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MODE OF ACTION AND SIDE-EFFECTS OF PHENFORMIN HYDROCHLORIDE

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The hypoglycaemic action of phenformin hydrochloride (phenethylbiguanide; "dibotin"; D.B.I.) has been observed in all types of diabetes. It has been the cause of some concern that its use can be associated with the appearance of ketonuria and acidosis in the presence of normal or slightly elevated blood-sugar levels (Hall *et al.*, 1958; Steiner and Williams, 1959). This occurs chiefly in the juvenile diabetic (Walker and Linton, 1959a). It is uncertain whether this anomaly is specifically caused by D.B.I. or whether it is due to absolute or relative lack of insulin. The object of this paper is to report some clinical features of the acidosis and to relate them to the present hypotheses of action of D.B.I.

Clinical Observations

Observations were made on a series of 109 diabetics of all types controlled on D.B.I. either alone or with supplementary insulin. Good control was often obtained, as judged by the accepted criteria. The results of part of the series are reported elsewhere (Walker and Linton, 1959b). Interest was drawn to the occurrence of ketonuria in the presence of normal or only slightly elevated blood-sugar levels. It was found that ketonuria was accompanied in 11 cases by frank reduction in alkali reserve.

It will be seen from Fig. 1 that a severe fall in alkali reserve was virtually confined to juvenile diabetics, although ketonuria appeared in all types. This seemed important and was thought to be related to the basic difference between adult and juvenile diabetes—that is, the presence or absence of endogenous insulin (Wrenshall and Best, 1956). It was then observed that there was an association between the appearance of acidosis and the amount of exercise taken. Close inquiry confirmed that any moderately severe physical exercise tended to produce ketonuria and acidosis in juvenile diabetics on D.B.I. It was further observed that the fresh urine from the patients on D.B.I. alone had a *p*H of less than 5.6, while the urine of other diabetics almost without exception exceeded this.

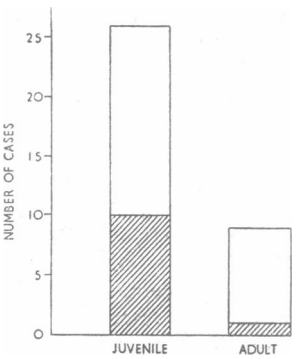

FIG. 1.—Incidence of ketonuria with or without acidosis in 102 cases. White columns = Ketonuria alone. Hatched columns = Ketonuria with acidosis. (Acidosis = alkali reserve below 20 mEq/l.) Note: "Juvenile" includes two juvenile-type adults with acidosis.

About this time the urgency of the problem was emphasized by the occurrence of two cases of very severe acidosis among the patients on D.B.I. (Walker and Linton, 1959a). Both were admitted to hospital in what appeared to be a diabetic coma. Case 1 had a blood-sugar level of 208 mg./100 ml. and an alkali reserve of 4.9 mEq/l. In Case 2 the respective values were 280 mg./100 ml. and 3.1 mEq/l.

The latter patient died despite strenuous empirical measures—intravenous glucose, insulin, and alkali—designed to combat acidosis. In neither case was there any obvious predisposing factor, and in both cases the biochemical upset was rapid in onset and severe in degree. Case 1 was controlled solely with 100 mg. of D.B.I. daily and is now controlled with 56 units of insulin. Case 2 was having 150 mg. of D.B.I. daily with 12 units of I.Z.S. ("lente" insulin).

A further case which threw some light on the problem was admitted some months later. There was severe acidosis and elevation of blood sugar; D.B.I. had been omitted for two days (blood sugar, 512 mg./100 ml.; alkali reserve, 15.2 mEq/l.) and again empirical methods were used. Insulin was given by intravenous and intramuscular routes, to a total of 280 units in the first 12 hours. In the first four hours, while blood sugars fell in the anticipated way, the alkali reserve deteriorated, reaching 5.8 mEq/l.; the alkali administered had been sodium lactate. Thereafter sodium bicarbonate was substituted, and the desired effect was obtained in a sharp rise of the alkali reserve.

Normally, intravenous administration of sodium lactate will result in an increase in the alkali reserve, as the lactate ion is either quickly metabolized in the Krebs cycle or converted to glycogen, leaving the sodium ion free to form sodium bicarbonate. In this case the further metabolism of lactate is probably blocked, and it contributed to the increased pool of lactate which is already present in patients on D.B.I.

Experimental Observations

It was decided to compare the response to exercise of patients on D.B.I. with that of normal and insulin-controlled patients, in terms of their blood sugar, alkali reserve, total blood hydrazones, and, in the latter part of the series, blood lactic acid levels.

A standard amount of exercise related to weight and age was given (Master and Oppenheimer, 1929). The exercise was not extreme and did not produce more than transitory changes in normal individuals. The specimens were taken before and after exercise and again 15 minutes later.

Results

Blood-sugar Levels.—There was no significant change.

Alkali Reserve.—The normal controls and the diabetics on insulin showed either no change in alkali reserve or a slight fall (Fig. 2). The groups of diabetics controlled by D.B.I. showed two types of response. With one exception, the unstable cases had a precipitous fall in alkali reserve after exercise, and 15 minutes later this fall was greater. The stable (adult) diabetics showed a fall in alkali reserve only slightly greater than that of the normal patients and diabetics not having D.B.I.

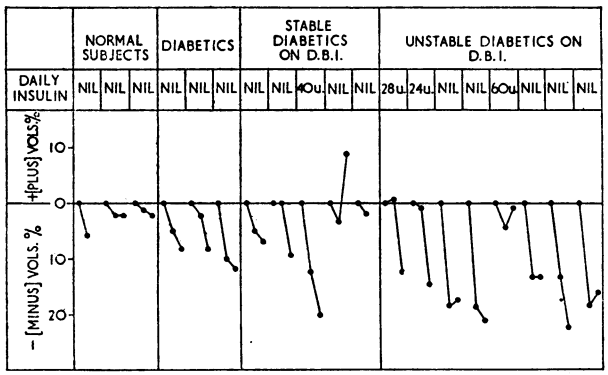

FIG. 2.—Change in alkali reserve in four groups of patients after standard exercise and 15 minutes later. Note the greater reduction of alkali reserve in unstable diabetics on D.B.I.

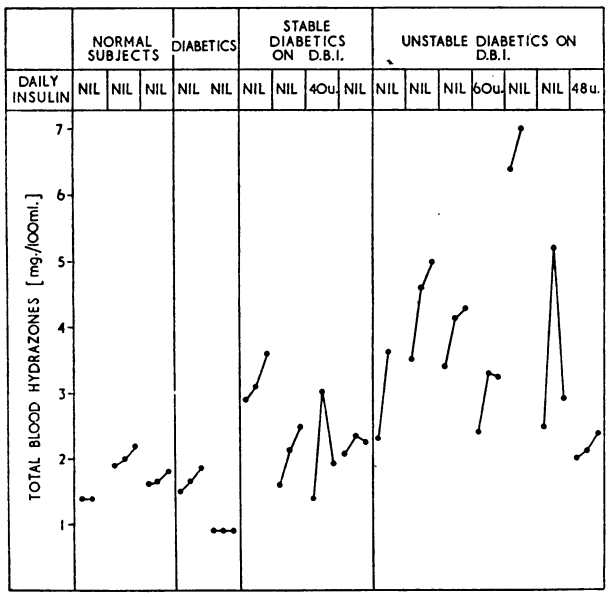

FIG. 3.—Total blood hydrazone levels before and after standard exercise and 15 minutes later. Note the higher initial levels and greater rise shown by unstable diabetics on D.B.I.

Total Blood Hydrazone (T.B.H.) Level.—This method was adopted as a simple, quick, and approximate means of detecting blood pyruvic acid. Friedemann and Haugen (1943) have measured pyruvic acid and T.B.H. before and after exercise and have shown that these are increased in proportion and the difference between them is small. Although a very approximate method, it was ideally suited to the investigation in hand. Fig. 3 shows that the levels were high in the unstable D.B.I. cases and climbed to higher levels after exercise. Again the stable D.B.I. cases were only slightly higher than the levels found in normal controls or insulin-controlled diabetics.

Blood Lactic Acid (Barker and Summerson, 1941).—As shown in Fig. 4, the change in blood lactic acid was

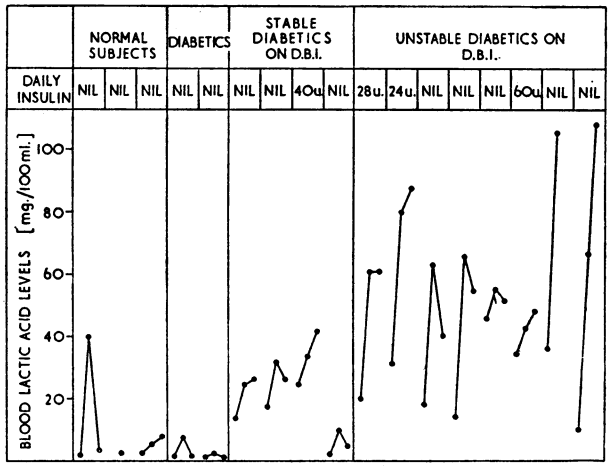

FIG. 4.—Blood lactic acid levels before and after exercise and 15 minutes later. Note the higher initial levels and greater rise shown by unstable diabetics on D.B.I.

the most striking one detected. The group of normals and diabetics on insulin showed a normal resting lactate level, a small rise after exercise, and a return to normal in the third specimen. The less stable diabetics on D.B.I. showed a high resting level, a large rise, and only a slight fall after 15 minutes. Stable diabetics treated with D.B.I. again differed little from normals.

Discussion

The hypoglycaemic effect of D.B.I. is independent of the presence of active β cells in the pancreas, in contrast to the arylsulphonylureas (Nielsen *et al.*, 1958). While glucose uptake is increased by D.B.I. *in vitro* (Odell *et al.*, 1958), the drug does not cause an increase in muscle or hepatic glycogen—in fact, the latter is reduced (Tyberghein and Williams, 1957; Williams *et al.*, 1957). The rise in blood pyruvate and lactate levels which occurs after the administration of D.B.I. is greater than that occurring with insulin (Klein, 1942; Fajans *et al.*, 1958). The hypoglycaemia and the increase in blood pyruvate and lactate are striking biochemical changes induced by the drug, and two hypotheses have been advanced to account for these phenomena.

The earlier hypothesis advanced by Steiner and Williams (1959) offers the explanation of defective utilization of lactate due to partial blockage of the tricarboxylic acid (T.C.A.) cycle. This they attribute to the demonstrable action of D.B.I. in poisoning certain necessary enzymes, particularly succinic dehydrogenase and cytochrome oxidase (Steiner and Williams, 1958). To maintain a store of high-energy phosphate bonds, an

increased emphasis is then placed on the normal glycolytic conversion of glucose to pyruvate, resulting in a lowering of blood-sugar level and increased production of pyruvate and lactate, which accumulate in the blood. A further factor which may contribute to the lowering of the blood-sugar level is decreased gluconeogenesis, for intermediates of the T.C.A. cycle are necessary for the conversion of some of the keto-acids derived from proteins to glucose. The net result of the process will be a depletion of liver glycogen, which in turn will favour the formation of ketone bodies from breakdown of fatty acid. Ungar (1959, unpublished observations), on the other hand, has suggested that there is increased production of pyruvate and lactate due to increased activity of the hexose monophosphate shunt.

The results here reported demonstrate that diabetics controlled by D.B.I. suffer from persistent biochemical abnormalities, despite apparently satisfactory control of the diabetes.

The abnormalities are of two types, which are not directly related, and either may occur in the absence of the other. The first anomaly to which attention was drawn was ketonuria with normoglycaemia. This occurred in diabetics of all types, and it is not yet possible to throw any light on the mechanism. It has been suggested that this represents a starvation ketosis ; but all patients in whom it was observed were having at least 170 g. of carbohydrate daily, and with a few exceptions their blood-sugar levels were between 100 and 200 mg./100 ml. It would seem that the phenomenon may be the result of low stores of liver glycogen, secondary to lack of insulin. It may be that D.B.I. does not duplicate the antiketogenic effect of insulin, and a form of "metabolic starvation" occurs: adequate carbohydrate and protein are ingested and retained, but intermediate metabolism is disturbed by the lack of insulin, the effects of which are only partly replaced by D.B.I.

The second and more important biochemical abnormality found is that of acidosis of varying degree, occurring exclusively in juvenile-type diabetes and usually accompanying ketonuria. This seemed to be due, at least in part, to raised blood lactate and pyruvate levels, the latter being measured by T.B.H. levels—these having been found to be raised considerably in patients otherwise controlled on D.B.I.

The elevated basal levels of T.B.H. and blood lactate can be explained by either of the hypotheses of action of D.B.I. mentioned above. The very moderate exercise to which the patients were subjected is enough to provoke a large and sustained rise in blood lactate and T.B.H. and a large fall in alkali reserve. This suggests that intermediate carbohydrate metabolism is abnormal in diabetics on D.B.I. While it would appear to favour the hypothesis which suggests that lactic acid is more slowly disposed of owing to delay in the T.C.A. cycle, it is conceivable that the sudden call for energy leads to metabolism of glucose by any route, including abnormal paths which give increased production of lactate.

Thus D.B.I. is an effective agent for reducing blood-sugar levels in diabetic patients, but in the absence of insulin there may be disproportionate accumulation of intermediate products. It seems likely that, in the stable diabetic, endogenous insulin compensates for this to some extent. It must also be emphasized, however, that this effect can and does occur in the presence of substantial doses of insulin. This suggests that the biochemical disturbances may not be due simply to lack of insulin, but may in fact constitute a direct toxic effect of D.B.I.

Summary

Phenformin hydrochloride (D.B.I.) is an effective oral hypoglycaemic agent and compares well with the arylsulphonylureas.

Gastro-intestinal side-effects are commonly reported but are not dangerous. The appearance of ketonuria and acidosis has received little attention ; it seems to be due to the drug's inability to duplicate all the actions of insulin.

Experiments are reported showing the effects of exercise on diabetics controlled by D.B.I. Unstable cases controlled by D.B.I. may show a marked fall in alkali reserve and a large rise in blood lactate and total blood hydrazones ; the changes are much in excess of those observed in insulin-controlled diabetics and in stable cases on D.B.I.

It is emphasized that the acidosis may be dangerous, and the use of D.B.I. in juveniles cannot be recommended at this stage.

It is a pleasure to acknowledge the help and encouragement of Dr. A. C. Aitkenhead, in whose unit this work was carried out. The biochemistry department of Law Hospital has assisted with many of the estimations, and Sister Ferguson and the staff at the Strathclyde Diabetic Clinic have also been of great help.

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The Association of Universities of the British Commonwealth has recently published a booklet, *United Kingdom Postgraduate Awards 1960-62*, the purpose of which is to set out in a form suitable for quick reference summarized information about fellowships, scholarships, grants, etc., tenable at universities in the United Kingdom. The booklet also includes a short list of awards that can be held outside the United Kingdom by U.K. graduates. No selling price is announced, as the A.U.B.C. is making the pamphlet available to universities and libraries (and to other institutions on request from 36 Gordon Square, London W.C.1).