EDITORIALS

CLINICAL AND PHYSIOLOGICAL IMPLICATIONS OF DIABETES INDUCED BY BENZOTHIADIAZINES

Chlorothiazide, the first of the diuretic and antihypertensive benzothiadiazines, was introduced into medical practice in 1958. In 1959 it was followed by hydrochlorothiazide, and since then other similar derivatives, some more potent, some longer acting, have been introduced into therapy. While these compounds were originally used for the treatment of edema and congestive heart failure, physicians soon recognized their usefulness as antihypertensive agents, and they have, in current practice, become the baseline of antihypertensive therapy. In 1961 some 30,000,000 prescriptions[1] were issued in this country for diuretic substances, and it is probable that the majority of these were for compounds of the benzothiadiazine (BZD) series.

Finnerty[2] was one of the first to notice the hyperglycemic effect of this group of compounds. Similar effects were noted by Goldner et al.,[3] Halprin,[4] Sugar,[5] Hollis,[6] Wilkins,[7] Freis,[8] Mach,[9] Saudan,[10] and Curchod.[11] Hyperglycemia after BZD was thought to occur in either mildly diabetic patients, or in those suffering from subclinical diabetes. Shapiro and his colleagues[12] showed in short-term experiments that BZD could have a hyperglycemic effect in hypertensive patients, and that this was accentuated by obesity, a family history of diabetes, and previous notation of an abnormal blood glucose.

In the clinical studies reported above, the deterioration in the metabolic status was relieved when the diuretic compounds were discontinued, though few adequate follow-up studies were included. In view of the known association of hypertension and diabetes (Karmer[13]), it was considered that BZD-induced diabetes occurred mainly in predisposed individuals. The hyperglycemic activity of BZD in experimental animals had not been reported until recently.

During the course of a controlled double blind study concerned with the evaluation of antihypertensive treatment, Wolff et al.[14] noted over a period up to four years an increasing incidence of hyperglycemia and clinical diabetes occurring in patients receiving BZD therapy, as compared with controls receiving placebos only. Clinical diabetes in these patients was of different degrees of severity and responded to oral hypoglycemic treatment. Eighteen months have now elapsed since five of the patients had developed diabetes on BZD, and antidiabetic treatment is still required to avoid symptoms of diabetes. No adequate baseline studies concerning carbohydrate metabolism were obtained in these studies, as the initial purpose was directed towards an over-all evaluation of the place of antihypertensive therapy in the treatment of essential hypertension, and the occurrence of abnormalities of carbohydrate metabolism was unexpected. Several of the patients developing clinical diabetes with BZD were thin and had no family history of the disease, but the limitations of relying upon the adequacy of a family history are apparent.

Early in 1962 the antihypertensive and sodium retaining benzothiadiazine, diazoxide, became available for clinical trial. Studies in hypertensive patients by Wilson et al.,[15-17] Okun et al.,[18,19] and Dollery et al.[20] soon revealed the diabetogenic activity of this agent, particularly when combined with a saluretic BZD. The first published evaluation of diazoxide in animals had apparently not revealed hyperglycemic activity; Rubin et al.[21] and Langdon et al.[22] first reported systematic observations of diabetogenic activity in dogs of combined diazoxide and trichlormethiazide. Gulbenkian et al.[23] and Tabachnick et al.[24] have since reported their studies concerned with the hyperglycemic activity of diazoxide in dogs, rats, rabbits and mice; and they refer to the work of Eggert et al. (not yet published) concerning the hyperglycemic activity of combined diazoxide and trichlormethiazide. Tabachnick et al.[24] also reported that a further blood glucose increase was observed when diazoxide (10 to 40 mg. per kilogram) was administered to depancreatized dogs.

Studies by Wolff et al.[25] have since revealed that the combined administration of the two benzothiadiazines produces a form of experimental diabetes of unusual interest. Marked hyperglycemic activity in dogs after a combination of diazoxide and trichlormethiazide was unassociated with changes in the beta cells, and the experimental animals remained sensitive to exogenous insulin. Though diazoxide by itself was hyperglycemic in the experimental dog and rat, its action was markedly increased by combination with any other saluretic BZD. Pancreatectomized dogs receiving combined diazoxide and BZD also remained sensitive to exogenous

insulin. Insulin binding in vitro was unaffected by these compounds.

Wolff et al.[26] have since extended these studies by surveying many commonly used forms of benzothiadiazine by themselves and in combination with diazoxide. In the Sprague-Dawley rat, a cyclic form of hyperglycemic activity has been demonstrated with many of these agents, which is potentiated when the drugs are combined with diazoxide.

Formanek[27] has reported deterioration of the glucose tolerance test in the albino rat following hydrochlorothiazide administration.

Of considerable interest is the finding that tolbutamide will acutely relieve the hyperglycemic activity of benzothiadiazines (Wolff et al.[26]). In this sense these compounds appear to resemble the experimental diabetogenic agent mannoheptulose. Coore et al.,[28] in studies of the secretion or release of insulin by the pancreas, find evidence of stimulation by glucose and by tolbutamide, but that the two act differently. Thus the effect of glucose, but not of tolbutamide, is blocked by mannoheptulose extracted from the avocado pear. This resembles the finding in some diabetics in whom tolbutamide can stimulate insulin secretion, but the islets of Langerhans no longer respond to a high blood glucose level. It is possible that BZD hyperglycemia may be more representative of many cases of maturity onset of human diabetes than any other known forms of experimental diabetes.

Recent studies by Wolff et al.[29] have demonstrated the ability of potassium to decrease the acute hyperglycemic activity of BZD. Further work is required to confirm these findings and to explain their nature. Reutter et al.[30] noted a diminished glucose tolerance in patients receiving BZD and correlated this with potassium loss. It is of particular interest that potassium in Wolff's experiments not only relieved the hyperglycemic activity of the natriuretic and kaliuretic BZD but also of diazoxide, which does not give rise to undue potassium loss, since it causes retention of electrolytes.

Clinical and experimental findings have shown that diazoxide greatly shortens the period required for clinical diabetes to appear, compared with the electrolyte excreting BZD. Diazoxide was withdrawn from clinical studies in 1962. The confirmation of BZD diabetogenic activity imposes upon the physician and surgeon employing these agents a caution to utilize them only when really indicated and no alternative treatment is available. As they are at present generally accepted as useful agents for the treatment of edema and hypertension, they will continue to be utilized, though the physician should be aware of their hyperglycemic propensities.

The demonstration of the ability of benzothiadiazines to induce the hyperglycemic state in the laboratory animal gives hope that studies of these compounds may lead to an increased understanding of the diabetic state and perhaps of the complications following in its wake.

ADDENDUM

While this paper was in press, Rapoport and Hurd (Rapoport, M. I., and Hurd, F. H.: Thiazide-induced glucose intolerance treated with potassium. Arch. Int. Med. *113*:3, 405-08, 1964) noted that potassium supplementation appeared to improve the carbohydrate tolerance that had deteriorated after BZD.

The results of a three-week experiment led the authors to recommend the routine administration of potassium with thiazides.

The data provided do not include the results of potassium administration to patients whose carbohydrate tolerance did *not* deteriorate with BZD; there was no control group of patients having BZD *only* for two weeks.

Administration of large amounts of potassium can lead to intoxication in the presence of renal disease, and this reviewer concludes that the problem of routine potassium supplementation to prevent glucose intolerance is still open to further investigation.

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AN HYPOTHESIS RELATING PHOSPHOLIPID SYNTHESIS IN THE ARTERIAL WALL, DIABETES AND ATHEROSCLEROSIS

It has been a frequent observation that the incidence of atherosclerosis is unusually high among diabetics. Despite this well-known clinical fact, the cause for this relationship is not understood. It has been known for a number of years that the ability to synthesize lipid from carbohydrate is less in the diabetic state. The recent popular belief that the fate of the vasculature is determined by the blood lipids which bathe the vessel wall has made the studies on diabetic liver and adipose tissue of particular interest because of the apparent role they play in regulating certain plasma lipids. Thus, liver slices prepared from alloxan-diabetic rats are almost incapable of forming fatty acids from glucose-C-14,[1] and both glucose oxidation and lipogenesis from glucose are reduced by 80 to 90 per cent in adipose tissue obtained from alloxan-diabetic rats.[2] However, neither studies such as these nor those on blood lipids have provided an adequate explanation for the correlation between atherosclerosis and the diabetic state.

It therefore seems reasonable to look elsewhere for possible clues. One obvious place is the arterial wall itself. It is conceivable that the changes occurring in diabetes can in some manner alter the metabolism of the arterial wall and, in this way, predispose it to the ravages of atherosclerosis. Studies on the metabolism of the arterial wall in normal and diabetic subjects in particular have been limited and, thus, relatively little is known regarding the carbohydrate and lipid metabolism of this tissue. However, the authors would like to present a hypothesis, based on the existing, albeit limited, information, which might relate diabetes and atherosclerosis to alterations in the metabolism of the arterial wall.

Evidence that the arterial wall can synthesize phospholipids is presented in the current issue of this journal[8] (see pages 182 to 188). This investigation corroborates the work of Zilversmit et al.[3,5] and Stein et al.[6,7] who have shown that normal aorta can synthesize phospholipids from various radioactive precursors of the phospholipid molecule such as phosphorus-32, acetate-C-14, and carbon-14 free fatty acids. Additional studies carried out by the authors of this editorial have provided evidence that uniformly labeled glucose-C-14 can also serve as a precursor for arterial wall phospholipids presumably by providing α-glycerophosphate.[9]

The significance of the phospholipid synthetic mech-