time insulin was not given until it was clearly shown that diet was ineffective.

Figures from the Joslin Clinic, as of 1970, indicated that 45 to 50 percent of their adult-onset diabetics were being treated with oral agents, despite protestations of the Joslin Clinic doctors that oral agents were only used after dietary treatment failed. Curiously enough, however, 45 percent required insulin, about the same percentage as in the preoral agent era. Only 5 to 10 percent were treated with diet alone.

This I think is a damning indictment of the way the use of these oral agents has been abused in this country. Instead of emphasizing the need for careful diet control in order to reduce weight, the physician and the patient both have gone to the easy way of therapy, of just popping another pill.

Senator NELSON. What study was that?

Dr. MILLER. This was reported by Dr. Alexander Marble of the Joslin Clinic at a panel discussion held at Yale in the fall of 1970. The Kefauver Act I think was passed in——

Senator NELSON. 1962, and this was 1957 when it was admitted to the marketplace, so you only had to prove safety at that time.

Thank you very much for your presentation.

I might say that any of the witnesses should feel free to comment at any time on any aspect of anyone else's testimony so we would get the best possible record.

Our next witness is Dr. Christian Klimt, professor and director of the Division of Clinical Investigation, University of Maryland.

Dr. Klimt, we are glad to have you here today.

STATEMENT OF DR. CHRISTIAN R. KLIMT, PROFESSOR AND DIRECTOR, DIVISION OF CLINICAL INVESTIGATION, UNIVERSITY OF MARYLAND, BALTIMORE, MD.

Dr. KLIMT. Thank you, Mr. Chairman, Senator Nelson and Mr. Gordon. It is a privilege to be asked to testify before this committee.

Since it appears to be customary to bring one's credentials before you, I have been engaged for the last 14 years in the conduct of clinical trials, first at Johns Hopkins, then at the University of Minnesota, and now at the University of Maryland. I have spent one year on leave of absence as scientific director of the Food and Drug Administration Office of Scientific Coordination 4 years ago. I am also a member of the World Health Organization's expert committee on diabetes. I am past chairman of the statistical committee of the U.S. Diabetes Association, and member of its editorial board.

Late in the 1950s the University Group Diabetes Program, UGDP, was planned because it had become apparent that in spite of the standard treatment of diabetes with insulin and oral drugs, diabetics continued to die from an excess of cardiovascular complications and continued to develop an excess frequency of blindness.

The study originally had two insulin treatment groups, a tolbutamide treatment group, and a control group. Tolbutamide, marketed under the trade name Orinase, was selected as the representative of the sulfonylurea type drugs, because it was the one oral hypoglycemic drug most frequently used at the time this study was planned. In

one insulin group patients received a fixed dose and in the other insulin group patients received a dose adjusted to maintain blood glucose levels in the normal range. Approximately 18 months after patient recruitment had started for these four treatment groups, a fifth treatment group was added. Patients in this group received phenformin which is a representative of the biguanide drugs and is marketed under the trade name of DBI. All patients in the study were given diet instructions.

The study was conducted in 11 clinics located in different parts of the continental United States plus 1 clinic in Puerto Rico. The participating investigators in these 12 clinics recruited a total of 1,027 patients. An individual's eligibility for the study was determined by a screening examination and an observation period of 4 weeks of treatment with only diet. Eligible patients were randomly assigned to one of the treatment groups and the allocation procedure was designed so that approximately the same number of patients was assigned to each of the five treatment groups at the end of patient recruitment.

At the time of the initiation of the assigned study medication, the patients were examined for their baseline health status. They were subsequently seen at 3-month intervals. All examinations were performed according to a common study protocol which was rigorously followed in all clinics. Modifications of the treatment protocol for individual patients was recommended for certain circumstances. Low blood glucose levels led to dosage adjustments to prevent such episodes. Elevated blood glucose levels resulted in dosage adjustments only in the insulin variable treatment group unless the patient had certain clinical signs and symptoms of diabetes.

All data were centrally collected and periodically analyzed. Each of the two oral drugs had a placebo counterpart and neither the patient nor the treating physician was aware which treatment was given to the patient.

We in the profession call this a double blind.

In 1969 an excess mortality, particularly cardiovascular mortality, was observed in the tolbutamide-treated group compared to the mortality observed in the other treatment groups. After extensive evaluation of available data, the investigators decided to discontinue the use of this treatment in the UGDP. This was decided because there was no sign of any benefit that accrued to the patient, and there was a possibility that harm was being done, particularly in the area of cardiovascular mortality. The findings were brought to the public notice and caused a tremendous publicity storm before the data were presented to the annual meeting of the American Diabetes Association by Dr. Prout. In fact, some 900 publications preceded the scientific publication of this study. The reports in the press were based primarily on an abstract of the presentation which was published shortly before the American Diabetes Association hearing, and was prematurely available and went to the Wall Street ticker. A detailed report of these findings was subsequently published as a monograph of the Journal of Diabetes.

The UGDP conclusions concerning tolbutamide have been challenged by a number of physicians and statisticians. The essence of

the criticism was that the tolbutamide treated patients from the beginning were more ill than the patients in the control group. Professor Cornfield will address himself to that question in detail. However, this argument has been carefully refuted. The difference in mortality and particularly cardiovascular mortality was visible in nearly all subgroups considered such as males and females, persons of Caucasian and non-Caucasian origin, patients with and without elevated blood cholesterol levels. An analysis which takes into account the differences in the baseline characteristics of the patients in the tolbutamide and control groups in which 14 factors were analyzed simultaneously, indicated that the difference in baseline characteristics could account for at most, 0.7 deaths. The observed difference in the number of cardiovascular deaths was 16, 26 cardiovascular deaths in the tolbutamide group and 10 deaths in the control group.

Approximately 2 years later in the spring of 1971, the second oral treatment, phenformin, was discontinued in the UGDP. Contrary to the tolbutamide findings were the difference in mortality had only appeared after 3 years of continuous medication. The increased mortality in the phenformin-treated group appeared very early in the study and was already visible in the data of the second year. It was associated with the development of increased blood pressure in comparison to the other treatment groups. This particular finding of phenformin had not been reported in the literature before, and as I have heard in Tel Aviv, has not been found in another study conducted in Great Britain by Dr. Harry Keen. Not only did more patients in the phenformin-treated group than in any other treatment group have an increase both in systolic and diastolic blood pressure, but patients who died had a higher frequency of new hypertension than did those in all other treatment groups in the UGDP. A large raise in the frequency with which the heart beats occurred shortly after the beginning of phenformin treatment. Other studies have shown that the heart rate is a very important predictor of likelihood of death from cardiac disease. Thus, while the results were superficially similar for the two types of oral hypoglycemic drugs, the mechanism of action is probably quite different.

The findings of the UGDP have been called controversial. In fact, Senator Nelson, they are only controversial because they are highly unpopular. They are unpopular with the patient who must adhere to a diet he does not like. He must, if he is symptomatic, inject himself with insulin. They are also unpopular with the physicians because diet education is tiresome and standardizing a patient on insulin requires close medical supervision, in contrast to supplying pills for the control of high blood sugar.

Senator NELSON. Let me ask you a question at this point. At the end of the first paragraph on page 3 of your prepared statement, you say the observed difference in the number of cardiovascular deaths was 16, 26 cardiovascular deaths in the tolbutamide group and 10 deaths in the control group.

Did the control group contain people who were taking insulin and people who were just on the diet?

Dr. KLIMT. People just on diet.

Senator NELSON. So the control group is just diet.

Dr. KLIMT. Just diet. All patients were prescribed the same diet as recommended by the American Diabetes Association. The control group received a placebo that is an ineffective drug which physically resembled the oral drug, but they did not receive any medication to lower their blood glucose.

Senator NELSON. So this particular statistic here was tolbutamide versus a control group on a placebo, but not in comparison with insulin.

Dr. MILLER. There were two other treatment groups on insulin, and the mortality in the two insulin treatment groups was essentially the same as in the placebo group, in the range of 10. So it was only the tolbutamide group that showed this excess cardiovascular mortality. Does that answer your question?

Senator NELSON. Yes.

Dr. MILLER. We had really three groups to compare with against tolbutamide.

Dr. KLIMT. The fact that the oral drugs have been termed drugs of convenience stems from the fact that they are both acceptable to the patient and the physician to a great degree. These drugs are also major moneymakers, and therefore the UGDP findings have been challenged by industry, as you have read in your introductory statement.

Senator NELSON. I think there is a rollcall vote in progress.

Dr. KLIMT. The controversy has been frequently referenced in the press and particularly the throwaway journals, like the Medical Tribune, which are financed in large part by the drug companies through advertising.

Now, the question for the future is, what benefits may be gained by drugs of this nature, compared to the risks involved?

In my opinion, the oral drugs carry an inherent risk and should be clearly labeled as carrying such a risk. Certain patients may nevertheless use knowingly such drugs, because they may otherwise lose their jobs. Truckdrivers and crane operators are examples in point. On the other hand, a whole list of new compounds derived from the same basic chemical, sulfonylurea, have been developed and are being submitted for approval and licensing to the Food and Drug Administration in the near future.

These compounds distinguish themselves generally from the existing ones by much greater hypoglycemic activity, in the order of 100 times as potent; and even when these drugs are given in small amounts, they are highly potent. They have not been tested for long-term toxicity or efficacy, and they have through maladministration, physician errors, and the like, led to cases of irreversible hypoglycemia and death, particularly in Germany, the country in which these drugs have been developed.

Senator NELSON. Let me interrupt you, Doctor. There is a rollcall, so we will just recess for 10 minutes.

[A brief recess was taken.]

Senator NELSON. I am sorry about the interruption, Doctor. There will probably be another one very soon.

Dr. KLIMT. I hope I can finish my statement. I am at the very end of my presentation. I was discussing the future and the likelihood that new developments of the same chemical compounds, the sulfonylurea type, become licensed.

Senator NELSON. Are they the same compounds?

Dr. KLIMT. They are in the same family, originating from the sulfonylureas. Glyburide and glibenclamide are some of the names of the drugs which are going to be marketed.

Senator NELSON. Have they been approved yet for marketing?

Dr. KLIMT. As I understand, they are about to be approved. They are very much at the stage where an NDA may be granted. I think Dr. Crout or Dr. Schmidt will be able to speak to that more competently than I. These compounds distinguish themselves by their higher potency from the existing sulfonylurea-type drugs by a factor of 100. They are so potent that a slight overmedication either by a physician or by patient error leads to irreversible hypoglycemic shock and death, a fact which has been brought out by a meeting in Dusseldorf in 1971 where by general account, some 200 deaths had already occurred from an overdose of these drugs.

Now, mind you, these were errors, but it is very easy to take one or two more tablets when you have sinned in your diet.

Senator NELSON. Well, you said irreversible hypoglycemic shock just from taking the double dosage.

Dr. KLIMT. Not even double the dose. Two pills more. If three would have been the dose to take, and the patient took five because he had eaten a meal which he was not supposed to, you can very easily get into trouble with these drugs.

Senator NELSON. When you say irreversible, do you mean it is inevitably fatal?

Dr. KLIMT. It has become fatal in a fairly sizable number of documented cases.

Dr. MILLER. The brain requires glucose for its metabolism. Without glucose, it will not function, and this causes irreversible hypoglycemic brain damage and death.

Senator NELSON. You are only talking about one mistake on one dosage. The patient is prescribed three, and takes five, that may be it?

Dr. KLIMT. That is what I am talking about. The need for physician and patient education.

Mr. GORDON. Who makes these drugs?

Dr. KLIMT. Hoechst in Germany is the producer of glibenclamide. There are others who make similar drugs. To my understanding, there are at least five companies who have similar drugs ready to be proposed for licensing.

Dr. MILLER. I believe Upjohn in this country has been doing clinical testing in this country.

Senator NELSON. Well, you say they have not been approved yet?

Dr. KLIMT. They have not been approved, but as Dr. Crout from the FDA tells me, they are very close to approval, having met their legal requirements to be licensed.

Senator NELSON. Will they have to meet the standards of safety and efficacy, and have they carried on studies that would indicate that this drug is, in fact, better than dietary control and is, in fact, safe? Have they conducted studies that would show that this drug acts differently from tolbutamide in the long haul?

Dr. KLIMT. No, that has not been done, and there are serious proposals entertained, both from industry to my knowledge, and from the FDA to get such a study underway. The question is how to bring

such a study before a forum that is impartial, not within the domain of industry, not within the domain of people who have a preconceived notion, but a totally objective study long term for the efficacy as well as potential hazards of these drugs.

Senator NELSON. Well, why couldn't they handle them in the way they handled all the other studies on efficacy under the 1962 amendment; that is, by the National Academy of Sciences-National Research Council?

Dr. KLIMT. The predicament is, of course, loss of patent protection. These studies are very long term, and the protection may have run out before such a study is completed. It would have to be a study after licensing and with the ability to withdraw the drug from the market if negative findings are found.

Senator NELSON. They dealt with that in part of the law.

I have to run over and vote again. I will be back.

[A brief recess is taken.]

Senator NELSON. I am sorry about the delay but there were three votes scheduled there on the HEW Appropriations bill back to back and we could not dispose of them any faster.

Please proceed.

Dr. KLIMT. I am actually at the end of my formal presentation.

I would like to recommend that drugs which are taken chronically, drugs which provide a major fiscal incentive to industry, that studies of the nature I have proposed also be financed by industry, but under outside sponsorship, conceivably in this case by the American Diabetes Association or a similar body, which would then let a contract for long term study of clinical benefits.

Senator NELSON. Well, are you talking about testing before the drug is approved, part of the clinical protocol for approval of the drug for safety and efficacy, or are you talking about——

Dr. KLIMT. Since a considerable time may elapse between patenting of a drug and an NDA approval, there would not be enough time in the 17 year limit that the patent law applies. If a drug has been patented 8 years before the New Drug Application is approved, then only 9 years would remain afterward. The study of which I am talking about would take at least 8 to 10 years so there would be nothing remaining in which the company would be protected from competition to regain its investment.

So, therefore, I believe that such a study would have to be done after licensing, but the funding of the study could be a condition of the licensing and could be completed before the drug receives its NDA.

Senator NELSON. Well you appear to make an argument to change the date when time starts running out on a patent. You might make an argument for that, but you certainly are not making any argument for marketing drugs that are not proved as safe and efficacious by appropriately controlled scientific studies are you?

Dr. KLIMT. In long term treatment, that is a very difficult matter to establish. The short term requirements are certainly met by phase 3 studies which are already a part of the requirements before an NDA can be granted.

I speak of phase 4 studies for clinical benefit and clinical risk which at the moment are not mandatory prior to licensing, which should be done and might be done after a licensing or provisional licensing has

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been given. A prototype of this procedure was followed with the drug L-Dopa for Parkinson's disease.

Senator NELSON. Was that marketed before the long term studies?

Dr. KLIMT. Yes.

Senator NELSON. Is not this quite a different case in that the compound of the new drugs is of the same family as tolbutamide and the one comprehensive study done indicates serious risk problems? Therefore, how dare we permit the same compounds, a compound in the same family, to go into the marketplace with this one long term study indicating that there are serious problems?

Dr. KLIMT. Not only is that true, but in the case of Parkinsonism, there is no alternative. There is no other effective treatment for some of the patients. In the case of diabetes that is not true. Those patients which do require treatment can be treated with insulin with no adverse effects. It is only a question of inconvenience which has to be overcome and, therefore, I fully agree with you. It is a different situation.

Senator NELSON. Does anyone else want to comment on that?

Dr. MILLER. Let me reinforce Dr. Klimt's statement.

We are considering the use of drugs in chronic diseases where a cure is not available. It should be evident that any beneficial effect on the disease must be balanced against the seriousness of long term side effects of the drug. In the case of Parkinsonism the use of Dopa can be justified because it has been shown to be uniquely helpful symptomatically in some cases. Nevertheless, long term clinical trials should be required to determine whether the risks of using Dopa indefinitely will outweigh the symptomatic benefit.

In the case of the oral hypoglycemic agents, on the other hand, no symptomatic improvement has been demonstrated that cannot be done better and more safely with diet and insulin. The UGDP study has shown without a shadow of a doubt that the risk of taking the oral drugs is serious as measured by an increased mortality rate and that there is no specific benefit as compared with diet and insulin.

It should be mandatory that any long term drug therapy for chronic diseases be evaluated with long term controlled clinical trials in order to determine the risk versus benefit ratio.

The new sulfonylurea drugs now being considered for release by the FDA are in the same family as Orinase and the other sulfonylurea drugs. Dr. Palmer will tell you tomorrow how the sulfonylurea drugs now on the market all have the same adverse effects *in vitro*. I think it should be crystal clear that it is unnecessary to introduce *a new drug of the same family* where toxic effects have already been demonstrated.

We do not need to add this to the problems of clinical medicine.

Senator NELSON. Thank you.

Does anyone else want to comment on that?

Did you complete your statement then?

Dr. KLIMT. I have completed my statement.

Senator NELSON. All right, thank you, Doctor, for your very fine statement.

Our next witness is Dr. Prout, associate professor of medicine, Johns Hopkins University and chief of medicine, Greater Baltimore Medical Center. Dr. Prout, we are very glad to have you before us

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.