Early Clinical Evaluation of a New Oral Non-Sulfonylurea Hypoglycemic Agent.* (23215)

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Recent medical literature has contained many reports of new, oral hypoglycemic agents(1,2,3). These seem to have hypoglycemic effect in certain types of diabetics, but are sulfonylurea derivatives and as such may have certain limitations. Recently Ungar *et al.*(4) reported that a new, oral non-sulfonylurea hypoglycemic agent was effective in both normal and alloxan-diabetic animals. Pomeranze(5) reported successful hypoglycemic action in early clinical trials.

This report is an early clinical evaluation of the hydrochloride of N^1beta-phenethylformamidinylimino urea, referred to hereafter as DBI. The object of this study was to determine whether DBI has blood sugar lowering properties and whether there are any immediately discernible or early toxic effects.

Materials and methods. Twenty known, proven or newly diagnosed diabetics were studied for periods varying from 2 days to 3 months. They were first hospitalized and given a constant, weighed diet. The patients were checked separately by 3 different observers at least twice daily. Previously known diabetics receiving insulin had their insulin discontinued and DBI substituted as needed. New diabetics were treated with DBI after the diagnosis was established. The laboratory studies consisted of venous, fasting, Somogyi-Nelson(6) blood sugar and capillary blood sugar determinations at varying intervals throughout the day. Urine sugars were determined by the Benedict method, fasting and at 11 a. m., 4 p. m. and 9 p. m. daily. A 24-hour total urine sugar was also done. Each patient had a white blood count, blood hemoglobin and platelet determination, as well as a complete urinalysis. Some patients had complete liver function tests which included sulfobromophthalein, thymol turbidity, alkaline phosphatase, cephalin flocculation and blood bilirubin studies. The 20 patients included 8 males and 12 females, whose ages varied from 34 to 80 and averaged 61 years. The duration of diabetes ranged from 1 to 33 years and averaged 18 years. Twelve of the 20 patients took insulin previously and their doses varied from 6 to 58 units daily. The average insulin dose was 28 units daily. After the blood sugar lowering ability was ascertained, the group was classified into one of 3 categories: (1) successful; (2) partially effective and (3) ineffective. Class I, Successful—indicated definite blood sugar lowering effect and included (a) those patients controlled on an adequate insulin dosage and weighed diet who were able to maintain the same degree of control with DBI plus weighed diet; (b) those with elevated blood sugars, previously uncontrolled, who showed a definite drop in blood sugar level on DBI plus weighed diet. Class II, Partially Effective—included those with a definite blood sugar lowering effect who were unable to tolerate effective doses because of side effect severity. Class III, Ineffective—included patients with no significant change in blood sugar level in spite of at least 2 days' administration of 150 mg or more of DBI daily.

Results. There was a demonstrable blood sugar lowering effect in 13 of the 20 patients studied (Fig. 1 and 2). Three others were classified as partially effective since the blood sugar lowering effect was apparent, although DBI was discontinued because of severe side effects. The patients designated as successful demonstrated a definite decrease in blood sugar levels along with diminished glycosuria and disappearance of 24-hour urine glucose output. With those patients continued on DBI for prolonged periods, discontinuing the DBI or substituting a placebo resulted in a return to elevated blood sugar levels. There were no hypoglycemic reactions observed. The maximum daily requirement of DBI was

* We are indebted to Dr. L. Freedman, U. S. Vitamin Corp., N. Y. City, for the DBI used.

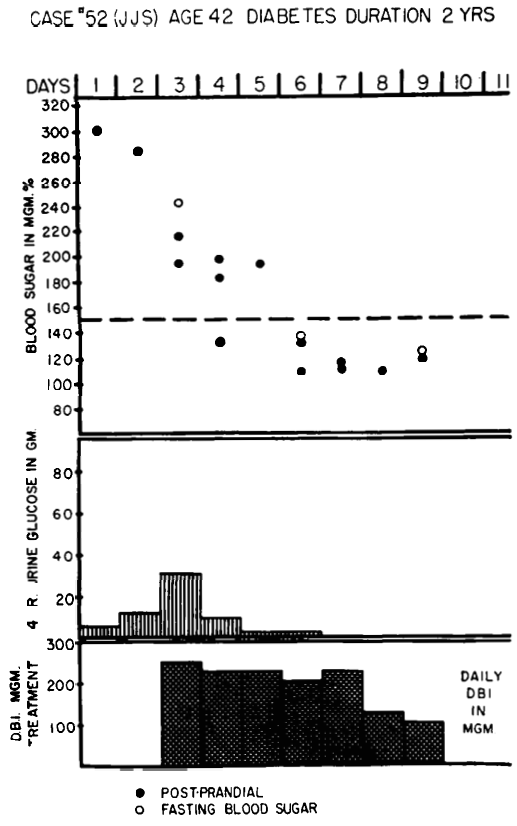

FIG. 1.

from 50 to 250 mg in divided doses. The first effective dose which lowered the blood sugar varied from 50 to 200 mg.

Thirteen of the group showed no side effects of any kind. The other 7 had side effects from slight to severe. These included 5 with nausea, 4 with diarrhea. 2 with vomiting and 2 with dizziness probably secondary to the vomiting. Three of the cases were uncomfortable enough to warrant discontinuing the drug. The symptoms improved within a few hours after the drug was stopped. In 2 of the 4 failures, the drug was ineffective in spite of daily doses of 200 and 225 mg. In the other 2 cases, the doses were insufficient because of side effects which appeared before the effective level had been reached. Except for these side effects, no other untoward findings or toxic manifestations have been found to date. The patient with the longest period of treatment has now received DBI 3 months.

Discussion. If it is true that DBI increases glucose uptake in isolated rat diaphragm and that it is fully active in alloxan-diabetic animals, this drug may have a potential of considerable significance, providing no toxic manifestations develop. At present the incidence of side effects is too high, but improved technics of administration or possible chemical changes might alleviate this difficulty. It is interesting to note that as yet the side effects seem to be limited to the gastrointestinal tract and have been observed even in the presence of high blood sugar levels. This suggests that the annoying symptoms are not related to hypoglycemia. Further study is needed to find range of effectiveness and to ascertain any toxic effects. The doses effective in this study are much smaller than those required to lower blood sugar levels in the reports of other oral hypoglycemic agents.

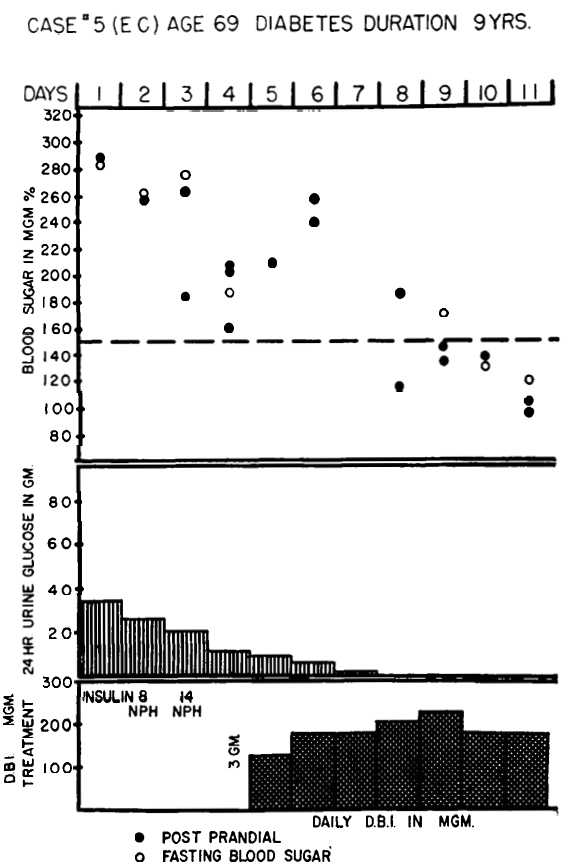

FIG. 2.

Summary. 1. This is an early evaluation of a new, non-sulfonylurea hypoglycemic agent. 2. In this study of 20 cases, DBI, the hydrochloride of N[1]beta-phenethylformamidinylimino urea, appears to have definite blood sugar lowering properties. The mechanism of action is not yet known. 3. There are annoying side effects in some cases which are restricted to the gastrointestinal tract and are not related to the blood sugar levels. 4. No other annoying or toxic effects have been observed at this time. 5. The size of the effective blood sugar lowering dose is smaller than that reported for other oral hypoglycemic agents.

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Received March 26, 1957. P.S.E.B.M., 1957, v95.

Desoxyribonucleic Acid (DNA) Content of Mammary Gland During Pregnancy and Lactation.*† (23216)

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It has been postulated that for any given species the somatic cell nuclei contain a constant amount of desoxyribonucleic acid (DNA)(1). This being true, determination of DNA would provide an accurate estimation of the number of cells formed during the developmental phase of a tissue, gland or organ(2). Upon the basis of this theory, studies have been conducted to determine total DNA of mammary glands of rats(3), rabbits(4) and mice(5) during normal and experimental development of the mammary gland in order to measure extent of mammary gland growth.

It was thought necessary to provide a sound basis for the above studies(3,4,5) by determining the DNA content per cell of mammary gland during growth and lactation.

Methods. Virgin, pregnant and lactating primiparous albino rats were used. Pregnancy ranged from 15-20 days and was determined by examination of fetuses. Animals which were used for determination of DNA of early lactation were all taken on the day of parturition. The days of late lactation ranged from the 18th to the 21st. The animals were killed and the 6 posterior glands were quickly removed and placed in 30 ml of ice cold isotonic sucrose containing 1% citric acid. The kidney, spleen and mammary gland were treated in an identical manner.

Tissue was homogenized for 2 minutes in a Waring Blendor(6) and strained through cheesecloth, 2 and 4 layers in thickness. This filtered homogenate was then used for subsequent fractionations. Filtered homogenate was centrifuged 30 minutes at 2100 rpm, 1100 rpm for 15 minutes, 800 rpm for 10 minutes and 600 rpm for 10 minutes. Final sediment was suspended in 10 ml of homogenizing solution and nuclei were then counted on a hemocytometer. Tissue residue was extracted with ice cold 10% trichloracetic acid and DNA determined by a method recently published(7). DNA per cell was then determined by dividing total quantity of DNA by known number of nuclei in the original suspension.

Results. It was observed that DNA of the nucleus remained within reported literature values in the virgin and the pregnant animal. In the virgin animal DNA content of pooled

* Contribution from Department of Dairy Husbandry, Mo. Agr. Exp. Sta. Journal Series No. 1736. Approved by Director.

† This investigation was supported in part by grant from Am. Cancer Soc.