A CLINICAL TRIAL OF CARBUTAMIDE (BZ 55) IN THE DIABETIC CLINIC

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While the previous paper describes our more detailed observations on a small number of in-patients treated with carbutamide, this one considers the larger number of diabetics treated as out-patients.

Methods

This series comprises 31 patients in all, excluding those who were first investigated in the ward. All but 3 were the 'mild maturity-onset' type of diabetic, who had previously been treated with small doses of insulin or diet only. There were 2 severe diabetics, who were liable to ketosis, and one of intermediate severity.

In general, any insulin which was being used was stopped some weeks before carbutamide was tried. The diet was not usually altered, but in a few cases a more liberal diet was allowed. As far as possible all patients in the trial were seen weekly and had weekly fasting capillary blood-sugar estimations. As well as this, the control was followed by collections of 24-hour urine once a week, by 50 g. oral glucose-tolerance curves before, during and after carbutamide therapy, or simply by qualitative urine-tests. The total white cells were counted before and during therapy, and in many cases the serum cholesterol, blood urea and liver function were estimated before and after 4 weeks of carbutamide.

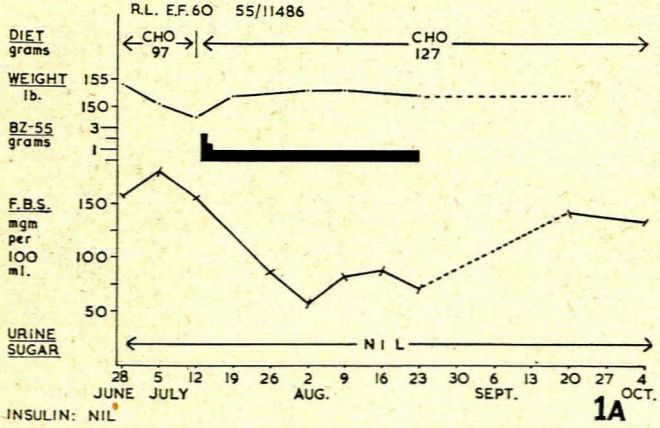

Fig. 1A.* R.L. A non-obese, mild diabetic with high renal threshold. On a larger intake, her fasting sugar gradually diminished with carbutamide, and rose after its discontinuance.

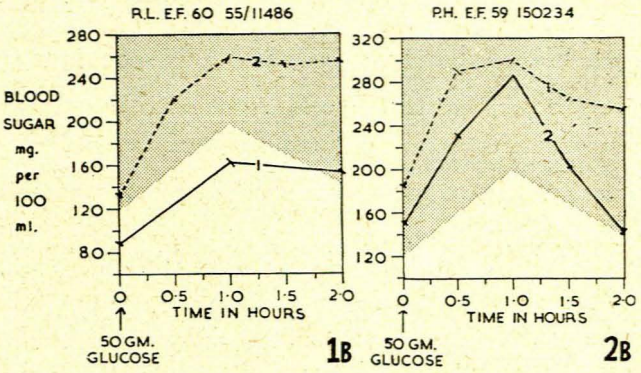

Fig. 1B. R.L., same patient as Fig. 1A. (1) 16 August 1956, on BZ 55 for 5 weeks. (2) 4 October 1956, off BZ 55 for 6 weeks. Her glucose-tolerance curve was far lower while on the drug.

Fig. 2B. P.H., same patient as Fig. 2A. (1) 23 August 1956, 1 week before BZ 55. (2) 2 October 1956, on BZ 55 for 5 weeks. An improvement in the glucose-tolerance curve while under carbutamide is evident, but the tolerance curve is still grossly abnormal.

The dosage of carbutamide was the standard one of $2\frac{1}{2}$ g. the first day, $1\frac{1}{2}$ g. the next day and 1 g. thereafter. The day's ration of tablets were taken all together in

* Conventions regarding figures as in the preceding paper (see footnote on p. 1223, second column). The shaded portion of the glucose-tolerance graphs indicates the abnormal, diabetic zone.

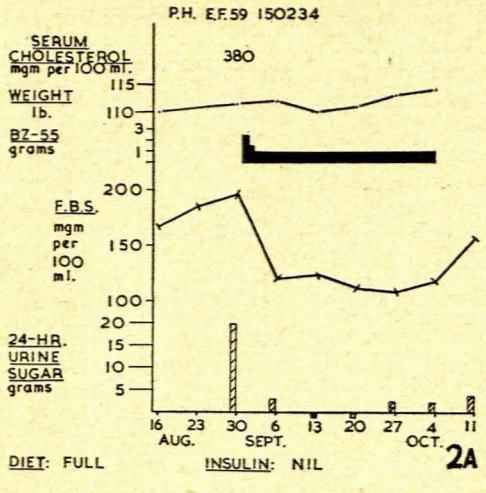

Fig. 2A. P.H. A thin female whose diabetes was of 5 years' duration. We encouraged her to eat everything. The improvement in fasting sugar and urinary sugar while on carbutamide is evident.

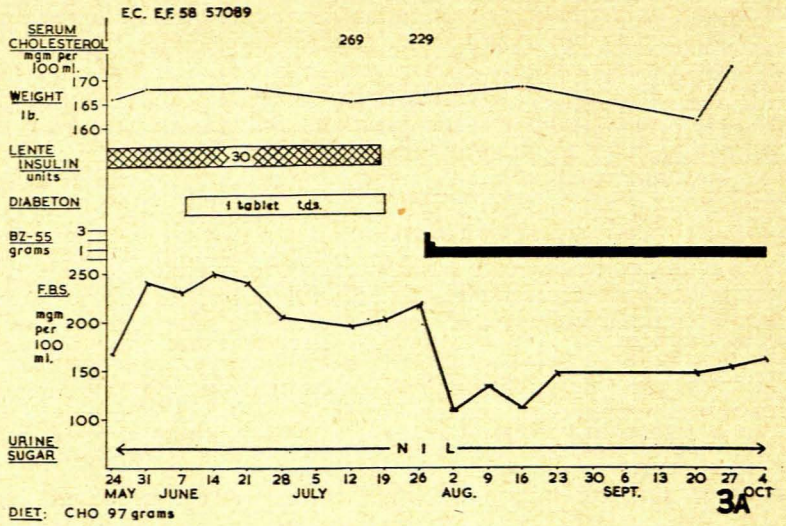

Fig. 3A. E.C. A non-obese diabetic of 5 years' standing, with high renal threshold, in whom oral 'Diabeton'† together with her insulin did not lower the fasting sugar, while carbutamide was effective with no insulin.

the mornings. The 50 g. oral glucose-tolerance tests were performed on patients who had taken a high carbohydrate diet for 1 week; capillary blood was used, and the modified Hagedorn-Jensen method of estimation.

Results

Of the 28 'mild' cases all but 3 showed a distinct response by reduction of blood sugar on repeated occasions together with reduction of urine sugar or improvement of glucose tolerance. In some of the newly diagnosed patients there was also symptomatic improvement of such complaints as pruritus vulvae and loss of energy.

It is not easy to express clearly just how patients responded by giving average or over-all data. For this reason the data from 5 typical mild cases are charted (Figs. 1-5). In order to express a 'mean' response also, the last 3 blood-sugar readings before carbutamide and the first 3 while on the drug in all 28 patients have been averaged. Before carbutamide the mean blood-sugar reading was 182 mg. per 100 ml. (standard deviation=45); while taking this drug it was

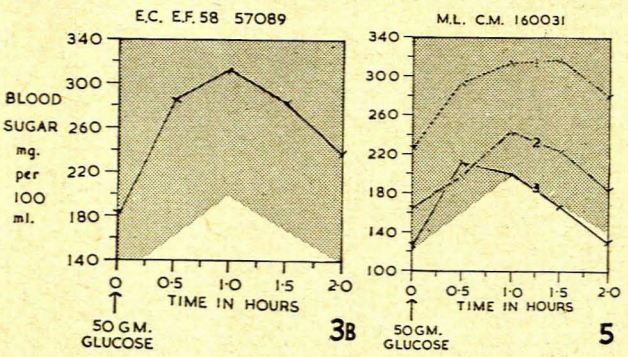

Fig. 3B. E.C., same patient as Fig. 3A. 2 October 1956, after 10 weeks on BZ 55. Notwithstanding the improvement in the fasting sugar while under carbutamide, the single tolerance curve taken during its administration is nevertheless grossly abnormal.

Fig. 5. M.L. An obese diabetic of 1 year's standing. Not on insulin. (1) 12 June 1956, before starting any drug. (2) 13 July 1956, after 1 month on 'Diabeton'. (3) 4 September 1956, after 1 month on BZ 55. There was a distinct improvement of glucose-tolerance on 'Diabeton', but a considerably greater improvement on carbutamide.

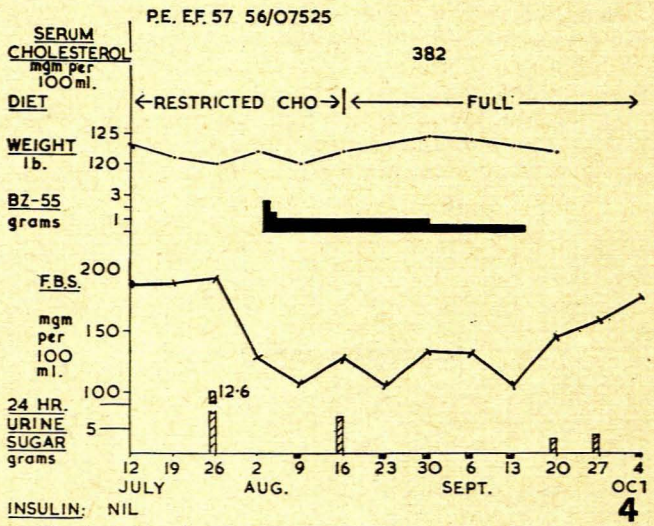

Fig. 4. P.E. A thin woman with mild diabetes of 8 years' standing, who had taken insulin for 6 years. Carbutamide was highly efficacious in lowering the fasting blood-sugar and 24-hour urine-sugar, even in dosage of ½ g. per day.

† 'Diabeton-M' is a proprietary preparation claiming to be extremely effective in controlling all types of diabetes. It contains 5 hydroxyanthranilic acid, vitamin B6, methionine, vitamin C, and a mysterious Japanese extract of 'Morus Bombycio Koidzumi (Moraceae)'. It appears, from our limited observations on this preparation, that it may occasionally have some blood-sugar lowering effect, but not comparable to that of carbutamide.

124 (S.D.=46). The difference between these two means is highly significant ($p=>\cdot001$). At the same time it must be pointed out that a mean figure of 124 signifies that in many individuals the fasting blood-sugar was still too high.

The 3 'mild' diabetics who did not respond at all were not distinguished by any obvious specific characteristics. All were middle aged, one was male, none had had diabetes longer than 10 years, 2 under 3 years. None had outstanding vascular or infective complications.

'Severe' cases. One 'severe' diabetic (R.S.) showed a distinct response to the standard doses of carbutamide, and withstood a withdrawal of insulin (Fig. 6), although the efficacy of the oral drug seemed to wane after a few weeks. The other 'severe' case and the 'intermediate' case showed no response.

Weight. We observed no particular tendency to gain or lose weight on BZ 55. It is well known that overweight patients taken off insulin may, in general, more easily reduce because of the cessation of the appetite-stimulating effect of this hormone. Our patients in this category, however, are too few to allow us to draw any such conclusion from this series.

DISCUSSION

Type of Response to BZ 55

Although 90% of our mild cases showed some response, this is not to say that carbutamide produced perfect control in more than a few. The British workers[11,12] have pointed out that the outstanding effect is on the *fasting* blood-sugar, but that actual glucose-tolerance (i.e. the amount of rise of the blood sugar after ingestion) is not altered. This effect is seen in our tests also (Figs. 2b and 3b).

The speed of response cannot be exactly assessed from weekly visits but in many cases there was a progressive drop in the fasting sugar for a few weeks.

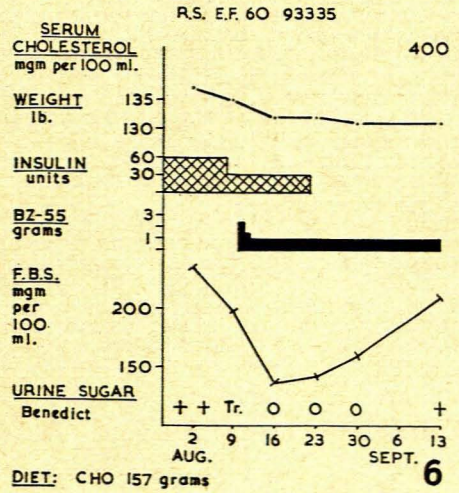

Fig. 6. R.S. A severe non-obese diabetic of 10 years' standing, poorly controlled on 60 units of lente insulin. Better control was obtained with half the dose of insulin, plus carbutamide. After complete withdrawal of insulin, the blood sugar gradually mounted.

We noticed a tendency to *relapse* in some instances, even while the patient was still maintained on the drug, as judged by an increase in the fasting sugar. After the BZ 55 was discontinued the control of the diabetes usually worsened, but not always immediately. There was no instance of the final state being worse than before the treatment. Of course we do not know what might be the result of discontinuing after one or two years' treatment, although reports indicate that sometimes there is a lasting effect.[8-10]

We did not observe a poorer response in patients whose diabetes was long standing, [8-10] nor in those whose initial fasting blood-sugar was over 275 mg.[12]

The 'Free' Diet

In the routine management of diabetes the authors all believe in dietary restriction—in the insulin-requiring case, to allow better control and, in the obese case, to reduce weight. However there are some mild diabetics who are thin or over-thin and who need a fair calorie-intake and a certain amount of insulin to maintain control. If carbutamide (or its successor) can maintain these patients free from glycosuria or hyperglycaemia, without insulin and on an absolutely free diet, there seems no logical reason for any restriction. This we were able to observe in 2 patients whose course is charted (Figs. 2 and 4).

A further young but obese woman of 34 was observed on a completely free diet. Carbutamide reduced her fasting sugar from 300 to 100 mg. per 100 ml. with her weight stationary at 210 lb. The drug was then stopped and a 1,000-calorie diet substituted. Within 4 weeks she had lost 10 lb. and the fasting sugar was maintained at around 155.

The 'Severe' Cases

It is certain that carbutamide cannot be recommended for this type of diabetic. Nevertheless, occasionally it proves to be more effective than would be expected, as in the case depicted in Fig. 6. In 2 further severe cases who were poorly controlled, BZ 55 was added to their insulin and had no evident effect whatever.

Toxic Effects

We observed no effect on the blood urea, liver functions, or serum cholesterol. Two minor rashes were encountered. In only 2 patients were the total white cells depressed below 5,000 per c.mm. One of these women developed total agranulocytosis and became severely ill, as has been already described.[20] We understand, also, that there has been more than one death in the USA from the same toxic effect. Incidentally the lack of ability of BZ 55 to reduce an initially high serum-cholesterol (if this is confirmed) is perhaps a bad omen concerning its efficacy in reducing long-term vascular complications.

CONCLUSIONS

We have no doubt that carbutamide represents an advance in the management of diabetes. Its efficacy in controlling the blood sugar in a high proportion of

diabetics of the 'maturity-onset' type is certain. The control, however, is still not perfect, because of the post-absorptive rise. Furthermore this drug is potentially dangerous, but it is surely the first of a number of substances of which later modifications will have similar or improved anti-diabetic action and less toxicity. The next substance is already with us—D 860 (orinase or rastinon)—in which the amino group is replaced by a methyl radicle. This compound apparently has no anti-bacterial action and appears to be free from danger to the leucocytes.

We therefore strongly recommend that carbutamide (BZ 55) should not at present be used outside a hospital in which special trials are being conducted.

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