Absence of Hypoglycemia and Hypophosphatemia Following Initial Dosages of Phenethylbiguanide (D.B.I.)*† (25344)

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That phenethylbiguanide (D.B.I.) produces hypoglycemic effects in alloxanized animals, whereas sulfonylureas do not, suggests that the mechanisms of actions of these oral insulin substitutes are different(1). Ingestion of relatively large single dosages of tolbutamide or chlorpropamide regularly produces hypoglycemia and hypophosphatemia in most patients whose diabetes developed in adult years(2-5). In this study, D.B.I. was administered in single dosages to diabetics in amounts which, if given daily for 2 to 5 days lower blood glucose levels and improve glucose tolerance in the majority of diabetics(6). The results indicate that such a single dosage of D.B.I. initially has no effect upon blood sugar, serum inorganic phosphorus, glucose tolerance or insulin tolerance.

Materials and methods. All patients taking insulin were transferred to regular insulin at least 2 days earlier and the usual dosage was omitted the day of study. In each instance neither ketosis nor lowering of serum total CO_2 content was present. Except in control studies 150 mg of phenethylbiguanide were taken *per os* 45 minutes prior to serial hourly samplings of venous blood or before the glucose or insulin tolerance test. Blood sugar and serum inorganic phosphorus levels as we determined are given in Tables I and II and Figs. 1 and 2.

Results. There is no evidence that these amounts of phenethylbiguanide exerted hypoglycemic or hypophosphatemic effects. Changes in serial samplings, and in glucose and in insulin tolerance tests were the same with and without phenethylbiguanide and any differences which appeared were not statistically significant.

Discussion. Hall and colleagues(7) reported a significant fall in blood sugar in 60% of their diabetics following a single initial dosage of 150 mg of D.B.I., but control observations without the drug, which in our laboratory show a definite spontaneous hypoglycemic trend on serial sampling(2,3), were not made. In our studies, phenethylbiguanide or D.B.I. administered to diabetics in a single dosage of 150 mg, a quantity which when continued on daily basis for 2 to 5 days regulates levels of glucose in the majority of diabetics(6), failed to exert either a hypoglyce-

TABLE I. Absence of Any Effect of DBI in Single Dosage, 150 mg at Minus 45 Minutes, in Venous Blood Sugar and Serum Inorganic Phosphorus of Diabetics.

	Without DBI		With DBI	
Hr	Mean change* ± S.D. (mg %)	(#)	Mean change ± S.D. (mg %)	(#)
	Blood sugar			
1	− 3 ± 17	(16)	− 7 ± 20	(16)
2	− 9 ± 14	(")	−12 ± 20	(15)
3	−25 ± 22	(")	−20 ± 26	(16)
4	−30 ± 23	(")	−24 ± 31	(")
5	−33 ± 22	(15)	−34 ± 41	(")
	Serum inorganic phosphorus			
1	+.02 ± .17	(15)	−.02 ± .30	(16)
2	+.01 ± .17	(")	+.01 ± .62	(15)
3	+.04 ± .24	(14)	+.03 ± .73	(16)
4	+.17 ± .28	(")	+.04 ± .72	(")
5	+.15 ± .33	(15)	+.17 ± .74	(15)

* From values at zero time.

TABLE II. Serum Inorganic Phosphorus Changes without and with DBI during Glucose Tolerance Tests and Insulin Tolerance Tests in Diabetes.

	Without DBI		With DBI	
Time (min.)	Mean change* ± S.D. (mg %)	(#)	Mean change ± S.D. (mg %)	(#)
	Glucose tolerance test			
30	+.15 ± .70	(9)	+.01 ± .17	(8)
60	−.19 ± .25	(")	+.05 ± .18	(10)
90	−.21 ± .31	(")	+.04 ± .28	(")
120	−.20 ± .25	(8)	−.01 ± .36	(9)
	Insulin tolerance test			
30	−.49 ± .24	(11)	−.66 ± .33	(12)
60	−.46 ± .54	(")	−.34 ± .58	(13)
90	−.37 ± .50	(")	−.43 ± .45	(10)
120	−.01 ± .60	(")	−.42 ± .34	(11)

* From values at zero time.

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† N′-β- phenethylformamidinyliminourea hydrochloride.

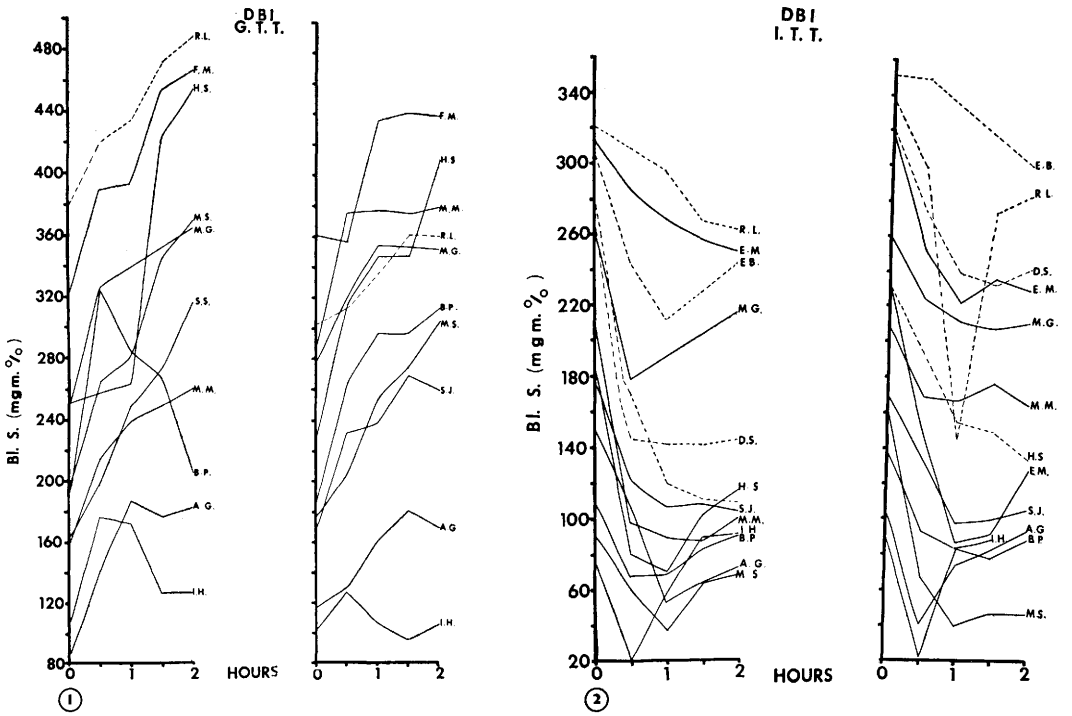

FIG. 1. Glucose tolerance tests without and with phenethylbiguanide (D.B.I.). Curves on left represent blood sugar levels in control glucose tolerance studies; repeat of tolerances after single dosage of D.B.I. (150 mg *per se*) at minus 45 min. are shown on right. Broken line identifies juvenile onset diabetes; solid lines refer to adult type diabetes. Mean changes from zero time in venous blood sugar in mg % following 1.75 g of glucose/kg body wt at zero time:

	30 min.	60 min.	90 min.	120 min.	
Without D.B.I.	69 ± 29	75 ± 28	107 ± 45	116 ± 61	These differences are not
With D.B.I.	39 ± 38	67 ± 48	76 ± 53	85 ± 66	statistically significant.

FIG. 2. Insulin tolerance tests without and with phenethylbiguanide (D.B.I.). Results of insulin tolerance tests without D.B.I. are shown on left; those following 150 mg of D.B.I. are on the right. Broken lines identify juvenile onset diabetes. Commercial crystalline insulin, 0.1 u/kg body wt was inj. intrav. at zero time. Mean changes in blood sugar in mg % from values at zero time:

	30 min.	60 min.	90 min.	120 min.	
Without D.B.I.	−71 ± 37	−85 ± 44	−78 ± 47	−72 ± 46	These differences are not
With D.B.I.	−52 ± 25	−77 ± 53	−66 ± 39	−68 ± 31	statistically significant.

mic or hypophosphatemic effect. In these respects, D.B.I. differs from sulfonylureas such as tolbutamide or chlorpropamide which on initial exposure do lower the levels of blood sugar and of serum inorganic phosphorus. However, in most trials with sulfonylureas, larger quantities were administered. This was not possible with D.B.I. because of gastrointestinal effects.

The results of glucose tolerance tests and of insulin tolerance tests support the findings obtained during serial measurements of blood sugar and of inorganic phosphorus for 5 hours after 150 mg of D.B.I. Again there is no evidence of a hypoglycemic or a hypophosphatemic effect.

This lack of response to initial dosages of D.B.I. coupled with ultimate effectiveness if therapy is continued, points to a cumulative effect, perhaps related to increasing levels of the drug or tissue responsiveness which may develop without accumulation.

Summary and conclusion. 1. Phenethylbiguanide (D.B.I.) in a single dose of 150 mg failed to induce a decrease in blood sugar or in serum inorganic phosphorus during succeeding 5 hour period in diabetic patients previously controlled with or without insulin.

2. This amount did not affect blood sugar and serum inorganic phosphorus changes during glucose tolerance tests and insulin tolerance tests in the same subjects. 3. Since these amounts of D.B.I. when continued on daily dosage do induce hypoglycemia, it is evident that such responses result either from accumulation of the drug in body fluids and tissues, represent acquired responsiveness upon continued exposure, or both.

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Duration of Progestational Effect in Rabbit Endometrium after Prolonged Administration of Progestogens.* (25345)

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Since the study by De Fremery, Luchs and Tausk(1), it has generally been assumed that progestative effect of progesterone on rabbit endometrium cannot be extended beyond 17 days. This could be explained by interaction of 3 factors: 1) lack of response of endometrium after 17 days; 2) lack of estrogen, the primary effect of which is considered necessary for progestative transformation and its continuity; 3) suppression of pituitary gonadotropins or a similar factor which might stimulate endogenous estrogen or progesterone formation. The complexity of the factors involved led us(1) to assume the existence of an "inhibitory mechanism which needs further elucidation." This paper is devoted to the above problem.

Technic. Experiments were carried out on 200 female rabbits weighing approximately 1,000 g each. They were primed by daily injections of 15 μg estrone (in 0.15 ml olive oil) for 6 days. After 1 day's rest, the progestational compounds were injected subcutaneously at dosage level of 0.5 mg (in 0.05 ml olive oil) daily. The progestational effect was assessed according to McPhail(2) after sacrificing rabbits within 1-80 days after commencement of injection of the progestational substance. At autopsy, 2 segments were removed from each horn and preserved in 4% formalin (1:10) for histological examination. Evaluation of progestational transformation was carried out according to McPhail(2), the sections of uterus scored as 0, 1, 2, 3, 4 respectively. Furthermore, ovaries were inspected to ensure that no corpora lutea were present. We did not use the technic of De Fremery, Luchs and Tausk(1) who followed progestational transformation in each animal by laparotomy and removal of a piece of uterine horn at different time intervals, lest it interfere with degree and continuity of progestational transformation.

Results. A. *Progesterone.* Table I shows that, during 80 days' treatment with progesterone, secondary transformation of endometrium could be obtained. We believe that this is possible after longer intervals; thus, in

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