Phenformin in the Management of Diabetes Mellitus

General Clinical Concepts

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This first of the two clinical panel discussions dealt with general aspects of the management of diabetes mellitus with phenformin (DBI). The seven panelists reported experiences with a total of about 1,000 patients, with half of this number observed for more than six months. The series of Krall and of Pomeranze were as large as 300 and more patients, many of them under treatment for more than two years. The series of Dobson, Lambert and Weller comprised 70 to 100 patients; Baldwin and Miller reported on twenty-seven and thirty-one patients respectively. The patient material included both maturity-onset and growth-onset diabetes, "brittle" diabetes and the various stages of severity of the disease as judged by insulin requirement on the one hand, and the presence or absence of complications on the other. An appraisal of therapeutic results is usually difficult in the absence of uniform criteria for selection of patients or for control, particularly so in diabetes where not only sound definitions as to what constitutes good control are badly lacking, but where also spontaneous fluctuations in the nature of the disease must be considered critically. While most of the panelists had selected for their study patients who had been treated previously with moderate doses of insulin or with other oral agents, some had included in their series patients who responded to dietary restrictions alone. Nevertheless, a rather impressive concurrence of observations became evident from the presentations of the various panelists, regardless of whether the strongest criteria of normoglycemia and aglycosuria were applied, or the lenient ones of maintenance of weight, symptom relief and establishment of well-being, and whether juvenile, brittle or growth-onset diabetes was discussed.

1. DBI is an effective hypoglycemic agent with an activity similar to that of the hypoglycemic arylsulfonylureas. Because of its short action curve it must be administered three times, or even four times daily.

2. Its clinical usefulness is limited by the development of nausea and vomiting and other signs of gastrointestinal incompatibility which occur with increasing frequency in doses higher than 150-200 gm. per day. Its daily dosage should therefore not exceed a maximum of 200 mg.

3. No toxic reactions in the hematopoietic or connective tissue systems, the liver or the kidney, or any other system tested, were observed, nor was there any evidence of severe hypoglycemic reaction.

4. Ketonuria develops not uncommonly in patients treated with DBI; this is interpreted as a sign of starvation ketosis and can easily be overcome by liberalizing the diet. It must be differentiated clearly from the ketonuria attending impending acidosis or aggravation of the diabetes.

5. There are two areas of clinical usefulness of DBI: (a) *As sole medication,* it may be used in those diabetic patients with maturity-onset of the disease who cannot be controlled on diet alone, and who have a moderate insulin requirement, or who respond favorably to other oral hypoglycemic agents. (b) *In conjunction with insulin or other hypoglycemic agents,* it may be used in the juvenile or growth-onset diabetes and in brittle diabetes, where it may eliminate the frequently wide blood sugar fluctuations, stabilize the glycemia

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and permit a decrease in the insulin dose.

Dr. Pomeranze's experience with diabetic patients *older* than forty-five years revealed no instance of drug sensitivity or toxicity. The chief cause of failure, however, appeared to be the development of gastrointestinal symptoms. These appear to be central in origin, do not respond to drug therapy, but are fortunately easily and precisely recognizable, and thus may act as a safety device, preventing overdosage. Pomeranze considers 200 mg./day as the upper limit of dosage.

All panelists agreed that with better knowledge of the limitation of the drug and better selection of the potentially responsive patients, not more than 10 to 15 per cent primary failures will be incurred and that if doses not higher than 200 mg./day are employed, incompatibility will necessitate discontinuation of the drug in not more than 20 to 35 per cent of responsive patients. Previously reported higher rates of failure or incompatibility were mainly due to inexperience in dosage and in selection of patients during the early trial periods.

Divided medication usually three times daily of 25-50 mg. each was recommended generally. This is necessary because of the relatively short action curve of DBI, which is about six hours. In some instances even four daily doses were used with the fourth dose given at bedtime (Krall).

In a study of seventy-one unselected diabetic patients who had been on restricted diets, Lambert found evidence of better control in the adult labile or brittle diabetic and in the juvenile patient receiving combined DBI and insulin therapy. Fifty-four per cent of these patients have been adequately controlled on DBI alone or in combination with insulin. Demonstrable blood sugar reductions occurred in 74 per cent of his patients receiving the compound. But here, too, the gastrointestinal side effects of anorexia, nausea, vomiting, and diarrhea were serious in as many as 40 per cent of patients. They subsided with lowered dosage. A suggestion of antithyroid activity by DBI was noted in two of six patients in whom the uptake of I^{131} was depressed. Dr. Lambert suggested that the drug may inhibit a reaction in iodine metabolism catalyzed by peroxidase.

Combined insulin-DBI therapy was uniformly regarded as a distinct progress in the management of the juvenile and the brittle diabetes and as a unique advantage of DBI (Krall). Combined treatment with other oral agents was found to be advantageous as well. Such combined treatment should, however, be reserved for those situations in which careful trials with one agent alone (insulin or the oral drugs) do not permit satisfactory control. Where one agent alone is effective, combined treatment may not serve any useful purpose, even if it permits a decrease in the dose of one of the drugs.

In discussing his series of ninety-three patients drawn from a charity outpatient clinic with preponderance of poorly controlled cases with many complicating diseases, Dobson found his experience to fall pretty much in line with that generally reported. None of his patients receiving DBI alone experienced any episode of severe hypoglycemia, and side effects severe enough to warrant cessation of therapy occurred in only 12 per cent of patients. He, too, found DBI particularly useful to improve the control of the brittle juvenile and poorly controlled patients, usually in conjunction with insulin.

Although some hypoglycemic effect of DBI is noted in the alloxan diabetic animal and in "surgical diabetes" of man, the clinical use of this compound in diabetes after total pancreatectomy is considered contraindicated as are the arylsulfonylurea compounds. DBI was found to be adequate, however, for the continued control of responsive patients during minor complicating diseases and during surgical complications (Dobson, Pomeranze). It was found effective also in instances of tolbutamide-escape, and observations were reported where tolbutamide sensitivity was restored after a period of treatment with DBI.

No experiences are available as yet concerning the effect of DBI on the degenerative diabetic complications, neuropathy, nephropathy, and angiopathy. While the drug has been used widely in these cases and no unusual progression has occurred, the periods of observation are still too short to expect evidences of regression or of prevention. Thus, Weller, studying patients for about eighteen months, has detected no apparent influence on the vascular complications of diabetes. But he too observed that only long-term studies will serve to evaluate this problem as well as that of any serious prolonged side effects that may as yet be undetected. Of seventy-one patients studied by his group, 65 per cent were described as totally responsive, while 35 per cent were deemed nonresponsive to DBI therapy.

Finally, Miller as well as Baldwin, in reporting their experiences joined the remainder of the panel in concluding that DBI when properly employed is a useful addition to the armamentarium for treatment of diabetes. But they too emphasized that many questions, particularly those related to the mechanism of action of the drug and of long-term toxicity are still unanswered, and that only the future will teach us whether the general clinical concepts presented at this panel will stand the test of time.