Special Report

LETTER TO THE EDITOR

August 14, 1972

Harvey C. Knowles, Jr., M.D.
Editor, DIABETES
American Diabetes Association
18 East 48th Street
New York, New York 10017

Dear Doctor Knowles:

I have received the statement concerning the labeling of oral hypoglycemic drugs published in the July issue of DIABETES and transmitted to me with the approval of the Board of Directors of the American Diabetes Association. I have reviewed the matters involved and I believe that the issues should be clarified for the readers of DIABETES.

The Food and Drug Administration's Drug Bulletin of May 1972 stated that "This labeling and therapeutic regimen for diabetes are consistent with the therapeutic recommendations of the American Diabetes Association and the Council on Drugs of the American Medical Association." Does the ADA now question its own recommendations which have been on record since 1970?

The "Editorial Statement" published in DIABETES *19* (Suppl. 2): Oct. 7, 1970, presents, under the heading "Therapeutic Recommendations," the following:

> "Tolbutamide, as well as other oral hypoglycemic agents, has no place in the routine treatment of chemical or latent diabetes, suspected diabetes, or prediabetes. Such therapy has never had a place in diabetic ketoacidosis or in those prone to it. The clearest indication for oral agents is diabetes of mild or moderate severity in a patient who proves to be poorly controlled with diet and who is unable or unwilling to take insulin.
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> "In adult-onset diabetes with hyperglycemia and glycosuria, symptomatic or not, and in the absence of ketosis, a trial with an appropriate diet should come first. If this does not establish satisfactory control, insulin is to be preferred to other therapeutic agents because it is more uniformly effective in controlling hyperglycemia and the UGDP study indicates that it may be safer."

Note that the quotation begins, "Tolbutamide, as well as other *oral hypoglycemic agents . . .*" Also note in the preceding paragraph:

> "The mortality study is at least suggestive enough to put a damper on what appears to be the indiscriminate use of all oral hypoglycemic agents in the treatment of mild or moderate, adult-onset diabetes. Although tolbutamide, for practical reasons, has been the only sulfonylurea drug investigated by UGDP, the chance that other compounds of this family may be similarly involved cannot be dismissed despite differences in molecular structure."

These statements with Dr. Henry T. Ricketts designated as author appear above the names of the Ad Hoc Editorial and Advisory Committee (Drs. Arthur R. Colwell, Sr., Norbert Freinkel, David M. Kipnis, Rachmiel Levine, Francis D. W. Lukens, and Randall G. Sprague) and the Professional Members of the Executive Committee of the American Diabetes Association (Drs. James B. Hurd, President; Stefan S. Fajans, President-Elect; Max Ellenberg, Vice President, Professional Section; Addison B. Scoville, Jr., Vice President, Central Council; William H. Grishaw, Secretary; Robert C. Hardin, Immediate Past President) indicating their concurrence in the "Therapeutic Recommendations" including extension of application of precautions to other hypoglycemic agents.

A letter dated January 23, 1971, addressed to me by James B. Hurd, M.D., President of the American Diabetes Association, stated that the Board of Directors considered oral hypoglycemic agents at its meeting on January 22 and that the Board approved the following amended FDA recommendation:

> "Pending the results of such studies (of all these drugs), the Food and Drug Administration recommends that the use of Orinase (tolbutamide) and other sulfonylurea type agents, Dymelor (acetohexamide), Diabinese (chlorpropamide), Tolinase (tolazamide), should be limited to those patients with adult-onset nonketotic diabetes mellitus which cannot be adequately controlled by diet or weight loss alone. In such cases, diet and insulin usually are preferable. However, in a given patient the decision to use a sulfonylurea drug or insulin should be a matter of the physician's judgment, guided by knowledge of the UGDP results cited above. Apart from their use on an investigational basis, oral hypoglycemic agents are not recommended in the treatment of prediabetes, suspected diabetes, or chemical diabetes. In this context chemical diabetes

is defined as asymptomatic diabetes in which all blood glucose values are normal except during a food or sugar tolerance test. Oral hypoglycemic agents are contraindicated in patients with ketoacidosis."

The FDA statement in the May 1972 Drug Bulletin is correct as it stands since the agency had never been advised of any retractions as of this date.

The Council on Drugs of the American Medical Association issued the following warning, also published in DIABETES *19* (Suppl. 2): Oct. 7, 1970:

"It should be pointed out that it is not possible to state that all sulfonylureas behave similarly to tolbutamide with respect to total mortality. However, since all sulfonylureas are structurally quite similar, these drugs should be considered similar to tolbutamide until proven otherwise. . . . Although structurally different, the biguanides such as phenformin may behave similarly to tolbutamide. . . . Although some flaws exist in the UGDP study, it clearly demonstrates that every effort should be made by the physician to control the symptomatic, maturity-onset diabetic with diet alone. Should this fail, treatment with insulin or oral hypoglycemic agents should be undertaken. If oral hypoglycemic agents are selected for therapy the results of the UGDP study should be kept in mind. Therefore, the consideration of treatment with oral hypoglycemic agents should be secondary to the use of insulin."

The statement that the UGDP conclusions apply equally to all sulfonylureas and all biguanides is another matter. This is a paraphrase of the actual statement in the FDA guidelines for the final labeling of oral hypoglycemic drugs which reads in part:

"Although similar data are not available for every oral hypoglycemic drug, it is reasonable to expect that the results of this study may apply also to all hypoglycemic agents in these classes."

The paraphrase may be unclear. It may be true that "As yet there are no scientific data which indict or exonerate other oral agents as having the same morbid sequelae as reported by the UGDP study for tolbutamide or phenformin." Yet a prudent physician and a prudent regulatory agency will take into account a possible hazard.

Finally it is agreed by all concerned that the judgment of the physician must determine appropriate treatment in each case with due consideration of the patient's requirements and the possible hazards of therapy.

Sincerely,

Charles C. Edwards, M.D.
Commissioner of Food and Drugs
Department of Health, Education, and Welfare
Public Health Service
Food and Drug Administration
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ABSTRACTS

Alberti, K. G. M. M.; and Hockaday, T. D. R. (Radcliffe Infirmary, Oxford, England): RAPID BLOOD KETONE BODY ESTIMATION IN THE DIAGNOSIS OF DIABETIC KETOACIDOSIS. Br. Med. J. 2:565-68, June 3, 1972.

Measurements of blood and plasma ketone bodies in fifty cases of diabetic coma were made with both Ketostix and specific enzymatic methods. Ketostix readings correlated only moderately well with enzymatically determined acetoacetate and very poorly with total blood ketones. Ketostix reacted weakly with acetone and not at all with 3-hydroxybutyrate. Several patients had high 3-hydroxybutyrate/acetoacetate ratios, especially the severely ill. Although the mean ratio was 5.2, values ranged from 1.9 to 31.7. Seven of twenty-two blood samples negative by Ketostix had appreciable ketones by the more specific enzymatic assay. The authors offer several suggestions for minimizing Ketostix error and also describe a rapid (forty minutes) enzymatic assay on whole plasma. P.H.S.

Bitensky, Mark W.; Gorman, Ronnie E.; and Neufeld, Arthur H. (Dept. of Path., Yale Univ. Sch. of Med., New Haven, Conn.): SELECTIVE EFFECTS OF INSULIN ON HEPATIC EPINEPHRINE-RESPONSIVE ADENYL CYCLASE ACTIVITY. Endocrinology 90:1331-35, May 1972.

Prednisolone has been shown to selectively reduce hepatic