A CLINICAL TRIAL OF CARBUTAMIDE (BZ 55) IN DIABETICS ADMITTED TO HOSPITAL

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While insulin has provided us with a means of combating the acute complications of diabetes, and is able to prevent hyperglycaemia and ketosis for long periods in intelligent and cooperative patients, it is not the complete therapeutic answer to the disease. Even patients who adhere strictly to the diet prescribed and give themselves the correct dose of insulin may develop vascular, ocular, renal, obstetrical and neurological complications. A drawback to the dietary treatment of diabetes is the concession that the average diabetic not infrequently allows himself (perhaps more often herself) the occasional cream bun or slice of cake. The disadvantages inherent in insulin include the difficulty of timing its action to meet physiological requirements, the inconvenience of daily injections, the non-infrequent disfigurement of fat atrophy, and the dangers of hypoglycaemia. An orally administered, non-toxic preparation acting adequately throughout the day and night would be a considerable advance, especially if it could control the brittle severe diabetic as well as the mild.

No preparation of insulin is likely to be effective orally, as this polypeptide is readily digested by intestinal enzymes. Many workers have sought for oral remedies in vegetable and yeast extracts; for example phaseolin[1] had a vogue in Germany, and myrtillin[2] was held to reduce alimentary hyperglycaemia, but even its discoverer could only say that it was feeble and uncertain as compared with insulin. Watanabe,[3] in 1918, showed that guanidine possessed the power of lowering the blood-sugar level, but only when given in poisonous doses. Frank, Nothmann and Wagner[4] found that synthalin (decamethylenediguanidine) retained this reaction on the blood sugar and was much less toxic; they used it on diabetic patients. Graham and Linder[5] participated in a trial organized by the Medical Research Council in 1928; they found that it did have an effect on glycaemia and glycosuria in some patients, but emphasized the frequency and seriousness of the toxic symptoms. The fate of the sugar which disappeared was never solved. Cobalt compounds will destroy the alpha cells of the islets of Langerhans but are too toxic for clinical use. Diethyldithiocarbamate is unreliable clinically.

As long ago as 1942 Janbon *et al.*[6] noted the hypoglycaemic action of a sulphonamide compound, and Loubatières[7] did extensive experimental work with this compound, but it also proved too toxic for human use. In 1955 Frank and Fuchs,[8] Achelis and Hardeback,[9] and Bertram *et al.*,[10] in Germany described the effects of a new sulphonamide derivative, N_1-sulphanilyl-N_2-n-butylcarbamide (BZ 55), both in man and experimental animals. These clinical workers reported that this drug could control most elderly or middle-aged 'mild' diabetics but was without effect in the young 'severe' type. A loading dose of 2½ g. on the first day and 1½ g. on the second were followed by 1 g. daily. A full therapeutic effect was seen within 3 days in many patients but only after 2 weeks in others.

In one series of 82 cases the occurrence of 6 skin eruptions and one case of hepatitis was recorded. The latter was probably unrelated to the drug. In the other series no side-effects were reported. The British workers[11–16] pointed out that many of the German patients were obese and were of the type usually controlled by diet alone in Britain. They felt that the best prospect for BZ 55 was in the treatment of the middle-aged or elderly diabetic (usually over 45 years), who would ordinarily require small doses of insulin in addition to dieting. Their series showed that BZ 55 could be satisfactorily substituted for insulin in about 70% of such cases and that it was relatively ineffective in young severe diabetics or in older diabetics requiring large doses of insulin or showing any tendency to ketosis. The Canadian workers[17] report similar results in smaller series of cases.

CLINICAL TRIAL (IN-PATIENTS)

Messrs. Eli Lilly supplied us with carbutamide (BZ 55) to conduct a clinical trial of this substance at Groote Schuur Hospital. This paper records our findings on

suitable patients admitted to the medical wards over the 4 months, July-October 1956.

Methods

There were 12 cases in this series. Many others were rejected for various reasons. One interesting reason for rejection was the finding that 3 patients remained sugar-free and with normal blood-sugar levels after their insulin had been discontinued.

The accepted 12 were all admitted to hospital either for the control of their diabetes, for the treatment of one or more of its complications, or for a separate illness. Four were seen weekly as out-patients after discharge from the wards. It must be stressed that this trial is one of *short-term* therapy only. Early-morning fasting blood-sugars were estimated daily as far as possible. Capillary and venous blood were taken but only one method of withdrawal was used in any one patient. The blood was taken before insulin or carbutamide was given. The blood sugar estimations were done by Hagedorn's modification of the Hagedorn-Jensen method. Full 24-hour collections of urine were preserved with toluol and the glucose content was measured daily by the method of Somogyi. Those seen as out-patients brought a 24-hour urine with them. The length of the control period depended largely upon the urgency with which beds were required.

The diet was in some cases unrestricted; in others it was low in carbohydrate, accurately estimated and measured by the diet kitchen. In all patients white-cell counts were done before and after and often during the administration of BZ 55. The blood urea, serum protein, thymol turbidity, thymol flocculation or zinc turbidity, and serum cholesterol were estimated before and after treatment. The serum bilirubin and quantitative Van den Berg were frequently measured. Patients were weighed at least once weekly.

Carbutamide was given immediately after breakfast. The routine dosage was 2½ g. on the first day followed by 1½ g. on the second and 1 g. daily thereafter. In some cases doses of 5 g. were given for short periods and in one case 10 g. The method of the change-over from insulin to carbutamide was variable, and is indicated individually in the figures. A relapse usually occurred soon after discontinuing carbutamide, but occasionally a more permanent stabilizing effect appeared to have been produced. Most of the patients could be classified as belonging either to the 'maturity-onset' mild type or 'growth-onset' severe type * of diabetes.

'Maturity-onset' Mild Diabetes

Case 1. J.P.H. (56/06239), European male aged 73 years, weight 159 lb., not obese (Fig. 1). This patient was admitted to hospital because of a left-sided pleural effusion and was then found to be diabetic. He had no 'diabetic complications'. Throughout his stay in hospital he was on a diet containing 127 g. of carbohydrate and as an out-patient he tried to maintain the same diet. Initially he received 15 units of lente insulin per day and was

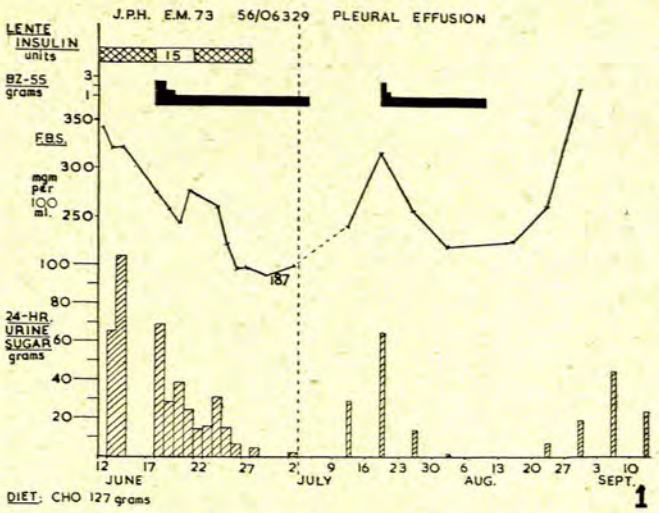

Fig. 1*. Note substantial reduction in blood and urine sugar even when insulin is discontinued. Successive relapses and remissions as BZ 55 is stopped and re-started.

excreting up to 110 g. of glucose with a fasting blood sugar of over 300 mg.%. On carbutamide the fasting blood-sugar fell as low as 187 mg.%. This effect was maintained after insulin was stopped. There was a corresponding considerable fall in the urinary glucose. While he was attending as an out-patient the carbutamide was stopped and the diabetes worsened but again responded to the drug. On stopping it a second time the diabetic state again deteriorated.

Comment. This case clearly demonstrates the efficacy of carbutamide and the necessity for its continuation in an elderly man with recent onset of diabetes.

Case 2. P.L.Z. (56/07076), European male aged 76 years, weight 195 lb. moderately obese (Fig. 2). He was admitted for the operative treatment of a cataract and was discovered to be diabetic. He was not given insulin. On a diet in which the only

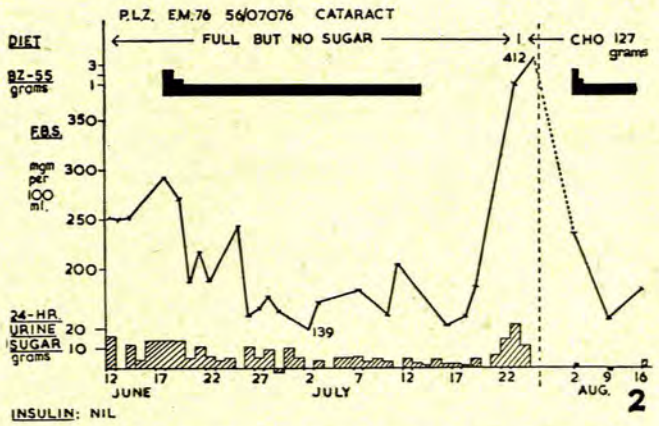

Fig. 2. Note repeated improvement on carbutamide. The urine sugar is lowest on carbutamide plus restricted diet.

* The terms 'growth onset' and 'maturity onset' are used simply to indicate the severe, insulin-sensitive, ketosis-prone, typically young, diabetic and the mild, often obese, typically older, patient respectively. Each variety *may* in fact occur at any age.

* *Note concerning all figures.* EM, AF etc. indicate European male, African female etc. FBS indicates fasting blood-sugar. CHO indicates carbohydrate in diet. Vertical dotted line indicates change from in-patient to out-patient status. Note that the time scale (abscissa) changes at this line. The absence of a block for 24-hour urine sugar indicates that no urine was available on that day; if there was no sugar on analysis this is shown by a small block *below* the base line.

restriction of carbohydrate was the withdrawal of sugar, carbutamide reduced his fasting blood-sugar from over 250 mg.% to as low as 138 mg.%, and his urine sugar also fell. He was severely diabetic 10 days after stopping therapy, improved with a diet containing 127 g. of carbohydrate and further improved by adding carbutamide. He lost 7 lb. weight during his hospital stay.

Case 3. D.F. (56/07253), European male aged 40 years, weight 192 lb. (Fig. 3). He was admitted after a myocardial infarction

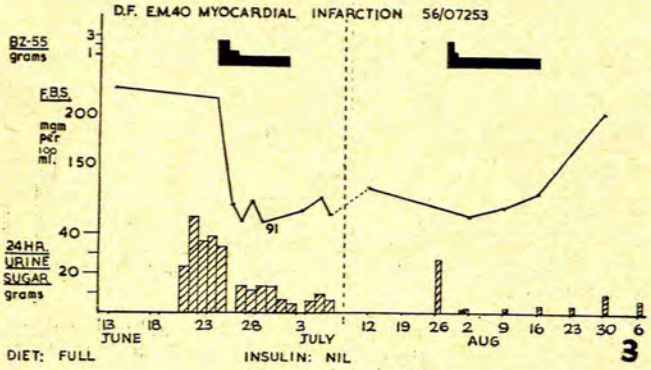

Fig. 3. Again, repeated improvement and relapse on taking and withholding carbutamide on restricted diet.

and was not known to have diabetes before this. His diet remained completely unrestricted. The repeated relapses whenever carbutamide was stopped (6 and 10 weeks after the infarct) indicated that his was not just a 'temporary' diabetic state following on the infarction. He developed a generalized itchy papular eruption while on his second course of carbutamide. This rapidly responded to oral antihistaminic treatment without withdrawal of carbutamide. Insulin was not used. Final weight was 191 lb.

Case 4. E.M. (56/22878), non-obese African male aged 60 years, weighing 152 lb. (Fig. 4). He was admitted with amoebiasis,

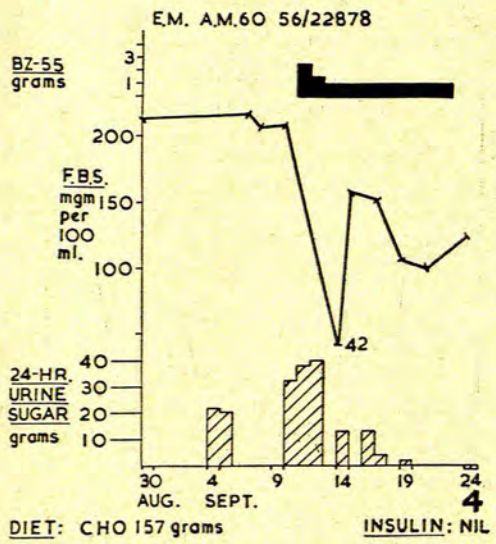

Fig. 4. Good effect of carbutamide. The low fasting blood-sugar was unaccompanied by symptoms.

found to be diabetic, and given carbutamide after he had been adequately treated for the primary disease. He was not a known diabetic and never received insulin. His diet contained 157 g. of carbohydrate per day. Carbutamide halved his fasting blood-sugar and reduced the urinary glucose considerably.

Case 5. G. de V. (55/13547), European female, aged 17 years, weighing 131 lb. (Fig. 5). On an unrestricted diet her mild diabetes

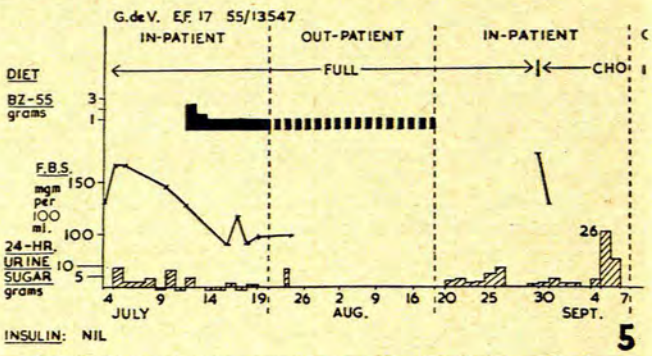

Fig. 5. Control of the diabetes by diet is inferior to that by carbutamide.

was improved by carbutamide, but as an out-patient she took the drug sporadically. On her second admission for a plastic operation of a relatively minor nature her glycosuria increased while off carbutamide, despite restriction of carbohydrate intake. Her sister is also a diabetic of mild type and responded to carbutamide.

'Growth-onset' Severe Diabetes

Case 6. B.R. (182626), lean European male, aged 20 years (Fig. 6). He was admitted for control of diabetes, having been treated with carbohydrate restriction and insulin for 2 years. When his 120 units of lente insulin was replaced by carbutamide his diabetes rapidly deteriorated, thus indicating the failure of this drug to substitute for insulin in his case. When insulin and

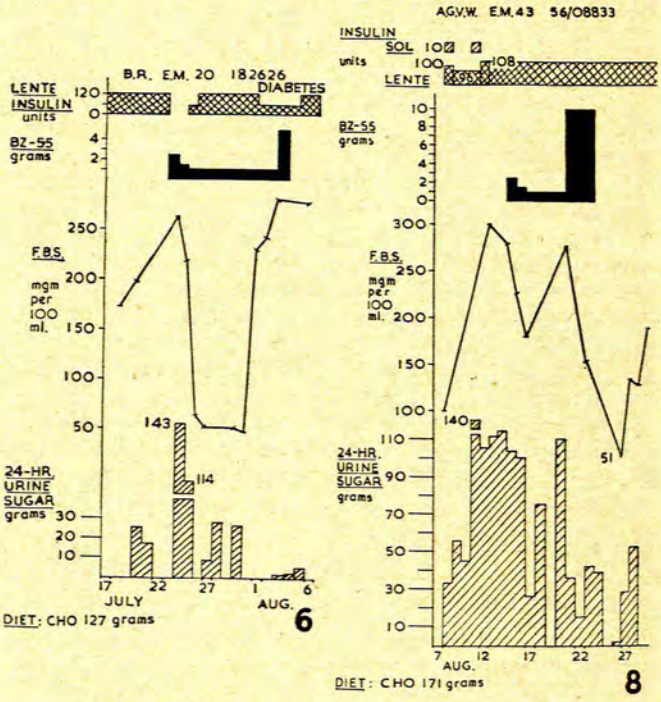

Fig. 6. Sustained morning-hypoglycaemia when BZ 55 was added to his regular dose (120 units) of insulin. One large dose of carbutamide possibly reduced the urine sugar after the insulin had been halved.

Fig. 8. Note distinct effect of very large doses of carbutamide after routine amounts had shown no activity.

carbutamide were given together his fasting blood-sugar fell to very low levels, his urinary glucose fell and he suffered from hypoglycaemic symptoms during the night and early morning. When the insulin dosage was halved and the carbutamide maintained his glycosuria and hyperglycaemia greatly increased. The effect of 5 g. of carbutamide daily was tried; it appeared to be partially successful in reducing these figures.

Case 7. D.G. (56/08338), lean European male aged 10 years (Fig. 7). He was admitted for control of his newly discovered

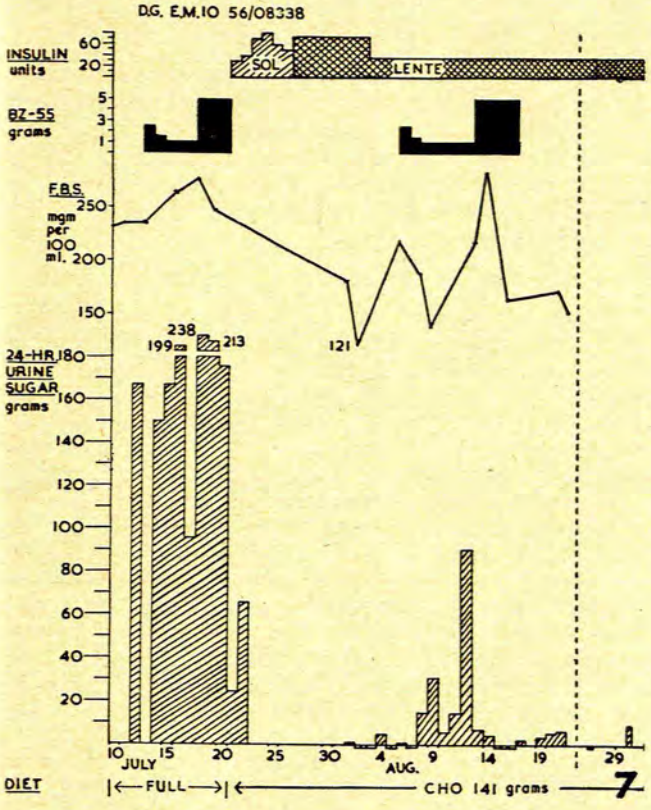

Fig. 7. Ineffectivenes of BZ 55 on its own to control the diabetes. Apparent effect of very large doses acting as an adjuvant to insulin and lowering both blood and urine sugar.

diabetes. On a normal diet he was excreting an enormous amount of glucose daily and his fasting blood-sugar was in the neighbourhood of 250 mg.%. This was completely uninfluenced by the standard dose of carbutamide or even by a dosage of 5 g. a day. maintained for 5 days. The diabetes was then controlled by insulin (60 units daily) and a restricted carbohydrate diet. His insulin dosage was then halved and carbutamide again given in routine dosage. The diabetes relapsed, but an increase of the carbutamide to 5 g. daily now seemed to have some effect. Thereafter he remained well controlled on the smaller dose of insulin without carbutamide. This may or may not have been the effect of the previous administration of carbutamide.

Case 8. A.G.V.W. (56/08833), lean European male aged 43 years. (Fig. 8). A severe diabetic of 2 months duration, he was admitted for control. Large doses of insulin (around 110 units) were unsuccessful. The addition of the standard doses of carbutamide was without effect; increase to 10 g. per day was effective in controlling the diabetes but relapse occurred soon after stopping the drug.

Case 9. N.J. (244204), Coloured female, aged 49 years (Fig. 9). She was poorly controlled on 150 units of lente insulin per day. She had been known to have diabetes for 3 years and had been

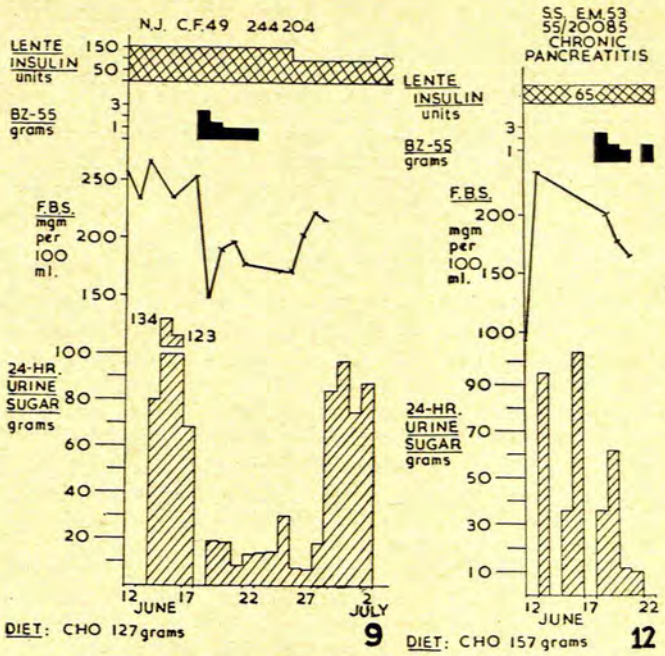

Fig. 9. A distinct effect of standard doses of carbutamide acting as adjuvant to insulin.

Fig. 12. Apparent improvement on carbutamide, with insulin continued.

receiving insulin injections during this period. She weighed 128 lb. With the same dose of insulin, carbutamide in standard amounts appeared to have a good effect, but when the insulin dosage was reduced by a third she relapsed.

Case 10. C.C. (56/14680), Coloured female aged 51 years, weight 146 lb. and slightly obese (Fig. 10). She had been a known diabetic for 5 months before her admission. At first control was

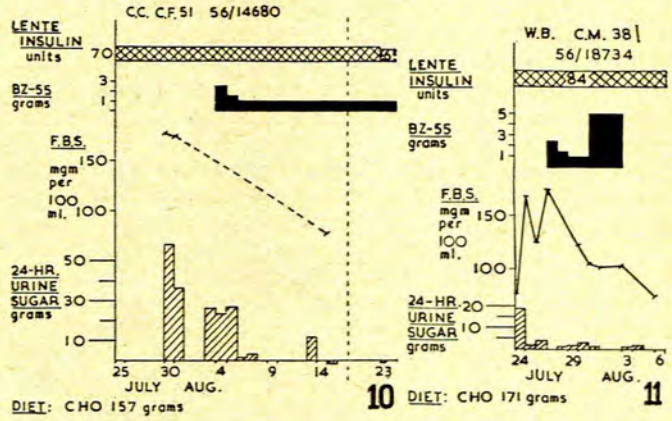

Fig. 10. Control of diabetes improved by standard doses of carbutamide, with previous insulin unchanged.

Fig. 11. Possible improvement of control on carbutamide.

fair with carbohydrate restriction alone but this proved inadequate and she was admitted in mild ketosis after being on small doses of insulin for 2 weeks. Her treatment during the control period was a diet containing 157 g. of carbohydrate and an injection of 70 units of lente insulin a day. Addition of carbutamide in standard doses had a good effect in reducing her glycaemia and glycosuria.

Case 11. W.B. (56/22878), slim Coloured male aged 38 (Fig. 11). He was admitted for control of severe diabetes, which had just been diagnosed. When carbutamide was added to his insulin, improvement seemed to follow, but in the short period of study this appearance may have been fortuitous.

Case 12. S.S., Coloured male, aged 53 years (Fig. 12). He had diabetes secondary to chronic pancreatitis, and appeared to show some response to carbutamide added to his insulin during the short period he was studied.

DISCUSSION

The 'mild' obese diabetic. There is no doubt that carbutamide is effective in controlling the hyperglycaemia and glycosuria in this type of case, as was adequately demonstrated in Germany and has been confirmed by all other workers (e.g. our cases 2 and 3). We strongly agree with the British workers, however, that obesity itself is a serious disorder and should be treated primarily by calorie restriction. Once weight has been satisfactorily lost, control of the diabetes usually ceases to be a problem.

The mild non-obese diabetic. At the present time it seems that this is the type of patient in whom carbutamide (or its successor) will have the greatest value. It will produce steadier control in some, obviate the necessity for insulin injections in some, and allow a less irksome diet in some. The efficacy of carbutamide in this group has been firmly established by other workers and is illustrated by its success in all four patients of this kind that we treated (cases 1, 3, 4 and 5). The Whittington workers[12] found that patients whose fasting blood-sugars were below 275 mg. per 100 ml. were more likely to respond well. Two of our subjects, however, had sugar levels higher than this and their response was excellent. This type of case can be safely dealt with as an out-patient, and is further considered in the following paper.*

Possibility of a free diet while on carbutamide. It is evident from cases 3 and 5 that adequate control of diabetes may be obtained in some instances with complete freedom from dietary control (i.e. allowing sugar, sweets etc. *ad lib.*). This also will be considered further in the next paper.*

The 'severe' diabetic. Another important place for an oral anti-diabetic agent will be as an adjuvant to insulin, producing better control and allowing the use of a single daily injection instead of multiple ones in the more 'brittle' cases, and allowing a reduction in insulin dosage in the others. Less is known of the activity of carbutamide in such cases, although the German authors considered it valueless. For this reason we concentrated particularly on the 'severe' in-patients. Several of these patients were taking very large doses of insulin indeed (see Figs. 6, 8, 9, and 11). We were left in no doubt as to the activity of carbutamide in insulin-requiring cases, although it was quite unable to replace the insulin completely. In fact we were surprised to find evidence of activity of carbutamide in *every* case of severe diabetes, although in 3 instances a very high dosage was needed (*cf.* Kinsell[18]). Certainly one would not dare to continue these doses of carbutamide for long, so that our findings in cases 6, 7, and 8 are, at the moment, of academic interest only.

On the other hand the standard dosage of carbutamide appeared to be effective in assisting control of the diabetes in cases 9 and 10, while in case 6 it actually aggravated the 'brittleness' of the diabetes by producing spikes of severe hypoglycaemia. Further trials of this type of case are needed, since there does seem to be a gleam of hope. Such trials will plainly need to take place in hospital, because of the danger of ketosis if insulin is reduced and of hypoglycaemia if it is not.

Speed of response to carbutamide. Bertram[10] stated that a significant effect might not be obtained until the end of the second week of carbutamide therapy. Our findings were more in keeping with the British workers,[11–16] who observed a response within 12-96 hours. Equally rapid relapse appeared to occur on withholding the drug.

Possible Fallacies

It might be argued that the increased attention paid to patients during the trial made them adhere more strictly to their diets, especially when the carbutamide was actually being given. We do not think this was an important factor in our cases. Some of the British workers used dummy tablets in order to eliminate that factor in their trials.

Secondly it must be admitted that the natural history of diabetes itself is unpredictable, as we found especially when removal of insulin improved diabetic control, or when a patient suddenly became sugar-free for no apparent reason during the control period and was then of necessity omitted from the trial. For this reason the demonstration of repeated remission and relapse of the diabetic state with the use and withdrawal of carbutamide is the clearest way of demonstrating its effectiveness (*vide* case 1).

Toxic Effects

In one patient (case 3) a toxic drug eruption was seen while on his second course of carbutamide. This responded rapidly to oral anti-histaminic therapy in spite of continuance of BZ 55. There were no other side-effects. Nine per cent of the British cases developed rashes, which always resolved when the drug was stopped. We saw no effect on the white-cell count even when very large doses of carbutamide were used. Leucopenia and agranulocytosis is, however, a very real danger, and a fatal case has occurred in the USA, together with another fatality due to a form of allergy.[19] (In our out-patient series there was one case of agranulocytosis.[20]) Duncan *et al.*[11] recorded a definite granulocytopenia in their series as a whole in the initial 2 weeks of treatment, which returned to normal in the majority despite continuance of BZ 55. Six of their 30 patients showed lowered platelet counts. Purpura has also been noted. Headache, malaise and drowsiness has been recorded on high dosage[11] and drug fever has occurred. Kinsell *et al.*[10] reported some depression of radioactive-iodine uptake in the initial period, which returned to normal on maintenance therapy. One patient became mildly hypothyroid after 5 months of carbutamide.[15]

* Page 1227 of the present issue.

Carbutamide may sometimes potentiate the effect of barbiturate and of alcohol, and patients should be warned of this possibility.

In our series, as in others, there was no change in the blood urea, serum protein, thymol turbidity, thymol flocculation, zinc turbidity, serum bilirubin or serum Van den Berg reaction.

SUMMARY

1. A clinical trial of carbutamide in diabetes mellitus was undertaken in the wards on a short-term basis.

2. The claim of other observers that carbutamide is effective in mild diabetes of 'maturity onset' is substantiated. In obese patients dietary restriction remains of primary importance.

3. The possible place of carbutamide (or its successor) in severe diabetes of growth onset is considered. It cannot replace insulin completely but it certainly seems more active in these cases than is usually believed.

4. Toxic effects are potentially serious.

We are indebted to all the physicians and other members of the staff of the hospital who cooperated in this trial.

For references see end of the following paper (page 1230).