today and will be glad to have you present your statement however you desire.

STATEMENT OF THADDEUS E. PROUT, M.D., ASSOCIATE PROFESSOR OF MEDICINE, THE JOHNS HOPKINS UNIVERSITY, AND CHIEF OF MEDICINE, GREATER BALTIMORE MEDICAL CENTER

Dr. PROUT. Thank you, Mr. Chairman, and members of the committee. I think it would be helpful if I only hit the high spots because of the lateness of the hour.[1] In lieu of a curriculum vitae perhaps I might mention that as a member of the board of directors of the American Diabetes Association I have been involved in discussion of the use of the oral agents and I also have a basic interest in the clinical trials.

As part of my interest in this entire subject I have been asked today to discuss certain broad aspects of the hypoglycemic agents. I would like to relate their use to some of the promotional efforts of the pharmaceutical companies on one side and the constraining influence of recent scientific evidence demonstrating negative aspects of therapy on the other.

Since I felt certain that my colleagues, Drs. Miller and Klimt, would have an opportunity to discuss the state of the art that led to the initiation of the University Group Diabetes Program as well as the actual findings, I should like to spend my time in examining our present state of knowledge as it relates to a need for different and more powerful hypoglycemic agents in the forseeable future.

I wish first to compliment the committee on its interest in this field and point out that its efforts in the area of control of the amphetamines have met with success. It would seem to me that positive benefits will result from the review of these problems by your committee today.

It would appear that the most sensitive and difficult problem now facing the Food and Drug Administration relates to the licensing of products and its inability to define the long-term effects of drugs that have been licensed on the basis of short-term experiments. Much of the information we just discussed relates to this; since this situation is unlikely to be satisfactorily changed within the near future, an investigation should be made as to whether the FDA should be required to define both the *maximum drug dosage* as well as the *duration of the drugs* that are licensed for use.

A section of the package insert on each of the new drugs should reflect the fact that long-term safety has not been tested and state quite specifically the limitations of the dose range and the duration of therapy for which the drug has actually been tested.

In brief, the package insert should more closely identify itself with its role as a protector of the consumer rather than to serve the interests of the industry.

Senator NELSON. What good does that do? The doctor will not see the package insert and neither will the patient.

Dr. PROUT. I will take that up in the second point and that is that since they have not been licensed for anything but short duration and

[1] See prepared statement, page 11107.

a limited dosage, anything that exceeds that should be brought to the patient's attention. The patient would then be asked to give signed consent because he is in effect in the midst of a long term experiment, whether he knows it or not. He should be duly informed that he is exceeding either dosage or duration, the extent to which the drug has in fact been licensed by the FDA. I think this would be an interim step to situations we now find ourselves in with drugs already on the market.

I would like to put forth the idea that a phase 4 study should also become the long term goal of the FDA for drugs that are licensed on short term basis. We can then continue to accumulate evidence on a long term basis and determine whether long term benefits continue or whether long term deficiencies appear.

In order to be certain that this type of information is readily available to the consumer, in reference to your question, Mr. Chairman, I would also like to suggest that consideration of the national formulary which has been discussed from time to time be more carefully considered as well. This should be written for the layman and available to him.

And finally, in the context of trying to educate both the layman and the physician, more support should be given to clinical pharmacology financially, not only at the university level but also in the community hospital.

Now, returning to the principle question of the oral hypoglycemic agents, I would like to enlarge on Dr. Miller's statement about the clinical aspects of these complex chemicals because one of the points that he alluded to and which needs to be emphasized is the fact that the sulfonylureas, in addition to the pharmacological elements that they have on the pancreas, should not be considered simply beneficient drugs for the pancreas alone. There is evidence that they are very complex chemicals that have widespread effects on other organs of the body and in other publications we have listed those as having effects on the thyroid, the skin, the eyes, and occasional blood dyscrasias have been described. Certainly the effect on salt and water metabolism by the kidney is well-known. These agents may effect complex enzymatic actions of the liver as well. More important, Dr. Palmer will bring before you tomorrow on the effect of these agents on the heart. This is a most important consideration since he has demonstrated the similarity of the chemical effect in patients of all the sulfonylurea agents that he has tested, including the newer oral hypoglycemic agents. We readily recognize that we have no mechanism at the moment for ascertaining long term detrimental effects of most of these drugs and because of this, it certainly behooves us to act on the information we have in reference to this class of drugs and therefore prevent their proliferation.

Although the term "controversy" has been linked with the oral hypoglycemic agents, the controversy is clearly now one of degree rather than of fact. No study has demonstrated any long term benefits that can be derived from the oral hypoglycemic agents. Numerous studies are now confirming the basic findings of the University Group Diabetes Program.

Mr. GORDON. May I interrupt just a moment. Could you repeat that statement once again?

Dr. PROUT. Although the word "controversy" has been linked with the oral hypoglycemic agents, the controversy is one of degree rather than of fact. *No studies* have demonstrated any long-term *benefits* that can be derived from the oral hypoglycemic agents.

Mr. GORDON. Is it not true that studies do show that they are completely ineffective after, say 3 or 4 years?

Dr. PROUT. We are on a slightly different wavelength than you are, but that is an important point, however. The hypoglycemic effect does appear to be of short duration in many of the patients in whom it is given. And they are certainly used by physicians and demanded by patients long after their initial utility has been lost. I was speaking before your question as to the absence of long-term benefits, not just as to the hypoglycemic effect but to the absence of benefits for the degenerative complications of diabetes as well.

Mr. GORDON. Well, while we are on these drugs, let me ask this: Is it not correct that Dr. Robert Bradley, Dr. Tan and several other doctors at the Joslin Clinic did a study—and it was reported last year before the American Diabetes Association—showing that after 3 or 4 years these drugs do not even have a chemical effect? They do not even lower the blood sugar level?

Dr. PROUT. Yes. I think Dr. Miller has a graph to illustrate the fact that there are three or four very good studies that demonstrate this.

Dr. MILLER. May I present this for the record?

Senator NELSON. It will be received for the record.

Mr. GORDON. In other words, after 3 or 4 years there is not even a chemical effect let alone a therapeutic effect. Now, since these drugs are inefficacious after three or four years and since the treatment of diabetes is a longterm treatment, what kind of a benefit to risk ratio do we have here? No benefit with risk.

Dr. PROUT. This I agree with.

Mr. GORDON. Is that correct?

Dr. PROUT. That would be correct in my opinion.

Mr. GORDON. Would it be fair to say, then, that these drugs are useless?

Dr. PROUT. I have no personal use for them in terms of my own practice.

Mr. GORDON. I am talking about long term effect now.

Dr. PROUT. No useful long-term effect and evidence of possible harm, that is correct.

Mr. GORDON. After 3 or 4 years.

Dr. MILLER. Support for that statement is shown on the graph just presented. Three large studies including one from the Joslin Clinic on over 1,800 patients show that at 5 years only 30 percent of the patients originally started on the drug were controlled by the oral agents and that in 10 years in less than 10 percent of the patients could a significantly effective blood sugar lowering effect be demonstrated. I think that answers the question that you raised.

Dr. KLIMT. In further qualifying this, you could say that during the short period, relatively short period, during which the drugs are effective, they do control symptoms of diabetes such as extreme itching, disturbance of the visual acuity, so over the short-term they have some symptomatic relief effects, similar to insulin. Long-term they would lose that.

Mr. GORDON. Now, coming back to the short-term treatment. Do you know of any studies that show that the oral antidiabetic agents are more effective than diet?

Dr. PROUT. In lowering blood sugar?

Mr. GORDON. Yes.

Dr. PROUT. Well, in the practical world of treatment, the answer would have to be yes to that. They certainly are more effective in the sense that given the difficulties of having patients adhere to diets leaves much to be desired. Nevertheless, these agents should never supplant dietary therapy, particularly since they may be deterimental.

The theoretical basis, however, is quite as important as you say. If we would spend more effort in teaching diet properly, then the benefits of diet can be realized, as Dr. Davidson has clearly shown and will show to you tomorrow, also.

Senator NELSON. I did not quite understand that answer. If the diet does not work, the pill would not work either if the patient doesn't take it. But are you saying if the patient complies strictly with the diet——

Dr. PROUT. Then it will be equally effective.

Senator NELSON. In reducing blood sugar?

Dr. CHALMERS. I think this question should be presented to Dr. Davidson because he has evidence that better than the pills in reducing blood sugar is strict adherence to diet, and that two-thirds of the patients he has treated have been able to maintain satisfactory control without drugs.

Senator NELSON. Why didn't the others benefit? Because it did not work or because they did not diet?

Dr. CHALMERS. The others did not lose enough weight and did not have enough drop in their blood sugar, but they did respond to insulin and still did not need oral agents.

Senator NELSON. Well, is the overall conclusion thus far that you do not foresee any purpose for these drugs in the marketplace?

Dr. PROUT. That is certainly my conclusion, based on the University Group Diabetes Program and the lack of long-term benefits as well as the point that is now being raised by counsel that even the hypoglycemic effects are of short duration. The final point that has just been brought out is that if we spent more time teaching diet we could get greater benefits without using drugs at all.

Senator NELSON. Does everybody agree with that?

Go ahead with your testimony, Doctor.

Dr. PROUT. Many physicians and some patients appear to pay the price of a 1-percent-per-year increase in mortality rate for cardiovascular disease which has been shown to accrue as the result of the oral hypoglycemic agents. If they do so knowledgeably and *with signed consent*, it is their right to do so. Not enough has been made, however, of the fact that these are potent hypoglycemic agents and that the case fatality rate is somewhere between 15 and 20 percent in the reported literature.

Senator NELSON. What does that statistic mean?

Dr. PROUT. In plain language, this states that an agent which has been used as a drug of convenience has been shown to have an uncontrollable ability to lower blood glucose to symptomatic levels. Among

the reported cases collected by Dr. Seltzer (Diabetes 21:955–966, 1972) between one-fifth and one-sixth of the patients have died when hypoglycemia occurred in association with the oral agents, sometimes used in association with other drugs, but when the oral agents were being used at the same time.

Now this evidence has accumulated over a decade in the use of these agents, which are relatively impotent in comparison to the second generation pills. They were also being used by practitioners who have had optimal experience in their regulation. I would therefore submit that there can literally be no justification for the introduction of a second generation of these medications which are even more potent, especially if it appears that these are to be introduced solely for the benefits of the pharmaceutical industry and at the expense of the consumer.

Senator NELSON. As I understand it, 1.5 to 2 million people are using these drugs. On that percentage basis, that would be 15,000 to 20,000 additional deaths or excess deaths resulting from the use of these drugs; would that be right?

Dr. CORNFIELD. 150,000, 15 percent of a million.

Dr. PROUT. No. One percent per annum in addition as a result of using oral agents. I think it would come out to something like five or ten, if this were applicable to the total diabetic population.

Senator NELSON. That would be 15,000 to 20,000, would it not?

Dr. KLIMT. It is per year, instead of per lifetime so in any given year you would expect 20,000 unnecessary deaths and I think Professor Cornfield has spoken to a lifetime excess.

Dr. CORNFIELD. I was simply giving a result of multiplying a million by .15. I think perhaps my confusion and maybe of others, is I am not clear exactly what the 15 to 20 percent is.

Dr. PROUT. Well, if you consider only the people that have been reported with hypoglycemia in the literature and compute the percent that died that is the "reported case fatality rate."

Dr. CORNFIELD. It is the number of people who have developed hypoglycemia.

So it is not 15 percent of all patients taking oral agents?

Dr. PROUT. That is right.

Dr. CORNFIELD. So it is not 15 percent of many, it is 15 percent of some smaller number.

Dr. PROUT. The overall mortality figure would be 1 percent a year of all patients taking oral agents based on the University Group Diabetes Program; 1 percent per year.

Senator NELSON. Do the studies show any strong positive reason for any patient in any particular condition whose interests were served by taking one of these oral drugs?

Dr. PROUT. One of the patient interests served would be their availability to patients who may not be able to take insulin for some reason. That is, they might not be able to handle an insulin syringe. Such patients use an oral agent for a short term hypoglycemic agent and might find it useful. Other than that and insulin allergy there are few other benefits that all of us could agree to.

Senator NELSON. Well, are you saying that at best in any event it would be short-term use you are talking about?

Dr. PROUT. Very likely.

Senator NELSON. And are you saying also that there are some patients, if they cannot use insulin, who even if they dieted, would not be able to control the glucose sugar level?

Dr. PROUT. I think it is possible to have the detrimental effects of the oral hypoglycemic agents without having the minor benefits of having it lowering the blood glucose. We were certainly able to document that.

Senator NELSON. I was not asking that. I was asking what condition would you have to have in which there would be some benefit for some patient in using these drugs. You said the inability to use insulin would be such a case. Now, are you saying that there are cases in which the drug would be beneficial in the short term in which a diet would not work?

Dr. PROUT. Again, I would answer that to say that there is a small group of patients who cannot use insulin and who in addition have gotten maximum benefits from diet and who might have symptomatic relief from the oral hypoglycemic agents. It would help them sleep at night, for example, without getting up to urinate and break their sleep. In that small subgroup, it would certainly be infinitesimal in reference to the total diabetic population; I would not close the door on some benefits nor on the rights of those patients who wish to take these drugs, to have access to them, provided they understood the risk.

Senator NELSON. But it still would be short term?

Dr. PROUT. It would be likely to be short term.

Senator NELSON. I am going to let Mr. Gordon continue the hearing, as I go and vote again so you will not be interrupted.

Dr. KLIMT. I would like to amplify on Dr. Prout's statement that not only is there a small group of medically indicated patients who would benefit by oral drugs knowing the excess risks which they may have, but there is a social indication for the use of these drugs again in a small subgroup of people who would lose their jobs otherwise. I am thinking here of truckdrivers who when they become insulin-dependent diabetics would lose their union license. Those cannot be educated at an age where they are close to retirement, and in these cases with their knowledge they may well choose to take oral drugs because they cannot take a regular diet, being truckdrivers. They cannot inject themselves with insulin, and they may choose to put themselves on oral drugs. It is such subgroups who, knowing what they would get into, may choose such treatments.

Dr. PROUT. I would like to suggest that the prejudice of industry against insulin is a result of our failure collectively to educate the public, the physician, and the diabetic, that they are in fact safer on the proper dose of insulin than they would be on the oral agent, and that if there are constraints in industry against the use of insulin, it is not something we should agree to live with forever.

I think Dr. Klimt's point is true at the moment, of course. There is prejudice against insulin in favor of the oral agents in the exact method that he states, but I would hope that we will not accept this in the future.

Dr. MILLER. If a patient is truly insulin dependent, he requires insulin to keep him free of symptoms. If the patient is symptomatic without insulin, his chance of getting a significant lowering of blood sugar effect from these oral agents is very small. Even Dr. Seltzer has admitted that in his article published recently. If the blood sugar is over 300, he says, you cannot expect the oral agents to be effective.

Mr. GORDON. Dr. Prout, proceed please.

Dr. PROUT. Thank you. I would like to amplify a little bit on Dr. Klimt's remarks concerning future oral hypoglycemic products. We see the great likelihood that the pharmaceutical industry will attempt to bring other drugs on the market whose safety and efficacy is at the moment, on the basis of present evidence at least, far from proven. A cardinal example of this will be the present attempt to obtain licensing for second-generation oral hypoglycemic agents. Among the drugs being considered are glyhexamide, glycodiazine, and glybenclamide. Others are under consideration, but these are the leading contenders. And of these, the last mentioned, the glybenclamide, is said to be the "most promising." It is effective in very small quantities. Hypoglycemic activity has been found in experimental animals and human beings with a dose of less than 0.1 milligram per kilogram of body weight. The suggested dose has been between 10 to 20 milligrams per day, but it has been known that some patients have been adequately maintained on less, perhaps one-tenth of that dose, and that the hypoglycemic experience elsewhere in the world has been formidable, although at present largely unreported in the world's literature. The hypoglycemic potency of these new agents is somewhere between 100 and perhaps 200 times greater than that of the presently available agents, and the need for these agents in the United States is yet to be demonstrated.

Indeed, if all else is controversial, we may safely conclude that the first obligation of Government is to protect the consumer and not to please industry. It is self-evident that this can best be done by insisting on proof of both safety and efficacy for the long- term use of more potent oral agents before they can be licensed, and I trust that this is the expressed desire of the present staff of FDA through its advisory committees.

I want to make it clear that I do not think we have any right to be prejudicial against the possibility that newer agents may have a use, but we certainly need to see the data before we can make a judgment.

Thank you.

Mr. GORDON. Well, to summarize, then, it is your opinion that since these drugs are to be used for long-term use, and there is no evidence for their safety and efficacy in such use, it is not in the public's interest to allow them to be marketed at this time. Is that correct?

Dr. PROUT. I see no great benefits to come from these drugs as such. The more general question is whether FDA should keep from the public potentially useful agents while we run long-term studies. I think that question has to be answered quite clearly, using L-Dopa as an example, but I do not believe it applies to the oral hypoglycemic family.

Mr. GORDON. Dr. Cornfield, would you proceed?