label of the drugs would be set in boldface type and would say: "Oral hypoglycemic drugs may be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin."

Cardiovascular mortality means death from disorders of the heart and circulatory system.

ADVANTAGE AND RISK

The warning would indicate that the drugs should be used only for adult patients not totally dependent on insulin, whose blood sugar cannot be controlled by diet alone and who can not or will not take insulin.

The warning would also say that the doctor should inform the patient of the advantages and potential risks of the drugs, and that the patient should participate in the decision whether to use them.

The F.D.A.'s warning would apply to a number of oral drug products in addition to the two manufactured by Upjohn. These include: Diabinese, Pfizer, Inc.; Dynelor, Eli Lilly & Co.; two forms of a drug called DBI, Geigy Pharmaceuticals; two forms of the drug Meltrol, USV Pharmaceutical Laboratories, Inc., and the drug Tolbutamide from Premo Pharmaceutics Laboratorities, Inc.

[Excerpt from The Pharmocological Basis of Therapeutics, Fifth Edition, Goodman and Gilman]

ORAL HYPOGLYCEMIC AGENTS

History. An important event in the history of the treatment of diabetes mellitus was the introduction of orally effective hypoglycemic agents. Janbon and coworkers (1942), in the course of clinical studies on the treatment of typhoid fever, discovered that a sulfonamide(*p*-amino-benzene-sulfonamido-isopropylthiadiazole) induced hypoglycemia. Janbon's colleague Loubatières (1957), made the fundamental discovery that the compound exerted no hypoglycemic effect in the completely pancreatectomized animal and suggested that the action was the result of stimulation of the pancreas to secrete insulin. There was no practical application of these findings until Franke and Fuchs capitalized on the discovery that the antibacterial agent *carbutamide* lowered the blood sugar in patients treated for infectious diseases. These workers demonstrated the apparent usefulness of carbutamide in the treatment of diabetes mellitus. Soon thereafter, the compound *tolbutamide* was introduced. This substance is not antibacterial, is less toxic than carbutamide, and soon became popular for the management of certain diabetic patients. Tolbutamide is a member of the class of oral hypoglycemic agents designated as *sulfonylureas.*

Another group of compounds, the *biguanides,* was developed independently of the sulfonylureas. Historically, the development began with the discovery in 1918 by Watanabe that guanidine is hypoglycemic in rats. Guanidine and its substituted derivatives were found to be too toxic to be therapeutically useful. *Diguanides,* two guanidine molecules joined by a chain of methylene groups, were more effective and less toxic than the substituted guanidines. SYNTHALIN A, a potent diguanide, was given clinical trial in diabetes, but it also was found to be too toxic for therapeutic use. Finally, *phenformin* (Ungar *et al.,* 1957), a member of the biguanide series (derived from two molecules of guanidine with elimination of ammonia), was found to have an apparently acceptable toxicity, and this compound has since had widespread use.

SULFONYLUREAS

Chemistry. A number of sulfonylurea compounds exert hypoglycemic activity. The commercially available preparations are *tolbutamide, acetohexamide, tolazamide,* and *chlorpropamide,* which have the following structural formulas: