The CHAIRMAN. May I ask a question? You state that although the UGDP study has its defects; it is an excellent study proving the case against tolbutamide. Is there a comparable study that proves the case for tolbutamide, really?

Dr. MEIER. No, there is not.

The CHAIRMAN. What did you mean by that, then? Is there no case? You were so equivocable in what you were saying awhile back and now I do not quite follow you. You endorse the UGDP study, but then you say the case against the drug has not been proved. Do you mean absolutely proved 1,000 percent, or is it 999, or what? I cannot follow your testimony at all.

Dr. MEIER. I understand your question, Senator.

A major point that I hope to leave with you is that in this area of clinical research we will often feel obliged to stop a study before we achieve a high degree of certainty. We wish it were otherwise. It would be very nice if we could say for certain. "These are the facts. Now everyone must fall into line and follow the facts." Under the circumstances we find that we must make decisions in the face of substantial uncertainty. Whereas I believe that the UGDP is the best evidence that we have, I believe that the study was indeed ended before we could be certain. Take note that I am not trying to make an especially cautious statement about a virtually proven fact. The evidence of toxicity is substantial, but in itself by no means conclusive.

The CHAIRMAN. Before you could be certain what?

Dr. MEIER. That the drug is toxic. Before we could be dead certain of that they pulled it off the study.

The CHAIRMAN. Before you could be certain that the drug was toxic.

Dr. MEIER. Yes, before we could be certain that it causes heart attacks. The evidence pointed that way but before it was certain, in my opinion, they quite properly withdrew tolbutamide on ethical grounds.

Senator, I wish I could say that a good study necessarily gives a solid answer to a reasonable question. A good study, ethically done, may leave us with considerable residual uncertainty. I am sorry if that is confusing but I feel that that is the circumstance.

The CHAIRMAN. It is confusing. I suppose you are familiar with the Kefauver amendments of 1962. In 1938, the Congress, because of the sulfanilamide disaster, passed legislation that there should be adequately controlled studies to prove the safety of a drug before it is marketed. Then in the midst of the dispute over the Kefauver proposals the thalidomide case arose and the Congress passed legislation that there has to be adequately controlled studies to prove the efficacy of the drug.

I think most scientists agree that this is sound. You should not put drugs on the market that are not safe, safe by a scientific measurement in a cost-benefit ratio. Any active compound, as everybody knows, has side effects and may be serious.

So we are dealing with a situation here where the question is do you put into the marketplace for broad usage or even a narrow usage a drug for which the efficacy has not been proved by carefully controlled scientific studies? There are no adequately controlled