Clinical Report of a New Hypoglycemic Agent. (23164)

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A wide variety of chemical substances of both natural and synthetic origin is known to effect reduction of glycemia on oral administration(1). During the past few years, investigators both here and abroad have demonstrated that oral administration of aryl sulfonylureas can substitute for exogenous insulin in mild, usually obese and elderly diabetic patients(2). The narrow range of applicability of these drugs has recently been stressed and, with some, severe toxic reactions have been reported. The site and mode of action are obscure. The search for a safe, effective oral insulin substitute still continues. A new synthetic drug N′-beta-phenethylformamidinyliminourea (DBI)* unrelated to the aryl sulfonylureas has been evaluated in the laboratory animal. Given orally, it effectively lowers blood sugar levels in alloxan treated diabetic rats, rabbits and Rhesus monkeys. A hypoglycemic effect is also seen in normal animals on oral administration(3).

The present report deals with observations in man on the acute action of N′-beta-phenylethylformamidyliminourea on glucose tolerance. Short term observations are also reported on diabetic patients when insulin and/or the drug are alternately given and withheld.

Method. Ten adult patients with diabetes mellitus and one subject without any evidences of a disturbance of carbohydrate metabolism were studied. The subjects were fasted overnight before each test and those with diabetes were not given any insulin on the morning of the test. Venous blood samples were taken before and at hourly intervals for 6 hours after the patients drank a solution containing 100 g of glucose. The tests were similarly repeated 1 week later when 100 mg DBI was given with the glucose solution. Blood glucose was determined by the method of Folin-Wu. Severe labile, moderately severe and non-insulin diabetic patients were included in the study. Three diabetic patients were observed for 6-10 day periods during which blood and urinary glucose were determined twice daily and insulin and/or DBI were alternately given and withheld. A 27-year-old male with labile diabetes mellitus of 8 years duration, a 38-year-old female with diabetes mellitus of 12 years duration controlled with 22 units of NPH insulin, and a 68-year-old female with diabetes mellitus of 28 years duration are included.

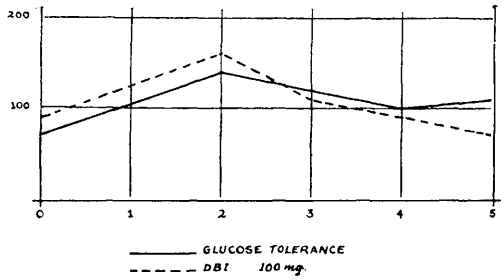

FIG. 1 (non-diabetic).

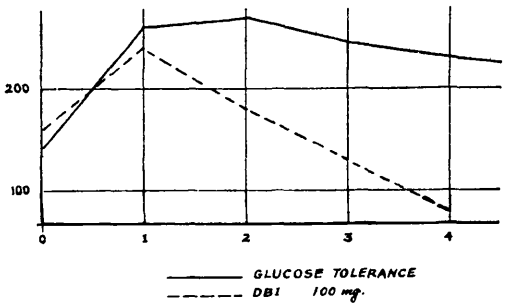

FIG. 2 (diabetic moderately severe).

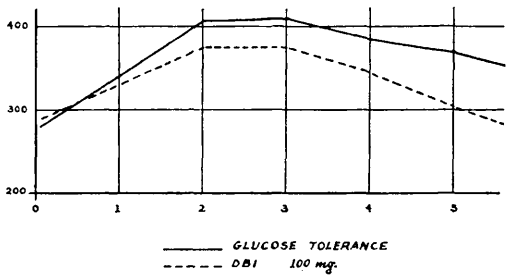

FIG. III (diabetic severe).

* We are indebted to Dr. L. Freedman, U. S. Vita. Corp., for generous supplies of DBI and the experimental data concerning it.

TABLE I. 10-Day Observation of a 27-Year-Old Male with Diabetes Mellitus; 8 Years Duration.

Days		9 A.M. B.S. (mg %)	9 A.M. U.S. (%)	3 P.M. B.S. (mg %)	3 P.M. U.S. (%)
1	NPH insulin, 70 units	184	trace	198	.25
2	*Idem*	168	"	202	.25
3	NPH insulin, 30 units	178	"	306	2
4	*Idem*	298	2.4	344	3.1
5	" & DBI, 100 mg t.i.d.	304	3	188	.25
6	*Idem*	156	0	180	trace
7	NPH insulin, 30 units; no DBI	158	0	244	1.5
8	*Idem*	306	3.5	385	4
9	NPH insulin, 30 units; DBI, 100 mg t.i.d.	311	4.2	264	1
10	*Idem*	166	0.25	144	0

Results. A significant decrease in blood sugar concentration occurred in the apparently normal subject and in the diabetic patients after ingestion of 100 mg of DBI (Figs. 1, 2, 3). The configuration of the glucose tolerance curve taken after oral administration of 100 mg of DBI was altered. This is unlike the action of sulfonylurea drugs which lower fasting blood sugar but do not alter the configuration of the glucose tolerance curve(4). Nausea and vomiting occurred during the fourth hour in one patient (Fig. 2) and required termination of the experiment. Blood glucose at this point was 80 mg %.

DBI adequately replaced 40 units of the 70 required units in a young severe labile diabetic patient (Table I) and totally replaced insulin in a less severe diabetic patient under 40 years of age and in a 68-year-old patient whose diabetes has been present 28 years.

Discussion. DBI effectively reduces blood sugar within 3 hours on oral administration. This effectiveness is maintained longer than 6 hours. The data reported herein suggest that DBI can be effective by mouth in decreasing the blood sugar of patients who develop diabetes before 40 years of age as well as those who have had diabetes more than 20 years. The data suggest that insulin requirement of patients with severe diabetes mellitus can be significantly reduced.

Conclusions. DBI by mouth produces an improvement in glucose tolerance in patients with severe as well as mild diabetes mellitus. It appears to be an active potent hypoglycemic agent, effective in patients with mild, moderate and severe diabetes mellitus. The results herein presented lend encouragement to wider experimental and clinical investigations.

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