studies that prove it. Yet there is a comprehensive 10-year study that raises a very serious cloud over both the safety and efficacy of this class of drugs. That is what we are dealing with, is it not?

Dr. MEIER. Indeed, it does raise a very serious cloud but you seem to be urging me to conclude that it is proved, and there is quite a difference between a very serious cloud and proof.

The CHAIRMAN. I am not trying to do that at all. What I am trying to urge you to appreciate at least is what the law is, and that is that you do not introduce active compounds for use in medical practice and use them broadly unless there is proof they do some good, and particularly when there seems to be some serious indications that they do harm. That is the issue here, is it not?

We used to put drugs into the marketplace prior to 1938, and there was no proof of safety and no proof of efficacy. And in the whole history of the development of drugs down through the history of mankind there is hardly half a dozen of them that survived as being safe or efficacious. Most of the drugs people have taken for hundreds of years had no efficacy at all. They might have been safe because they did nothing.

But we are dealing with a question here of a study that indicates there are serious side effects and a study that indicates that there does not appear to be any possible usefulness except in limited cases. That is the issue we are dealing with.

Dr. MEIER. I agree, and I think the difference we are arguing about is the difference in how solid the evidence is. I would further agree that we need to define policy in the face of uncertainty, that we cannot wait for final proof.

The CHAIRMAN. Let me ask you this question. If you had the UGDP study before the drug was marketed, do you think it would be marketed under the law?

Dr. MEIER. I doubt it.

Shall I continue?

The CHAIRMAN. Yes. Go ahead.

Dr. MEIER. It is true that the UGDP had defects. It is true, also, that it falls short of proving the case against tolbutamide. Nonetheless, as Professor Cornfield remarked in testimony here last September, the UGDP today provides the best available information on the possible toxicity of tolbutamide.

As to defects, there are no studies which are entirely free of them, and it was the judgment of our committee that this study was well conceived and executed, and that those defects we could identify did not give reason to doubt the findings.

As to it being inconclusive, that was inevitable in the nature of the case. Once the investigators became convinced that there was substantial evidence of toxicity, and not of corresponding benefit, they had no choice but to withdraw the drug.

Thus we are left with an ominous yet inconclusive result, and I believe that this is a typical outcome which we may expect to see repeated in many other instances. It may be, in such a case, that the community of physicians will decide that, although not conclusive, that the evidence is sufficient to abandon the drug. Or, on the contrary, as in the UGDP case, they may conclude that the evidence does not require them to give it up.