PRELIMINARY OBSERVATIONS ON PHENETHYLDIGUANIDE

BY

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The alarming toxic effects of "synthalin A" (Bodo and Marks, 1928; Creutzfeldt, 1957) led to its withdrawal from use, although it was pharmacologically promising. The related compound phenethylguanide (D.B.I.) has been reported to be totally lacking in toxicity, the only barrier to its use being the high incidence of nausea and vomiting (Krall and Camerini-Davalos, 1957; Pomeranze *et al.*, 1957). While the hepatic output of glucose is reduced, like synthalin, it causes hypoglycaemia in eviscerated animals, and is thus not wholly dependent for its effect on the presence of active beta cells in the pancreas (Frank *et al.*, 1926; Nielsen *et al.*, 1958). It is able to influence peripheral glucose utilization, as shown by muscle culture, an effect which, unlike the sulphonylureas, it shares with insulin (Williams *et al.*, 1957). It was our aim to assess its value in the out-patient treatment of diabetes mellitus.

Choice of Patients and Dosage

Fifty-two patients were selected for their ability to co-operate in urine tests, and, where it applied, in the adjustment of insulin dosage as indicated by the tests. None had evidence of hepatic or renal disease. Ages varied from 12 to 75, and weight was in all cases within 10% of accepted normal standards. Twenty-nine were on insulin and the remainder were freshly diagnosed cases, or those in whom dietary treatment had proved inadequate. Loss of weight, glycosuria, and a blood-sugar level in excess of 200 mg. on three occasions, each two hours after a main meal, was regarded as evidence of this. To prevent confusion through patients dieting carefully only after active tablets were given, placebo tablets were administered in the last two weeks of the preparatory period, and, in fact, eliminated two of the intended subjects by showing that dietary control sufficed. A diet in the region of 170 g. of carbohydrate was given, except to those in vigorous employment, when it was increased appropriately.

Two 25-mg. tablets of D.B.I. were administered daily for the first week of treatment, and this dosage was increased at subsequent weekly or fortnightly visits to a maximum of 200 mg. daily if necessary. Morning and evening urine specimens were examined at the clinic, and a blood sugar estimation was carried out two hours after a main meal. The criteria of control of diabetes were: (a) morning and evening urine tests were almost sugar-free; (b) blood sugar, two hours after a main meal, was less than 140 mg./100 ml; (c) weight was constant; and (d) diabetic symptoms were absent.

The successful patients were treated for periods varying from three to six months.

Results (See Table I)

For convenience the patients are divided into four groups: (A) Adult diabetes: patients over 40 in whom insulin requirement did not exceed 40 units daily. (B)

Stable juvenile diabetes: judged from absence of acetone and a moderate or mild diabetic glucose-tolerance curve as in group A. (In group A 20 out of 24 were recently diagnosed and had not yet been given insulin; in group B 3 out of 8 were similarly new cases.) (C) Adult diabetes in which insulin dosage exceeds 40 units daily. (D) Juvenile diabetes in which insulin dosage exceeds 40 units daily. It is appreciated that the division is to some extent arbitrary. Adults sensitive to insulin in low dosage with a tendency to acidosis may be concealed in group A, and members of group D will graduate with age into group C. Group A is that which is usually successfully controlled by the sulphonylureas.

TABLE I

Group	No.	Success*	Partial Success†	Failure
A (adult)	24	21 (88%)	1	2
	4 on insulin	2 on insulin		1 on insulin
B (stable juvenile)	8	4 (50%)	3	1
	5 on insulin	1 on insulin		on insulin
C (adult unstable)	13	3	7	3
		28%		
D (juvenile)	7	1	4	2
		14%		
Total	52	29	15	8

* "Success" indicates that insulin was withdrawn, or not required to obtain control.

† Partial success indicates a fall in insulin dosage of more than 20 units.

1. *Successes*.—Although the mode of action of D.B.I. and the sulphonylureas is not identical, the same group (A) was most favourable for treatment with D.B.I. as they would be with the sulphonylureas. 88% of group A diabetics were well controlled by D.B.I., which compares favourably with the anticipated results of treatment with carbutamide or tolbutamide. In two cases the drug apparently had no effect; in one case nausea made use of the drug intolerable. Group B gave a success rate of four in eight cases, and three of those not completely successful showed a fall in insulin dosage of over 20 units. Groups C and D, although differing in age, showed no real variation in their susceptibility to the action of the drug. On the reduced dose, control of diabetes was more accurate as measured by blood sugars, urine tests, and incidence of hypoglycaemia. Of the unstable cases, only three in the older group and one younger patient were controlled without insulin. Those in whom the insulin dose was substantially reduced but not eliminated are regarded as partially successful if urine control was good. The mean duration of treatment of the successful patients was 18 weeks, with a spread of 12 to 24 weeks.

2. *Dosage and Insulin Replacement*.—In 10 patients scattered throughout the four groups, the hypoglycaemic effect was greater in the first week or two, and thereafter the dose of insulin had to be increased substantially before a final control figure was reached. When a substantial effect was found with the initial small doses, further advance did not usually increase the insulin replacement or hypoglycaemic effect. This gave the impression of a threshold of hypoglycaemic action. The effective dose was not predictable from any of the other factors we observed. The dose of D.B.I. used in the successful cases varied. Stable adults were controlled by smaller amounts, the average dose and range being: group A (21), 105 mg. (50–150 mg.); group B (4), 150 mg. (100–200 mg.); group C (3) 167 mg. (100–200 mg.); group D (1), 150 mg. In the partially successful cases the daily dose of D.B.I. was increased to 200 mg. and in

three cases to 300 mg. when nausea was not troublesome. Table II shows the insulin replaced in the four groups.

3. *Appearance of Alimentary Symptoms* (see Table III).—This has been a problem in our series as in others. Fourteen (27%) had nausea and 6 (12%) complained of mouth dryness and discomfort, making a total of 39%. In only 4 cases, one in each group, was nausea the reason for the drug being withdrawn. Its frequency was higher in the stable adult cases, but these tolerated it well probably because it was milder. On the appearance of nausea the dose was reduced by 50 mg. daily and the patient was reminded to take the drug after food; while the appetite was frequently poor for a week or two, it returned to normal and the dose of the drug was cautiously advanced, often beyond the initial amount. Mouth symptoms were transitory in all. The nausea did not coincide with the appearance of acetone. Diarrhoea was met in only one patient, with nausea.

TABLE II

Group	No.	On Insulin	Range of Dose Fall	Mean Fall	Insulin Discontinued In
A	24	4	32-16	22 units	2
B	8	5	36-12	18 "	1
C	13	13	40-8	24 "	3
D	7	7	32-12	22 "	1

TABLE III.—Side-effects

Group	No.	Nausea	Mouth Symptoms	Total Alimentary Symptoms (see Text)	Acetonuria
A	24	8	3	11 (46%)	3 (13%)
B	8	2	0	2 (25%)	2 (25%)
C	13	3	3	6 (56%)	3 (28%)
D	7	1	0	1 (14%)	3 (42%)
Total	52	14	6	20	11

4. *Acetone*.—This appeared in 11 cases, and in none of them was it associated with the usual high blood-sugar levels. Six of the cases were in the unstable groups, and 2 of the four Group A cases had shown acetone in the urine before, while under our care. In 4 cases it appeared with hypoglycaemia, and in the others the blood-sugar level varied from 160 to 220 mg./100 ml. (mean 193 mg.). With one exception it disappeared promptly with an increase in the patient's intake of carbohydrate over the planned diet. In this patient acetonuria persisted until the drug was withdrawn. In 5 cases the alkali reserve of plasma was estimated; it was at the lower limit of normal in 3 and approximately 10 volumes/100 ml. below normal in 2. This contrasts with the very low alkali reserve of plasma in pre-coma and is clearly a different entity. In each of these patients weight had fallen from loss of appetite, and starvation ketosis is thought to be the cause.

5. *Toxicity*.—Frequent W.B.C. counts were carried out; also liver function tests (alkaline phosphatase, thymol turbidity, serum bilirubin). In none were the tests abnormal.

6. *Hypoglycaemia*.—In no case did the administration of D.B.I. cause hypoglycaemia when it was not accompanied by insulin.

7. *Comparison with Carbutamide*.—In 12 cases a comparison with carbutamide was possible as the patients were treated with both. It was our impression that carbutamide is less powerful. In Case 7 the usual order

was reversed in that D.B.I., although producing normoglycaemia, caused nausea of such a degree as to make the drug intolerable. Carbutamide did not reduce the blood sugar subsequently. In the other cases carbutamide had failed initially for the reasons stated (see Table IV).

TABLE IV

Case No. and Group	Carbutamide	D.B.I.
39 (D)	No effect	No effect
40 (C)	" "	" "
48 (A)	Late failure	" "
41 (C)	" "	Control
44 (A)	" "	" "
38 (A)	Failure with acidosis	" "
46 (C)	" "	" "
49 (C)	No effect	Partial control
21 (C)	" "	" "
22 (D)	" "	" "
52 (C)	" "	" "
7 (A)	" "	Nausea, failure

Summary and Conclusion

In our experience the action of D.B.I. on the adult stable type of diabetes is impressive. Nausea is controlled rapidly by a reduction of dose, and the cases in which it makes treatment impossible are too few to vitiate its value as a hypoglycaemic agent. Unnecessarily high dosage is probably the explanation of the frequent appearance of this symptom in some other series (Hall *et al.*, 1958; Pomeranze *et al.*, 1957). Late failure of control (Williams *et al.*, 1957) did not occur in our group, with one possible exception, although the short period of observation does not allow one to be dogmatic. Ketonuria may develop in the presence of a normal or low blood sugar and is therefore not of the alarming type which usually appears in diabetes. It usually disappears with the use of a high carbohydrate diet and is probably related to starvation ketosis. The striking absence of toxicity indicates that the drug should continue to be used in the adult diabetic, and it may have a place in the treatment of stable juvenile cases also. Like the sulphonylureas, in spite of its different mode of action it is unsuitable for unstable cases if used alone.

D.B.I. appears to control or partially control some cases which do not respond to carbutamide, its hypoglycaemic effect thus being more powerful.

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