the final report on this study, which has not yet been published in the literature. FDA, at Dr. Wissler's request, is supporting further study of the pathologic findings by several independent pathologists.

Dr. D. F. Wu, et al., reported on the effects of tolbutamide on heart function in dogs, with chemically induced diabetes, at the meeting of the American Federation for Clinical Research this past May. The investigators reported that after 1 year of treatment with tolbutamide the left ventricular function was reduced and cardiac morphology altered compared to control groups.

The animal studies do not necessarily bear directly on the excess cardiovascular mortality seen in tolbutamide-treated humans in the UGDP study, but they do suggest overall mechanisms by which this might have occurred.

Now, as you know, Mr. Chairman, it has been the view of the FDA since 1970, that the findings of the UGDP study should be reflected in a warning in the labeling for oral hypoglycemic drugs and in turn, in the use by physicians of these drugs. Let me emphasize that this view does not require that we conclude the study provides absolute proof of hazard. The UGDP study is an adequate and well-controlled study—by far the most extensive and best examination of the long-term effects of oral hypoglycemic agents yet ever undertaken.

The finding of an increased cardiovascular mortality in tolbutamide and in phenformin-treated patients cannot be attributed to any shortcomings of study design or execution. This finding, despite any residual uncertainty that may remain, requires a clear warning to physicians. Prudence dictates that a warning be issued whenever there is sufficient evidence to believe that a drug may be hazardous or carry a risk, and that such a warning is necessary for the safe and effective use of the drug by physicians and patients. Enough time has now passed for interested persons to have studied the Biometric Society report and the recent detailed UGDP report on phenformin. The Agency has, therefore, published for comment a regulation proposing new labeling for the oral hypoglycemic labeling. Interested persons may comment on the proposal by September 5, 1975, and a public hearing will be held on August 20, 1975. Final labeling regulations will not be published until after all comments and materials have been considered.

Our proposed labeling has two sections of particular importance; a boxed warning stating that there may be an increased risk of cardiovascular death associated with the use of oral hypoglycemic drugs and a new indications section that limits use of these drugs to patients whose symptoms or blood glucose abnormalities cannot be controlled by diet alone and who cannot take insulin for one of a number of specified reasons.

Now, I would like to discuss both of these sections in greater detail. And they are both reproduced in full in an attachment to the statement. The warning describes the UGDP study and its findings. It has been contended that certain studies said not to support the findings of the UGDP study should be mentioned in the warning section to provide the "fair balance." We have concluded, however, and made clear in revised regualtions that if scientific data exist to support a warning, the warning must be presented in unambiguous