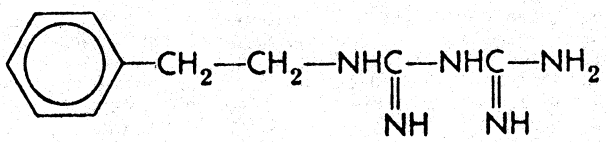
lowing which inability to maintain control developes, are said to experience "secondary failure." The incidence of this type of failure may be very high, regardless of the agent chosen.

In patients with pancreatic islet-cell tumors, the blood glucose concentration drops rapidly after intravenous injection of tolbutamide and remains low for about 3 hours. A similar effect is not observed in other hypoglycemic states, and tolbutamide administration can thus be used as a diagnostic test. Serum immunoreactive insulin determinations should also be performed. Care is necessary, since fatal hypoglycemia has occurred.

In addition, reports have appeared of the successful treatment of reactive hypoglycemias due to a variety of causes with sulfonylureas (Anderson and Herman, 1971).

BIGUANIDES: PHENFORMIN

Chemistry and Preparations. The only commercially available preparation in the biguanide series of hypoglycemic agents is *phenformin.* Its structural formula is as follows:



Phenformin

Phenformin Hydrochloride, U.S.P. (DBI, MELTROL), is marketed as 25-mg tablets and as a 50- and 100-mg time-disintegration capsules.

Mechanism of Action. The biguanides differ significantly from the sulfonylureas in the mechanism of their hypoglycemic effect. Thus, phenformin does not act by stimulating secretion of insulin by the pancreas, hypoglycemia is not readily induced in normal human subjects, the concentration of insulin in the plasma is not increased, and the morphology of the β cell is uninfluenced. Basically, three actions have been described. *In vitro,* phenformin, in relatively large doses, increases glucose utilization by enhancing anaerobic glycolysis (*see* Williams and Porte, 1974). This is thought to occur as a result of, or coincident with, an inhibition of cellular respiration. As a result, adenosine triphosphate (ATP) concentrations fall and those of lactate increase. A second action of the drug is to decrease gluconeogenesis (*see* Gordon and de Hartog, 1973; Haeckel, 1973). The third and most recently recognized is inhibition of intestinal absorption of glucose and probably certain other substances as well; for example, decreased absorption of vitamin B_{12} has been observed (Berger *et al.,* 1972). Phenformin does not act in the normal subject (at least as readily as it does in the diabetic), presumably because the increase in peripheral glucose utilization is compensated for by an increase in hepatic glucose output.

Phenformin has been used experimentally to correct the hypoglycemia that may follow abnormally rapid intestinal absorption of glucose (Permutt *et al.,* 1973).

Absorption and Duration of Action. Phenformin is adequately absorbed from the gastrointestinal tract. The drug has a short half-life (3 hours) and a correspondingly brief duration of action. The hypoglycemic effect may be prolonged to between 6 and 14 hours with the use of timed-disintegration capsules.

Toxicity. Phenformin may cause a metallic taste, nausea, anorexia, vomiting, diarrhea, or cramps in some patients, particularly if the dose is greater than 200 mg per day. Reduction of the dose or withdrawal of the drug results in prompt disappearance of the untoward reactions. Weight loss and weakness may sometimes occur.

The cause of *ketonuria* during phenformin therapy has been the subject of debate. It is most common in patients with unstable juvenile-onset diabetes treated with a combination of insulin and phenformin. While it may at times reflect an insufficient insulin dosage, at other times it is associated with normal plasma glucose concentrations. Therefore, in patients taking both insulin and phenformin in whom ketosis develops, plasma glucose concentration should be measured before the insulin dosage is increased, to avoid hypoglycemic reactions.

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