CHLORPROPAMIDE* (DIABINESE) IN DIABETES, WITH SPECIAL REFERENCE

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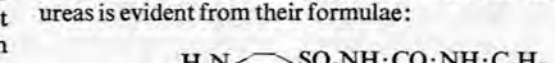
In this age of great therapeutic advances we are witnessing the apparent paradox of pharmacological substances—the sulphonylurea drugs—being used for the correction of a physiological aberration such as diabetes on the one hand, and on the other hand of a physiological agent—cortisone—being used for the treatment or 'cure' of a variety of inflammatory and allergic conditions.

With the discovery of insulin it seemed that the final answer to diabetic treatment was at hand, but as time has gone on it has become clear that insulin is necessary only in a proportion of diabetics. In the acute-onset diabetes of the juvenile type, often associated with ketosis, insulin will largely correct the physiological abnormality. The maturity-onset type of diabetic—who has been shown to have available insulin in his plasma—is not fundamentally benefited, as far as we know, by exogenous insulin.

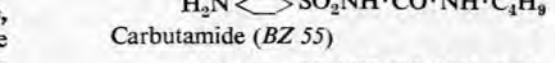
Attempts to correct the hyperglycaemia in diabetes by drugs other than insulin proved unsuccessful or impracticable until the advent of the sulphonylureas. It is problematical whether the other biochemical abnormalities of diabetes mellitus are corrected by these pharmacological agents.

In the treatment of diabetes mellitus our aim should be the search for the biochemical abnormality and its correction. The sulphonylurea drugs may prove to be a stepping stone in this direction.

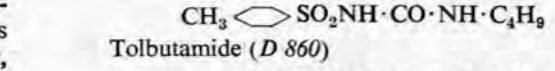
The similarity of the chemical structure of the sulphonylureas is evident from their formulae:



Carbutamide (*BZ 55*)



Tolbutamide (*D 860*)



Chlorpropamide

Carbutamide (BZ55) is generally believed to be too toxic for routine use. With the replacement of the NH_2 group by CH_3 (tolbutamide) the toxic effects were greatly diminished,

* Produced by the Pfizer Laboratories, of America, under the trade name Diabinese. We are indebted to Messrs. Pfizer, of Johannesburg, for initial supplies of this drug.

but unfortunately the hypoglycaemic activity was also somewhat decreased.

Chlorpropamide is the latest addition to these drugs in general use. A chlorine radical has replaced the NH_2 or CH_3 group.

There are many puzzling features connected with the clinical applications of these drugs. If we consider the maturity-onset type of diabetes only—why do some patients in this group respond to the sulphonylureas and others not? A proportion of the diabetics who respond satisfactorily to tolbutamide fail to respond after continued treatment. Why should this secondary failure occur? Why may patients respond to chlorpropamide when tolbutamide has failed either initially or later? Is there a difference in their action (or is the apparent difference merely one of absorption and blood level)?

In this series of cases the clinical effect of chlorpropamide in diabetes mellitus has been studied and special attention has been paid to those cases in which there had been secondary tolbutamide failure.

METHODS AND MATERIAL

The 56 diabetics studied here were seen at the diabetic clinic of Groote Schuur Hospital. Of these, 52 (all but 4) were of the maturity-onset type, all over 40 years of age. Generally they had been seen over a period of years and all but one had been treated with other hypoglycaemic agents previously.

The fluctuations in blood sugar have been observed in some of the cases over a period of years (in a few cases one of us, J.B.H., has observed such fluctuations with remissions and relapses in the diabetic state for over 10 years). This has enabled us to form some idea of comparative response to the various hypoglycaemic agents.

The subjects were asked to report for a fasting blood-sugar estimation (Hagedorn-Jensen method) approximately once a week. In addition many of them kept records of qualitative tests of the urine. Chlorpropamide was given in a dosage of 2 tablets (2×250 mg.) a day. On rare occasions the dose was increased to 3 tablets and sometimes it was reduced to 1 a day.

Where a good hypoglycaemic response had been achieved on chlorpropamide, as indicated by fasting blood-sugar estimations, a glucose tolerance test was done in some cases. Some patients were further examined by an augmented cortisone tolerance test while remaining on chlorpropamide.

A further 4 acute-onset diabetics who were on insulin were also given chlorpropamide to determine whether this would lower the insulin requirement in these cases.

'Excellent' response indicates a reduction of the fasting blood sugar to within the normal range (under 120 mg. per 100 ml.) and virtual absence of glycosuria. 'Poor' indicates no apparent effect. 'Partial' indicates some definite effect of chlorpropamide; although the blood sugar did not become quite normal, control may yet be considered very satisfactory in some of the cases so classified.

RESULTS

Excellent hypoglycaemic response was obtained in 24 of the maturity-onset cases, 'partial' in 17 and 'poor' in 11.

In none of the 4 acute-onset diabetics could the dosage of insulin be lowered whilst on chlorpropamide.

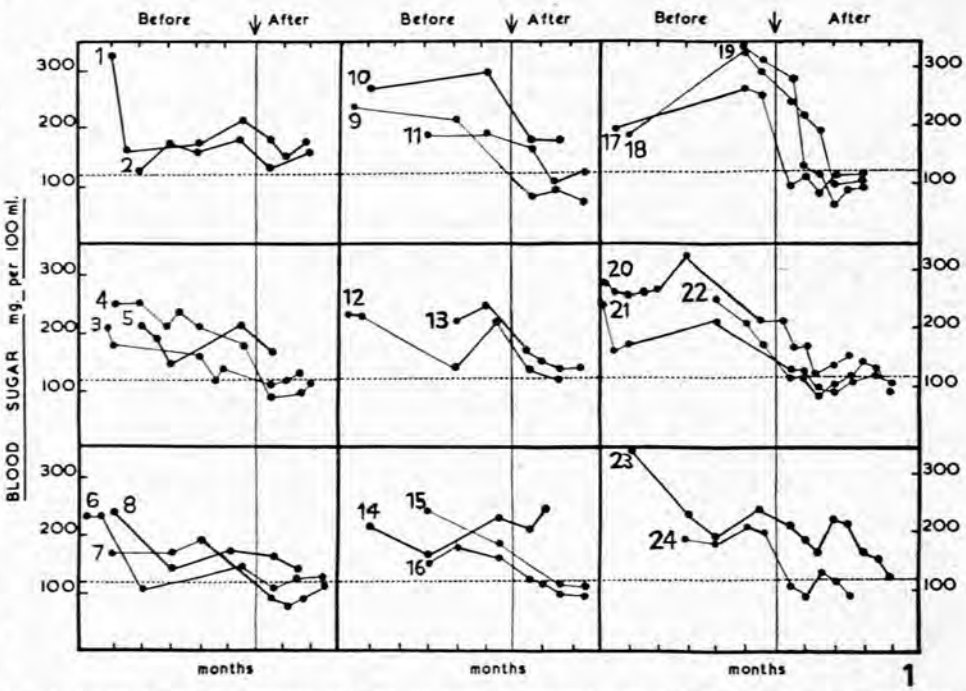


Fig. 1. Chart showing response of first 24 patients treated with chlorpropamide (fasting blood sugars before and after chlorpropamide).

A composite graph (Fig. 1) gives some idea of the response to chlorpropamide in the first 24 patients treated by one of us (J.B.H.).

Relation to previous tolbutamide effect

Of the 52 maturity-onset patients, 51 had previously had tolbutamide and 43 had failed to respond to this drug. In the latter group there were 18 primary tolbutamide failures and 25 secondary failures. The test imposed on chlorpropamide in this particular trial was therefore a very stringent one. An excellent response to chlorpropamide was obtained in 20 of

TABLE I. CHLORPROPAMIDE RESPONSE IN RELATION TO PRIOR EFFECT OF TOLBUTAMIDE

Tolbutamide Status	*Response to Chlorpropamide*		
	Excellent	*Partial*	*Poor*
Primary failure ..	8	6	4
Secondary failure ..	11	8	6
Partial response ..	0	2	0
Maintained control ..	4	1	1
Not used (on insulin)	1	0	0
	24	17	11

the 43 tolbutamide failures, and a partial response in a further 14. (Table I shows a further break-down of the chlorpropamide response in relation to prior tolbutamide effect.)

Relation to race, sex and body build

All the patients were White except 3, who were Cape Coloured. Two of these 3 responded very well to chlorpropamide. There were only 11 males in our series. Less than one-third of our White patients were considered obese—illustrating our belief that obese diabetics should be treated by diet only as far as possible.

Relation to duration of diabetes

Table II indicates that an excellent response is quite likely even where diabetes has been present for over 10 years.

TABLE II. RESPONSE TO CHLORPROPAMIDE IN RELATION TO DURATION OF DIABETES

Duration of Diabetes (years)	*Response to Chlorpropamide*		
	Excellent	*Partial*	*Poor*
Under 10	19	11	7
Over 10	5	6	4

Relation to previous administration of insulin

More than one-third of our patients had previously been taking insulin. Table III makes it clear that there is no

TABLE III. RESPONSE TO CHLORPROPAMIDE IN RELATION TO PREVIOUS USE OF INSULIN

Previous Insulin	*Response to Chlorpropamide*		
	Excellent	*Partial*	*Poor*
Yes	9	8	4
No	15	8	8

apparent difference in response to chlorpropamide in the two groups. One patient, an obese Coloured female of 60, was poorly controlled on 90 units of insulin daily, and completely failed to respond to tolbutamide. Her response to chlorpropamide is classed as excellent.

Toxic effects

Serious toxic effects were not encountered in this series. One male patient, who failed to respond, said that attacks of Menière's vertigo were more frequent when he was taking chlorpropamide. A complaint of 'feeling queer', associated with palpitations, necessitated stopping the drug in 2 cases. Patients with symptoms of gastric intolerance were able to continue taking the drug when magnesium trisilicate powder was prescribed and the dose of the drug reduced. Many of the patients who showed a good hypoglycaemic response also experienced increased well-being.

INDIVIDUAL CASES

A summary of 3 case reports will serve to give more information about the nature of the response in the individual case.

Case 1 (*No.* 19 *in Fig.* 1)

A typical good response was obtained in D.R., a middle-aged European female, whose remissions and relapses in diabetes had been followed over a period of 12 years. Tolbutamide, which had at first produced an excellent result, failed to influence the hyperglycaemia on continued treatment. The administration of 2 tablets of chlorpropamide (0·5 g.) effected a prompt response. A fasting blood sugar of over 300 mg. per 100 ml. was lowered to less than 100 mg. per 100 ml. and 2 weeks after starting chlorpropamide remained at that low level. Urine tested 4 times a day remained sugar free.

Case 2 (*No.* 20 *in Fig.* 1)

E.C. is a middle-aged European female in whom fasting blood-sugar tests over a period of years had always given results between 200 and 300 mg. Before administration of chlorpropamide this patient was on 20 - 30 units of lente insulin and 4 - 6 tablets of tolbutamide a day, with fasting blood-sugar levels remaining consistently between 200 and 300 mg. Chlorpropamide in doses of 2 (later 3) tablets a day for the first time in years brought down the fasting blood sugar to a near-normal level of (140–150 mg.)

Case 3 (*No.* 13 *in Fig.* 1)

R.D., a European male aged 42 years, was seen 2 years previously on a dose of 60 units of insulin daily. He was found to have low fasting blood-sugar levels, the urine being constantly sugar-free. Insulin was slowly reduced and after a while stopped; the fasting blood sugars remained normal for about 2 years, when hyperglycaemia manifested itself. Three tablets of chlorpropamide lowered the fasting blood sugar from 240 mg. to 130 mg. and the patient has remained well on 3 tablets a day. Insulin has not been found necessary

DISCUSSION

In this investigation, chlorpropamide was shown to have a powerful blood-sugar lowering effect. Oral glucose-tolerance tests (using 50 g. of glucose), however, whilst the patients were being treated with chlorpropamide, still showed a considerable hyperglycaemia in the majority of the cases

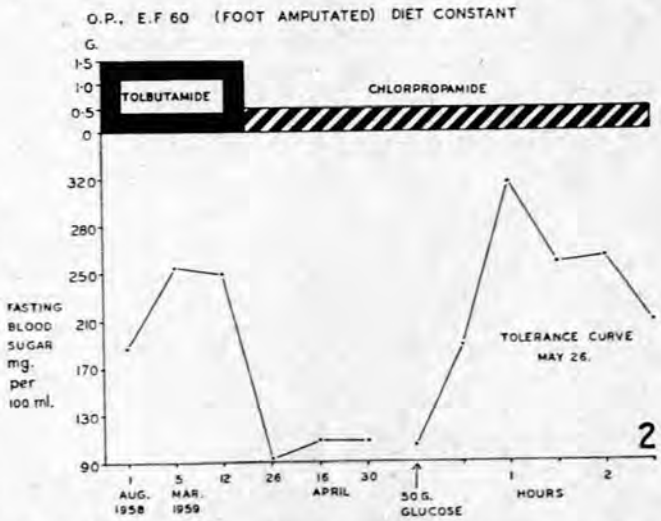


Fig. 2. Case 17 in Fig. 1. Good response to chlorpropamide, but note abnormal glucose tolerance despite low fasting levels.

(e.g. Fig. 2). As found with the earlier sulphonylureas, therefore, the major effect of chlorpropamide is in the basal or fasting blood-sugar level, rather than on the disposal of ingested carbohydrates.

Chlorpropamide was found in this series to be frequently very effective where there was primary or secondary tolbutamide failure (e.g. No. 19 in Fig. 1). In some instances 1 tablet of chlorpropamide (250 mg.) was more effective than 6 tablets of tolbutamide (3 g.). It would appear unlikely then that there is a purely quantitative difference in action of these drugs, but we performed no studies of blood levels.

This series is plainly not large enough to judge the toxicity of the drug, which has been implicated in the appearance of jaundice in certain cases overseas. Its more powerful hypoglycaemic effect may give rise to serious reactions, though we have seen none.

It would appear that chlorpropamide may be effective in maturity-onset diabetes, whatever the age, sex or body build of the patient, whatever the duration of diabetes, whatever response there had been to tolbutamide, and whether or not insulin had been used previously.

Our present practice is to start with tolbutamide (maximum dose 1 g. 3 times a day) where a sulphonylurea appears indicated (i.e. in maturity-onset cases in which diet alone has failed). If the response is not satisfactory, or if secondary failure occurs, a trial of chlorpropamide is made.

SUMMARY

1. The response to chlorpropamide has been assessed in 56 diabetic patients, all but 4 being of maturity-onset type.

2. The drug was satisfactory in a high proportion of cases, and appears to be particularly useful in patients in whom there has been primary or secondary tolbutamide failure.

3. No serious toxic effects were seen in this series.

We should like to thank Prof. J. E. Kench and his assistants for their great help.

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