

When Friends or Patients Ask About . . .

William H. Crosby, MD, Coordinator

**The FDA
and Hypoglycemic Drugs**

John K. Davidson, MD, PhD

THE NELSON Committee hearings in the US Senate (Sept 18 to 20, 1974) explored the *safety, effectiveness, and use* of hypoglycemic drugs. A dozen witnesses, including the Food and Drug Administration (FDA) Commissioner **Dr. Alexander Schmidt**, gave testimony concerning the implications of the University Group Diabetes Program (UGDP) articles for medical practice. Concern was expressed because the FDA Bureau of Drugs had not required appropriately written package inserts warning physicians and the drug-consuming public of the dangers inherent in the indiscriminate use of sulfonylureas and phenformin hydrochloride. There was agreement that caloric restriction with weight reduction is the preferred method of treatment for the maturity-onset diabetic who is above ideal body weight, and that such therapy is always safe and with intensive education and follow-up is usually effective.

The UGDP investigators ended the *tolbutamide* (sulfonylurea) study in 1969 and the *phenformin* study in 1971, when careful statistical analysis

showed a death rate more than twice that expected for each drug when compared to the death rates in the three other groups in the study (*placebo*, a *standard dose of insulin* that resulted in a moderately elevated mean fasting blood glucose level, and a *variable dose of insulin* that resulted in a near-normal mean fasting blood glucose level). Death rates in the placebo and insulin groups were similar. There were no significant differences in the rate of development or progression of chronic complications (retinopathy, nephropathy, neuropathy, arteriopathy) in the survivors of any of the five treatment groups.

**Are Oral Hypoglycemic Drugs
Safe and Effective?**

In addition to the increased cardiovascular mortality with tolbutamide therapy or with phenformin therapy of approximately 1% per year, there are many other adverse effects of oral hypoglycemic drugs. These include prolonged sulfonylurea-induced hypoglycemia and phenformin-induced lactic acidosis, both of which have terminated fatally in a number of patients.

Extrapancratic effects of the sulfonylureas include hypothyroidism, skin rashes and photosensitivity, corneal opacities, blood dyscrasias, increased fibrinolytic activity, hypo-

natremia, water retention, jaundice, liver-enzyme inhibition, heart effects (including inotropism, increased oxygen need, and microgranulomas), elevated blood pressure, altered electroencephalogram in epilepsy, and increased stomach-acid secretion.

The sulfonylurea drugs compete for carrier-protein binding sites with many other drugs, including sulfonamides, salicylates, phenylbutazone, monoamine oxidase inhibitors, thiazides, and barbiturates. The pharmacological effect of all of these drugs, including the sulfonylureas, may be increased when they are displaced from their combining sites; thus, combination drug therapy may have many unanticipated toxic consequences. The difficulties in maintaining stable anticoagulation therapy in the pres-

The Author: John K. Davidson received his BS degree in 1943 and MD degree in 1945 at Emory University, Atlanta. He was a research fellow of the American Diabetes Association from 1961 to 1965 at the University of Toronto, where he won the Starr medal in 1963 for his work on nonsuppressible insulin-like activity and studies of beta cell function. He received the PhD degree in Physiology in 1965 at the University of Toronto, and joined the faculty with appointments in physiology and medicine. He returned to Emory University in 1968, where he is now director of the Diabetes Unit at Grady Memorial Hospital and professor of medicine. He has been on the Board of Directors of the American Diabetes Association since 1970, and directed its sixth Allied Health Postgraduate Course in Atlanta in 1974. His research interests are in insulin immunity, immunologic insulin resistance and its treatment with sulfated insulin, and investigations of various techniques of implementing effective diet therapy and weight reduction in obese maturity-onset diabetics.

If you wish to suggest a topic or write an answer for this feature, write to William H. Crosby, MD, Scripps Clinic and Research Foundation, La Jolla, CA 92037.

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