group of older women, age greater than 53, the tolbutamide cardiovascular death rate is almost five times that of the placebo group. It is in this group of older women where the tolbutamide excess cardiovascular mortality is most dramatically shown.

Finally, I wish to comment on the problem of planning and analyzing clinical investigations in which patients are expected to be on chronic medications for a period of many years. It is important in planning these long-term studies to allow the clinician to change the medication if it is in the best interests of the patient. This can result in an altered dose or even a change in the medication. The UGDP protocol did allow the clinician this freedom. A protocol which does not allow this flexibility may not be in the best interests of the patients under study.

The CHAIRMAN. In evaluating this study, did you or did you not conclude that the authority of the clinician to alter protocol, which I assume some did, had any adverse effect, or did it prejudice the study in any way?

Dr. ZELEN. No!

In addition to modified or changed medications, patients may, on occasion, not take their medication at all. In the Biometrics Report, these problems were examined in considerable detail. It is our conclusion that the greatest statistically significant difference between tolbutamide and placebo occurs in the group who have taken their prescribed medication in exactly the manner specified in the protocol for the entire period of followup.

To conclude, I wish to state that the interpretation of the data is difficult due to the small number of deaths relative to the total number of patients. In our endeavors we have analyzed the data in many other ways which have not been put in our final report. Our conclusion is that the weight of evidence points to tolbutamide as being responsible for the excess cardiovascular mortality.

If I may, Senator Nelson, I would like to comment on some general aspects of clinical trials that have surfaced during our discussion.

Obtaining scientific evidence using the clinical trial method is the most difficult way of obtaining scientific evidence and should be used only as a last resort. I speak from long experience. My research group, the statistical laboratory at the State University of New York at Buffalo, is involved in over 60 clinical trials at the present time in all areas of cancer treatment. It is very difficult, time consuming, there is a great deal of aggravation arising from the vagaries of the funding agencies.

I think to mount long-term studies, either of oral hypoglycemic agents or anything else, should only be taken after much careful thought and after all other ways of attempting to obtain such evidence have been thoroughly examined. Mounting these trials should not be done very casually.

The CHAIRMAN. Thank you very much.

Our next witness is Dr. Palumbo, the assistant professor of medicine, Mayo Medical School, Rochester, Minn.

You may present your statement however you desire and extemporize on it if you desire.