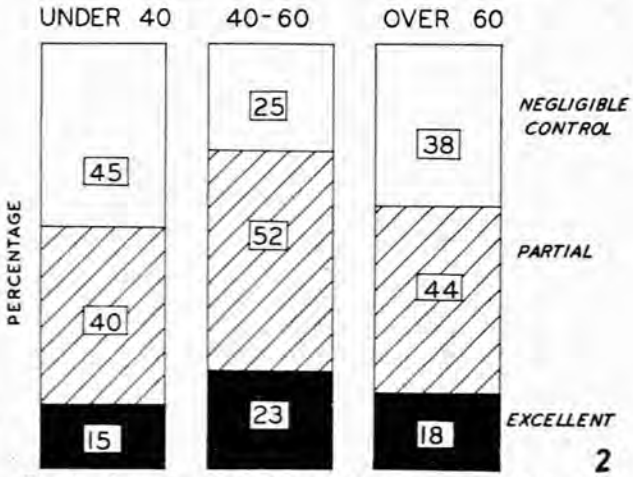


Fig. 1. Control with D 860 in White and non-White mild diabetics.

Fig. 2. Control with D 860 according to age of onset in mild diabetics.

* There has been some confusion concerning the terms used to distinguish these two groups of diabetics. It should be noted that 'severe' and 'mild' bear no relation to the amount of insulin which the patient may be taking. The 'severe' diabetic will always need some insulin; the mild diabetic may be taking none or 100 units. Some mild cases, as the German writers have stressed, are relatively insulin-resistant, and these may respond well to tolbutamide. The 'mild' diabetic does not go into ketosis even when untreated.

less well on D 860 than the Europeans. Thus 49% of them completely failed to respond, as compared to 26% of Europeans. Further analysis of the White and Coloured patients failed to uncover any particular distinction between the groups which might tend to produce such a difference of response. Among the non-Whites were 4 African Bantu, 2 of whom responded extremely well. Our results seem to indicate that D 860 is of less value in Coloured people in Cape Town than in Whites.

Age. All the mild diabetics were over 40 except for 5, in 3 of whom partial control was attained on D 860. Analysis revealed almost exactly the same percentage responses in the 40-60 and in the 60-80 age-groups. Of 3 patients over 80, 2 failed to respond at all.

Age at onset of diabetes

Our figures suggest (but do not prove) that the age-of-onset group 40-60 respond best (Fig. 2).

Length of time diabetic (Table II)

49 of our patients had been diabetic for more than 10 years, including 17 for more than 20 years. The proportion of this

TABLE II. LENGTH OF TIME DIABETIC AND CONTROL WITH D 860

	Excellent Control	*Partial Control*	*Negligible Control*	*Total*
10-20 years diabetic	8 (25%)	9 (28%)	15 (47%)	32
Over 20 years diabetic	6	7	4	17
Total over 10 years diabetic	14 (28%)	16 (33%)	19 (37%)	49

group whose response was excellent was actually *higher* than in the whole series, although there was also a higher percentage of complete failures.

Body size

We have divided the mild diabetics into 3 groups—obese, medium and thin. To our surprise, as Fig. 5 indicates, the obese group (55 patients) actually responded less well to

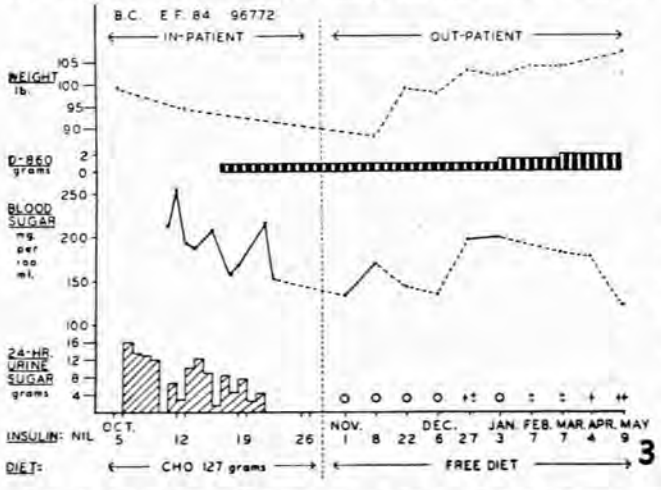


Fig. 3. B.C. A very thin old lady, in whom weight gain was accomplished on a free diet, while maintaining fair control of diabetes with D 860.*

* In all figures the sex, race, and age of the patient are shown at the top. F.B.S. = fasting blood sugar.

D 860 than the others. It was gratifying to find that the response of the 23 thin patients was so good, and this suggests that, provided the lean, 'severe' type of diabetic is excluded, the *mild* lean diabetic does as well as the obese diabetic, or better. We feel that this lean diabetic is particularly the one who needs 'tablet' therapy, as opposed to the obese diabetic, who needs dietary restriction. Among this lean group were 7 who were put onto a completely free diet and actually encouraged to 'eat everything'; of these, 6 gained weight (Figs. 3 and 4), which they had previously been unable to do;

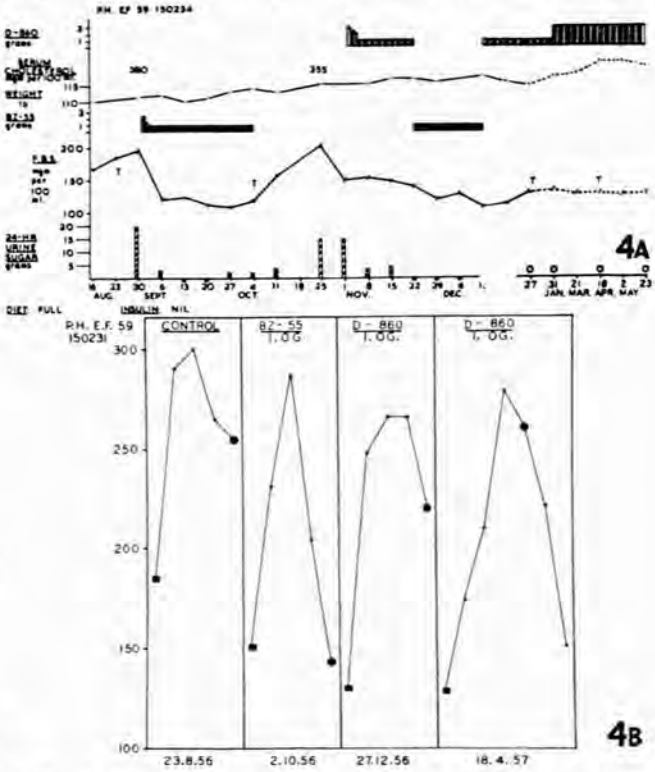


Fig. 4. P.H. (*a*) This thin woman was able to gain weight on D 860 with a free diet. (*b*) Glucose tolerance curves (at points marked T in Fig. 5*a*) show reduction of fasting levels on D 860 and BZ 55, but persistence of abnormally high curve (e.g. diminished sugar tolerance). Fasting and half-hourly blood-sugar levels after 50 g. of glucose orally are shown as dots, with heavy dots for fasting and 2-hour readings.

3 of the 7 were excellently controlled on D 860 despite their free diet, and in 4 the control was partial or good. There seems no reason to restrict the caloric intake of a diabetic who can be well controlled on oral therapy and who is very underweight.

Prior insulin treatment

Of the 200 patients, 111 had been taking insulin before D 860 was started. The length of time over which insulin had been taken appeared to have little effect on the likelihood of response to D 860, although there was some rise in the proportion of patients who completely failed to respond as the length of time increased.

There was little correlation between the size of the insulin dosage and the likelihood of response, except that the percentage failing completely was rather higher in those

taking over 40 units a day (48%). Actually an excellent response was seen in a higher proportion of patients who had received insulin (24%) than in those who never had (19%).

There were 4 patients who had been taking 100 units of insulin or more daily before D 860 was tried. Two had a partial response on D 860 alone (both were better controlled by this than they had been on 100 units of insulin!), and 2 had no response.

Change in body weight on D 860 therapy (Fig. 6)

We have been struck with the frequency with which patients have gained weight on D 860, despite the fact that they were supposed to be on a restricted diet. Far fewer lost weight, which is what was expected of them. There may be psychological reasons for this, and we have no control series *not* on

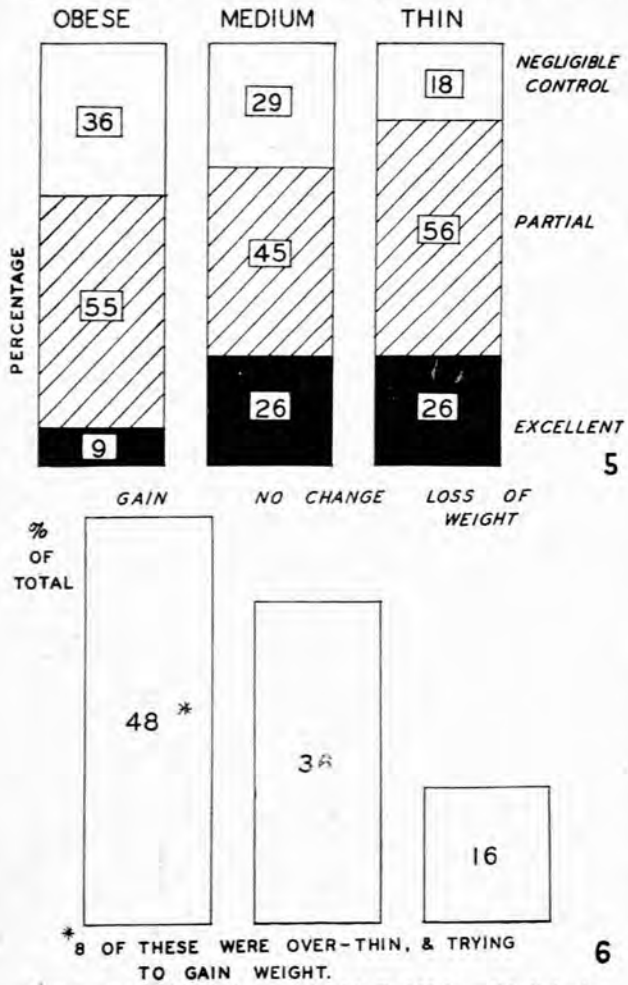


Fig. 5. Body size and control with D 860 in mild diabetics.
Fig. 6. Indicating change of more than 3 lb. in patient's body weight after 3 months on D 860.

D 860; so that this finding is not necessarily significant. Nevertheless nearly 50% of our patients who were watched for more than 3 months definitely gained weight (see Fig. 7).

Long-term action of D 860

We have records of 37 patients who have been taking D 860 for more than 6 months (Figs. 3, 4, 7 and 8). In 13 of them

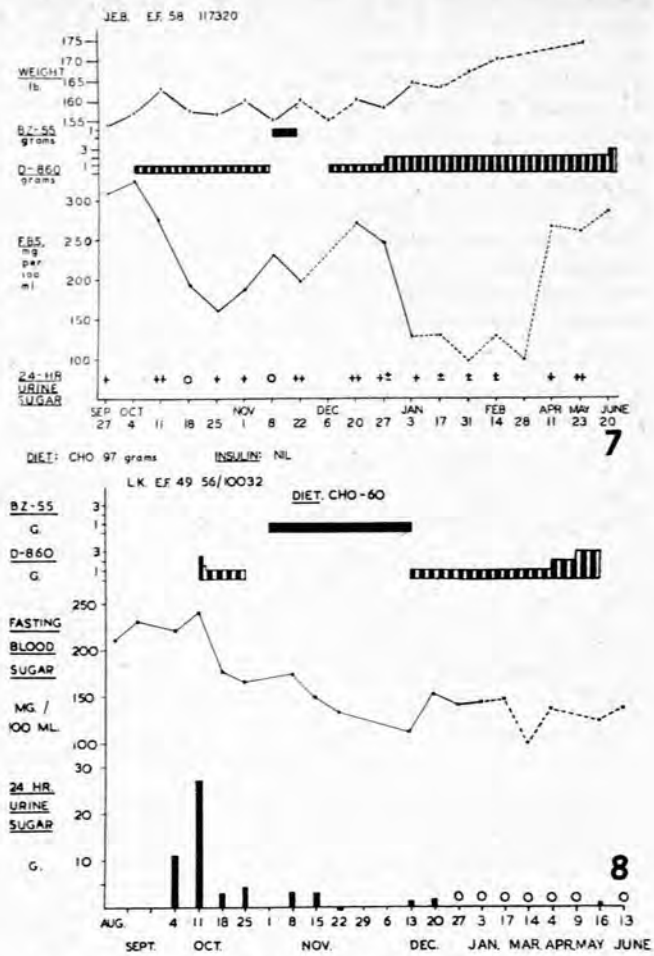


Fig. 7. J.E.B. Good initial effect, wearing off. Improvement with increased dose, again wearing off. Note weight gain.
Fig. 8. L.K. Reasonably good, maintained control; not improved by increased dosage.

there has been a definite diminution in its effectiveness (e.g. Fig. 7). In some the response has been improved by increasing the dose, and none have yet returned to insulin, but some may need to do so later. In general we have not found 3 g. to be more effective than 1 g., although 0·5 g. is frequently found to be a submaximal dose.

Diabetic vascular complications and control

In our series 15 patients had marked retinopathy, and of them only one had an excellent response. The presence of diabetic complications otherwise did not appear to affect the likelihood of response to D 860.

Toxicity of D 860

A few patients complained of nausea, dizziness, tiredness, and 2 patients of vomiting shortly after starting the tablets. These symptoms later passed off and it is difficult to assess their true relationship to the D 860. There were 4 patients who developed rashes; 3 of them were mild (purpuric in one, urticarial in one, papular in one) and soon passed off; the 4th was more severe.

Case C.S. A Coloured female aged 50, with mild diabetes of recent onset, was put onto 3 g. of D 860 a day in place of 40 units of insulin. In 2 weeks a very severe stomatitis appeared, which did not clear up until D 860 was stopped. The blood count was normal. An itchy purpuric rash also occurred on the arms and legs, and later this rash was twice caused to reappear some 12 hours after single gram doses of D 860.

This was the only case in which D 860 had to be discontinued because of its toxic effects. We have seen no depression of leucocyte count.

Pregnancy

D 860 can be used during pregnancy. Two pregnant patients are at present well controlled with it.

Times of 'stress'

Patients on D 860 may require insulin if they develop infections or undergo other 'stress'. On the other hand, D 860 may well prove very useful in patients undergoing operation, since the danger of hypoglycaemia is obviated and catheterization and intravenous glucose are less necessary. We have seen instances of both these states of affairs.

Speed of action and effect of discontinuance of D 860

In patients who were well controlled on D 860, a relapse has occurred in every instance where it has been omitted. Occasionally the relapse appears rapidly, as in one patient in whom glycosuria was repeatedly found the same day when no tablets were taken and in whom it equally rapidly disappeared when the tablets were taken again. Others did not relapse for one or two weeks. We have no evidence that D 860 is curative.

The hypoglycaemic effect of D 860 was mostly seen within three or four days of starting treatment, sometimes more rapidly, and sometimes not for two or three weeks. Because of this it is probably worth continuing a trial of this drug up to 3 weeks where practicable. Since D 860 may be to some extent cumulative (though less so than BZ 55) a loading dose of 3 g. the first day, with gradual reduction, is often used.

Blood-sugar level on D 860

D 860 appears to act largely by reducing the fasting blood-sugar level, but it has much less affect on the actual tolerance to glucose. We have several times found patients with normal fasting levels but abnormally high postprandial blood sugar, while others with normal fasting sugar showed very high 1-1½ hour figures on glucose tolerance tests (Fig. 4*b*). Too much reliance, therefore, should not be placed on the fasting sugar as the sole test of response to D 860.

Hypoglycaemic symptoms due to D 860 alone are rare and mild. We think we have seen such symptoms in 3 patients, but have not proved this. In such cases the patients may be more comfortable after halving the dosage of D 860. When it is given with insulin, hypoglycaemia should be watched for, since occasionally the effects of the two antidiabetic agents appear to be additive.

Use of D 860 *and insulin together*

Because of our method of change-over from insulin to D 860 we have not very much experience of the use of the two together, nor do we believe that this will often prove helpful. It seems to us that insulin or D 860 alone almost always provides as good control as a combination. Where D 860 is given to a mild diabetic already on insulin and a better result is obtained, it will usually be found that insulin is unnecessary.

Recommendations concerning the use of D 860 *in general practice*

1. It should never be used in the severe young diabetic, nor in any diabetic who has ever been in ketosis.
2. The obese diabetic should be treated in the first instance by a reducing diet.
3. D 860 may safely be tried in a mild diabetic who is not on insulin, who still has glycosuria and hyperglycaemia despite a low carbohydrate diet, and who has no ketonuria.
4. It is not always easy to know in which diabetics it is safe to stop insulin. In general practice it would be safer either not to use D 860 in diabetics already on insulin *or* to use it only in addition to insulin in patients who are poorly controlled on insulin alone and then, if control is improved, slowly to reduce the insulin. We would not recommend changing from insulin to D 860 in any patient whose diabetes is well controlled in general practice.
5. Adherence to dietary regime is still necessary, though, as indicated in this paper, it may be considerably relaxed in the thin diabetic who is controlled on D 860.

CONCLUSIONS

1. In general, like everyone else we find that the severe diabetic is unsuitable for D 860; certainly unless admitted to hospital for special observation.
2. D 860 is effective in a high proportion of patients whose diabetes started over the age of 40 and who are of 'mild' type. Otherwise we can see no very definite correlation between likelihood of response and age, sex, length of diabetic history, previous insulin dosage, time, presence of complications, or body weight. Apparently Coloured people respond less well on the whole, but *in any mild case the only way to know if a patient will respond to D* 860 *is to try.*
3. German workers[3] have reported close correlation between age and response to D 860, as well as between age of onset and response, and between increasing body weight and response; and a negative correlation between prior insulin dosage and response and between length of time insulin had been used and response. Some of the differences between their conclusions and ours may be because they have not separated their severe from their mild cases, so that some of their series are automatically weighted on the side of youth, big insulin dosage, and leanness, with correspondingly poor response in these groups.
4. We repeat our belief that obese patients should primarily be treated by dietary restriction and not with insulin or D 860, except in emergency. On the other hand the lean mild diabetic may be very suitable for D 860 and perhaps for an increase in diet.
5. *To summarize*, then, the particular value of D 860 appears to be

(i) in the mild thin diabetic,

(ii) in other mild diabetics in whom diet alone does not produce sufficient control, and

(iii) in mild diabetics perhaps especially at the time of an operation.

(iv) It should be of special value to obviate the danger of hypoglycaemia in mild diabetics with high or low renal thresholds.

(v) Similarly in patients suffering from angina, myocardial infarction or peripheral vascular disease, where hypoglycaemia is to be avoided, D 860 should be safer than insulin.

(vi) In patients who are stupid, or are subject to unpleasant hypoglycaemia, or insulin allergy or atrophy, D 860 may be particularly valuable.

SUMMARY

The results of the use of D 860 in 250 diabetic patients at Groote Schuur Hospital are presented. Certain conclusions are drawn and recommendations made on the basis of this analysis.

The D 860 used in this trial was largely supplied as 'Rastinon' by the Newport Trading Corporation of Johannesburg. Latterly some 'Artosin' has been given to us by Noristan Laboratories of Pretoria. We are very grateful to both of these firms.

I thank herewith all physicians associated with this trial at Groote Schuur Hospital, especially the other members of the Diabetic Clinic, and most especially Prof. G. C. Linder.

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Some recent British experiences with tolbutamide are given in the Brit. Med. J. 10 Aug. 1957, including an editorial summing-up.