Because of the increased cardiovascular hazard which appears to be associated with oral hypoglycemic agents, the drugs should be used only after full consideration of the special warning.

Special warning: Diet and reduction of excess weight are the foundations of initial therapy of diabetes mellitus. When the disease is adequately controlled by these measures, no hypoglycemic drug therapy is indicated.

Because of the apparent increased cardiovascular hazard associated with oral hypoglycemic agents, they are indicated in adult-onset, non-ketotic diabetes mellitus only when the condition cannot be adequately controlled by diet and reduction of excess weight alone, and when, in the judgment of the physician, insulin cannot be employed because of patient unwillingness, poor adherence to injection regimen, physical disabilities such as poor vision and unsteady hands, insulin allergy, employment requirements, and other similar factors.

Since the association of tolbutamide and phenformin with increased cardiovascular hazard is shown by strong evidence although not yet conclusive proof, it must be reflected in labeling by a warning which clearly states that insulin should be used in preference to oral agents where that is feasible, because of benefit-risk considerations.

This new evidence of an increased risk is placed in a Special Warning section, explicitly cross-referenced by a statement in the Indications section because special labeling is required to correct the current erroneous impressions of many physicians accustomed to using these drugs according to their former labeling.

A copy of the new labeling for the oral agents is attached as Appendix B.

III. CONCLUSIONS

Your petition has been extremely helpful in prompting us to evaluate and articulate our position on the labeling of drugs.

Because of the importance of the issues that you raised and that are discussed in this response, we are taking the liberty of sending a copy of this response and the attachments to all of the individuals who signed the petition or wrote to me indicating their support for it.

Finally, I again wish to thank you and all the others who participated in the petition. We welcome critical review of all of our actions. It is not just the right, but indeed the responsibility of physicians and all other citizens to petition us whenever they believe that inadequate or incorrect action has been taken, or that action which should be taken has not been undertaken. In this way, we can be helped to do a better job.

Sincerely yours,

CHARLES C. EDWARDS, M.D.,
Commissioner of Food and Drugs.

(NOTE.—Attachments supplied by the FDA were too voluminous to be incorporated in this volume, and were retained in Committee files.)