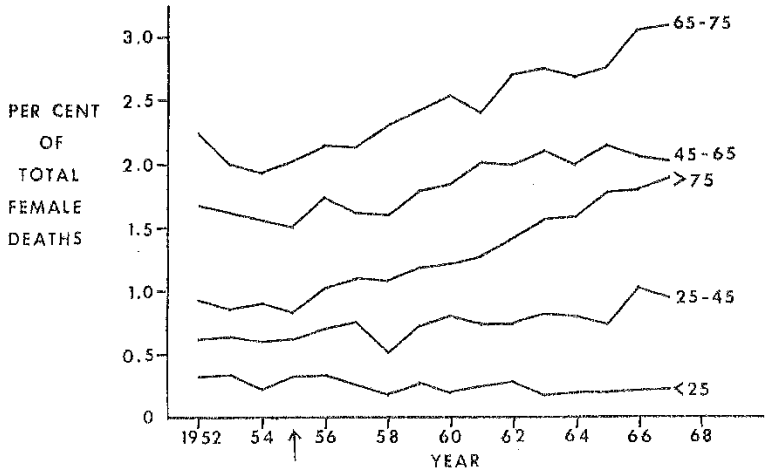
PER CENT OF TOTAL FEMALE DEATHS DUE TO DIABETES
ACCORDING TO SPECIFIC AGE GROUPS
IN WEST GERMANY, 1952 - 1967



KNUSSMAN (1971)

Senator NELSON. Our final witness is Dr. Thomas Chalmers, president, the Mount Sinai Medical Center, dean, Mount Sinai School of Medicine of the City University of New York.

Dr. Chalmers, we are very pleased to have you here today. Your statement will be printed in the record, and you may present it however you desire.[1]

STATEMENT OF THOMAS C. CHALMERS, M.D., PRESIDENT, THE MOUNT SINAI MEDICAL CENTER, DEAN, MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK

Dr. CHALMERS. I shall not read this statement. It is the longest one, and a lot of what is contained in the statement has already been covered by the previous discussion.

Senator NELSON. It will be printed in full in the record. If you want to elaborate on any points that were not covered or those that were, just go ahead.

Dr. CHALMERS. I will summarize the important points and then make some recommendations which I think are important at this time. I am neither a diabetologist nor a statistician as are the four people on my left, and I appear before you as a sometime specialist in clinical trials. I have been interested since 1950 in the conduct and in the design of clinical trials, and the interactions of ethics and clinical care in such trials. I have conducted a number of trials myself, and have recently been serving on a number of policy advisory boards and have

[1] See prepared statement, page 10987.

been involved in the development of a fair number of trials throughout the country.

It was because of this experience when I was serving as associate director for clinical care of the National Institutes of Health, at the time that the donnybrook about the UGDP findings hit the press, and there were accusations of distortions and such things against the UGDP investigators, that Dr. Robert Marston, then director of the National Institutes of Health asked me if I would investigate the study and inform him as to whether the studies which the NIH had supported so long and arduously were in fact faulty.

I had not in any way been connected with these studies up to that time, and I got all the information from Dr. Donald Whedon, a whole filing drawer of material, which contained all the correspondence of the group and all the progress reports, and I went through them very carefully to make up my own mind about the validity of the study.

I have listed seven of the accusations which seemed worth discussing, and to my satisfaction I answered them all and came to the conclusion that the UGDP was a valid study, and that the quoted other studies that disagreed with the conclusions were not valid and did not in any way deny the validity of the UGDP studies, and that there is no evidence that the drugs have a beneficial effect, and they might be toxic.

Senator NELSON. There is no evidence that they have a beneficial effect?

Dr. CHALMERS. None that have a beneficial effect. I am now talking about mortality and morbidity, long term, and especially about the possibility of prevention of cardiovascular disease, which is one of the reasons why they have been used in the past. They do lower the blood sugar in most patients but that effect may wear off in a [illegible] years.

There is no evidence that they accomplish what they have been prescribed for, prevention of vascular complications, and that there is some evidence that they may in fact cause excess mortality. I say by an increment of 0.5 percent in my manuscript to be cautious. I am told by my colleagues that it is really 1 percent per year, and if there are 2 million people taking the drugs in this country, that is 20,000 extra, possibly unnecessary deaths per year.

It is important to emphasize that there are more and more bits of evidence of different kinds which are confirming the UGDP. You have heard of the retrospective studies which have shown a higher death rate in people with myocardial infarction. You have heard of the fact that the drugs have a specific effect on the heart which will be described in greater detail for you tomorrow, and you have heard the World Health statistics material, and all of these seem to add up to the fact that the drugs may not be as safe as their advocates claim.

One important point that I would like very much to make, however, is that the UGDP studies and all of these additional bits of evidence have not had any perceptible impact on the practice of medicine in this country, and as a matter of fact, in Canada. If you turn to page 11 of my prepared statement, there is a table of data on the use of hypoglycemic agents gathered by the National Disease and Therapeutic Index, an agency which specializes in the gathering of data on how often drugs are used. They have techniques which I cannot describe in

detail, that have to do with how many times a physician within a set time period mentioned orders a drug on a prescription or a hospital record, and they have come up with a figure in 1967 of 15 million for oral hypoglycemic agents. This grows steadily to 17,600,000 in 1970, and then with the report of UGDP, it dropped down by half a million, but within 2 years was back up to its old rate of climb so that now it is at 19½ million.

Consumer data gathered by the PAS group in Ann Arbor, Mich., showed there was a slight drop at the time, but the sales are obviously steadily rising.

I think it is important to dwell a little more on why this happens, and to emphasize the fact that it apparently is an educational process, that physicians practicing medicine have not become convinced of the validity of the UGDP. In fact, at various meetings where we talked about and asked if anyone had read the report of the UGDP in the journal *Diabetes*, we found that practically nobody had. They have read the reviews, and they have read the criticisms, and unfortunately most of those are supported by pharmaceutical houses, or appear in the so-called throwaway journals. They have not analyzed the data themselves.

So, this is the major problem which we have to face up to, that the information from good clinical trials does not have any advocates who bring that information to the practicing physicians. The information from bad clinical trials, if they confirm previous, preconceived notions and support the sales of drugs are brought to the practicing doctors.

Senator NELSON. Well, if it has had neither a temporary nor a permanent impact on the prescribing physician, even though the study has been made public, is there a study that is better that has been made by anyone that comes to a contrary conclusion about these drugs?

Dr. CHALMERS. No. We went into these in some detail while you were out of the room and concluded, Dr. Cornfield on my left concluded, that none of them could compete with the UGDP for quality in any way and none of them contradicted the UGDP.

Senator NELSON. Well, what keeps this information in this study from coming to the attention of the practicing physicians?

Dr. CHALMERS. One thing is that it has never been mentioned as yet in the package insert of the Food and Drug Administration, in the form of which some of us here think it should be mentioned——

Senator NELSON. But the argument there is the physician does not see the package insert anyway; just the pharmacist gets it.

Dr. CHALMERS. He does not see it, but if he pays no attention to it he is liable to be liable.

In other words, it is a statement of danger which I think he is compelled, if it is in the package insert, to present to his patient. It has been said several times this morning that we all believe that the drugs should be on the market for the occasional patient.

Senator NELSON. It should be on the market.

Dr. CHALMERS. It should be on the market.

Senator NELSON. Well, I haven't seen any case made for that yet. As I recall, you have found only a tiny fraction that might need it under any circumstances.

Dr. CHALMERS. Yes, but I personally think that physicians ought to be allowed to prescribe it for that tiny fraction, for the patient who

will not diet and have symptomatic hypoglycemia and cannot take insulin. It should be possible to use the drugs at least on a short-term basis, providing the physician can get his truly informed consent. By that I mean that the physician should get the same kind of consent one might get with any research drug, that is, he tells the patient all of the benefits and gets the patient to agree that he wants to take the increased risks, because he feels he ought to take the risk.

I do not think one can preclude that possibility by not having the drug available.

Senator NELSON. Well, how else would you get the information to the physician. You say the package insert. The package insert may or may not be seen by the physician. Most likely, I suppose not.

What other steps should the FDA take?

Dr. CHALMERS. The FDA has a letter which it sends around to practicing physicians in which it reminds them of various bits of information that it feels are important. I think one has to, however, rely on normal channels of postgraduate medical education, continuing education, to see to it that information is sent out to doctors in forms which they can assimilate rapidly and effectively.

As it is now the only financial impetus to do so comes from drug company advertising.

Senator NELSON. Well, how many of the journals, the medical journals, carried comprehensive articles on those studies? Did the JAMA carry it?

Dr. CHALMERS. They have, and they usually are followed by frantic letters from people who disagree. The reviews that are published nowadays are, I must say, examples of the fact that doctors are slipping back to using the drugs more often. They have forgotten about the UGDP. Maybe these hearings will remind them again of the importance of the problem.

Senator NELSON. Has anybody done a survey of the medical publications, both the medical journals and those that are throwaway publications supported just by advertising? Has anybody surveyed those to find out whether they carried these articles or this study and how extensively?

Dr. CHALMERS. I surveyed one and there were 19 articles on the UGDP, and 18 of them were highly critical. They reported everything that happened in the regular press or meetings having to do with the UGDP's fundings, but they extracted from these happenings the critical items and left the rest out.

Senator NELSON. Was this true of the medical journals as well as the other publications?

Dr. CHALMERS. The medical journals do not usually include this kind of ongoing review. They include original articles that are submitted each year that is the main source of their educational activities.

Senator NELSON. Do you mean they would not run extensive excerpts or summary of the UGDP study?

Dr. CHALMERS. Well, it is old stuff now. The UGDP studies were reported in 1970.

Senator NELSON. When it came out?

Dr. CHALMERS. When it came out there were editorials in the JAMA that said they were good studies and doctors ought to pay attention to it.

Dr. MILLER. I think you are pointing at the real heart of the matter, the question of postgraduate medical education. When students are in medical school they are oriented toward the scientific approach to medicine and required to look at the original data and to look at it critically. They are tested on that. Once they leave the sacred halls of the medical school, what do you have? Postgraduate medical education, let's face it, is in the domain of the drug industry. The drug industry is spending approximately $5,000 a year per physician for this education. The detail man costs the drug company $50 for every visit he makes to a physician to get a few minutes of time. We also have the phenomenon of drug advertising in every medical journal where the material required by the FDA is only in fine print, but the irrelevant illustrations are large and beautifully drawn, and the advertisements are easy to read. Often misleading statements are present.

You have the problem, a new and most vicious one, of the medical "throwaway" which comes unasked and unpaid for across the desk of every physician in this country, in which the articles are written by nonscientific people, in general, and which, if you look at them critically and carefully, are obviously slanted or, I believe, only for one purpose, and that is to sell drugs.

When there is something that indicates a bad effect of a drug or a problem, this is not emphasized. I think you can remember the problem of Abbott and the contaminated intravenous fluid. The Medical Tribune did not even mention it, even though there were hundreds of deaths resulting from this disaster. The Medical Tribune would print diatribes against the UGDP repeating it week after week and never in any way describing any of the actual results, the objectivity of the study, the scientific design, et cetera. And I think there are other examples which all of us in the medical field are aware of.

This is the problem. If the drug industry is allowed to spend a billion dollars a year for advertising to the physician, I think this speaks for itself. That is a billion dollars a year down the drain. But it is not just a billion dollars that the consumer is paying for in the price of drugs: it is a billion dollars for perverting the physician's mind so he is not aware of the actual scientific facts.

What Dr. Chalmers is referring to is the fact that we are not using sufficiently modern methods of communication, modern methods of education, to get the facts to the physician. The task is a Herculean one; there are 200,000 articles a year published in the medical literature, and for this one single disease, diabetes, there are 4,000 or 5,000 articles a year—who has time to read these? How many have the time to look at these critically? How many have the scientific background to evaluate them?

This, I submit, is a problem that we must all face. I wonder whether we can permit this laissez faire system of medical care, where we have an industry which is dedicated, as it should be, in our economy and our system of government to making money, how this can be allowed to interfere with the primary responsibility of the medical profession to bring scientific knowledge to the patient for his benefit.

All the money that has been spent through the years—that is in the last 50 years—to develop the scientific basis for medicine and medical schools has really brought very little, in the final analysis, to the benefit of the patient. This is where the problem is in the NIH. How do

41-746 O - 75 - 4

you translate the scientific facts which are pouring out of the laboratory, how do we translate these for the benefit of the patient?

There are no superficial treatments, no band-aids that will take care of this problem.

Senator NELSON. Go ahead, Dr. Chalmers.

Dr. CHALMERS. It is time for me to present the four recommendations that I have. Three are in the statement submitted, and then I have a fourth.

First, I believe very much that the Food and Drug Administration should include a strong warning in its package insert for the oral agents because I do believe that this will have some influence on practicing physicians.

Second, I recommend that the Food and Drug Administration should not release the new agents at all until studies have been done to show that they are safe. In other words, although we have great need for the new drugs, it is possible that they may have the same effect as tolbutamide and phenformin, and therefore, the burden should be on people who want to add more potent drugs to prove they are safe in the long run, which means to do a study as good as the UGDP.

Mr. GORDON. May I ask a question at this point?

If the UGDP investigators felt it was unethical on the basis of hazard to continue the use of these drugs, how about a doctor prescribing these drugs? Is it not unethical for doctors to prescribe these drugs?

Dr. CHALMERS. I think we have to be careful how we use the word "unethical" because in each man's mind it has a different interpretation. I happen to think it is more ethical to include a patient in a therapeutic trial or a study such as the UGDP than it is to prescribe a drug as if it had been proven to be safe, when in fact it has not.

With regard to new agents, it certainly is more ethical to study them in a randomized, controlled trial than to release them without that study ever having been done.

Mr. GORDON. I am talking about the older drugs now. You stopped using tolbutamide and phenformin. Have the UGDP people stopped using tolbutamide and phenformin because they could see no benefits and they knew there were risks? Didn't they stop using them because they felt it was unethical to keep using them? Isn't that correct?

Dr. CHALMERS. Or unwise.

Mr. GORDON. But yet, doctors are using them every day.

Dr. CHALMERS. I do not think that those doctors are taking into sufficient account the problem of relative risk, and are not facing the fact that a third of their patients do not need any medication for their high blood sugar and would do just as well when they come off. A third can be handled by diet alone and a third will require insulin. It leaves us only the last third that might be considered for the oral agents, if they refuse to take insulin.

But since the UGDP suggests that there is a greater risk in taking oral agents than insulin, the patient should be in on that decision and should give his informed consent.

Senator NELSON. These studies seem to indicate that it is risky to use it, long term, at least, and that furthermore after a couple of years,

based on that chart, it does not have any significant effect on lowering glucose anyway.

Is that correct?

Dr. CHALMERS. So they are facing an excess risk without any possibility of benefit.

Senator NELSON. Well, you finish your points. I would like to pursue that question.

Dr. CHALMERS. Well, I had one further comment about the trial of the new agents before they are released.

We should not think in terms of requiring an awful long time added on after the drugs are ready to be released, but instead, the pharmaceutical firms ought to be pushed into starting their controlled trials as soon as the dosage is adopted and as soon as they think they have a marketable drug. In that case the trials will be over in 5 years. We would be almost 5 years into trials of the other new hypoglycemics, glybenclamide and the others.

In other words, I disagree with Dr. Klimt about the phase 4 trials. I think these clinical trials should be started as early as phase 3. If the immediate gain is great enough to warrant the release of the drug before the long-term toxicity has been determined, that decision can be made, but at least the process of detection of long-term toxicity should be begun in the earliest stage of development. The lag in getting new drugs on the market in this country is, I think, more attributable to the lag in getting good studies going than it is to any excessive regulation.

The other two recommendations I have are a little more blue sky and they have to do with the fact that we are approaching national health insurance and we ought to be thinking about some of the substantive problems about health at the same time.

The UGDP cost $7.3 million to carry out and yet——

Senator NELSON. How much?

Dr. CHALMERS. $7.3 million. And yet I am calling for many more similar studies. If we had started several studies like the UGDP 10 years ago, we would have no argument now.

Senator NELSON. And that was funded by NIH.

Dr. CHALMERS. Funded by NIH and funded with a great deal of pain by NIH because it was taking a lot of money away from more fundamental research which, in the long run, might have a better payoff because you might find a cure or prevention of diabetes instead of merely a better treatment. There are innumerable situations in medical care in which we ought to have studies like the UGDP going on now, but they are not funded because of a shortage of funds. One reason is that they have to compete at the NIH with important basic research.

We should recognize that if we spend $100 billion on health care in this country per year, and Social Security spends what—$40 billion—it probably will be a lot more than that when national health insurance comes along—and if we did what any good industry does and put aside a small percentage to find out how better to spend that money, it would fund all the clinical trials which are necessary to find out which drugs are better.

That it would be a profitable thing to do is illustrated by UGDP example. The fact that we might have saved 20,000 lives per year by

having stopped using the oral agents 4 years ago, would pay for an awful lot of clinical trials. And $100 million a year spent on oral agents represents a lot of money that could have been used to support clinical trials.

We should have two mechanisms for supporting such trials. One, the transfer of social security or national health insurance funds to the NIH for administration of clinical trials; and second, as Dr. Klimt has suggested, pharmaceutical firms should be urged to support those trials through nonpartisan institutes, nonprofit institutes, which could accomplish much the same thing.

My final recommendation, again, has to do with the imminence of national health insurance. I believe the Federal Government has got to become interested in this problem of continued education for physicians, that we cannot expect them to do it solely on their own. It is costly and expensive to them and it is costly to medical centers to mount educational programs, and it would be critically important to have some encouragement in the form of provisions for continuing education in national health insurance legislation.

Doctors should not only be recertified but they should be helped in maintaining the knowledge that would allow them to be successfully recertified.

We can do our share by teaching medical students how better to analyze data and be better investigators on their own, and not be taken in by salesmanship.

In the long run we have to find more means to support continuing education.

Dr. PROUT. Mr. Chairman, I would like to reemphasize the points that the U.S. Government is one of the major contributors to pharmaceutical industries in the fact that through the VA and the Armed Forces and through social services and other programs, the Government agencies buy large quantities of drugs, many of which have been proven to be useless and are a complete waste of health dollars.

And so I submit that some of these health dollars that we are all looking for can be found in a careful examination of what drugs are useful and in eliminating those that are not. The Government can begin by believing the studies that are worthwhile and done with Government support. Tax dollars should not continue to pour into the pharmaceutical industry buying worthless drugs, but be used for more fundamental health needs.

Senator NELSON. Well, on the cost question, as I understand it, the manufacturer's price is $100 million, and at the consumer level——

Dr. PROUT. It would be double that.

Senator NELSON. Well, let's say it is double the manufacturer's price. In any event, a minimum of $100 million would be saved by the users and taxpayers—over $100 million.

The question that I would like to have you all address yourselves to is this: Here we have the UGDP study, which raises serious questions as to safety. Most of the people getting the drugs do not need it except in a rare case as you gentlemen agree that they might. Since there is a very major, serious question of efficacy, in your opinion, will the FDA be in compliance with the provisions of the statute as to safety and as to efficacy, if they approve this new generation of drug, which is 100 times as potent as the old ones, as I understood you to say.

Would they be in compliance with the law given this study which indicates that it does not have very much use in the short term and has no use at all in the long term plus some serious side effects? What would be your interpretation of the law as to the new generation of drugs based upon the one comprehensive control study that is available?

Dr. CHALMERS. There is enough suspicion that there may be long term toxicity with the new agents because I understand they do have a positive inotropic effect on the heart, like tolbutamide, and therefore, they may cause cardiovascular disease. There is enough suspicion to require that they have a long term trial of safety before they are released for general use.

I cannot see any loss in postponing that release.

Senator NELSON. What about your interpretation of the law as to safety and efficacy? The law is that there has to be substantial evidence of safety and efficacy.

Dr. CHALMERS. I do not think there is substantial evidence of safety and efficacy.

Senator NELSON. The law reads as follows:

> The term "substantial evidence" means evidence consisting of adequate and well controlled investigations, including clinical investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved on the basis of which it could be responsibly concluded by such experts that the drug would have the effect that purports to or is represented to have, under the conditions of use prescribed, recommended or suggested in the labelling or proposed labelling thereof.

Now under that standard would you say that the new generation of drugs on the market——

Dr. KLIMT. Sir, it would all depend, and this is where the phraseology of the law is somewhat ambiguous—what is efficacy?

If the drug house claims that the drug lowers blood sugar and the physician implies that this is a treatment of diabetes, he thinks it is efficacious. If clinical effectiveness, meaning reduction in suffering and the prolongation of life and the moderation of complications, is the question, then we have no such evidence. But if the chemical response is, indeed, the one that can be addressed to, then we do have evidence which satisfies the law.

I believe, therefore, that the law ought to be more clear on what it means in terms of effectiveness; namely, a clinical benefit to the patient and not just an indirect supposed benefit; namely, by the lowering of a chemical component which is similar to the lowering of blood pressure, similar to other drug effects, where the clinical response has never been totally proven.

For example, in lowering blood chloresterol levels. This is the question that was raised with me. The blood glucose lowering has been demonstrated by these drugs is not disputed.

Mr. GORDON. Over a long period also?

Dr. KLIMT. No; not over a long period.

Senator NELSON. But I do not think efficacy directs itself to the consequence of whether it has a certain chemical consequence. It directs itself to the question whether it is of therapeutic value to the patient. I imagine you can give all kinds of drugs and demonstrate that a drug will produce a chemical result and demonstrate it very

clearly, but it may not have any therapeutic value to the patient. That is the question as to efficacy, I think.

Dr. KLIMT. If this can be defined clearly, we would be one giant step ahead. If efficacy is, in fact, the clinical benefit for a patient rather than the implied benefit through a modification of his metabolism, then we would be clear what it is being said. There would be no question that it has not been proven in the case of these drugs, and there is not any urgent need for these drugs.

Senator NELSON. I think that is the interpretation as we have gone along. After all, when the FDA decided to take fixed combination anti-infectives out of the marketplace on the grounds that they were "ineffective as a combination," they did not really mean that they did not have some beneficial effect but they were less effective in combination than when they were singly administered. One of the classic cases was Panalba, which was a combination of tetracycline and novobiocin. All tests, including Upjohn's own tests, which the FDA got hold of, indicated that in combination they were less effective, although there is no doubt that the tetracycline was having an effect on the appropriate target organism. But the patient suffered side effects unnecessarily from the novobiocin, so they determined that it was "ineffective as a combination" but they were dealing with a drug that was effective by dictionary definition but it became less effective in combination. In addition, the combination presented unnecessary risks.

It was considered an "ineffective" drug which did not comply with the standard of effectiveness required in the 1962 statute.

Now, you gentlemen have testified that the one major study indicates it really does not have much use at all. So that is a much stronger case than the fixed combination antibiotic cases, it seems to me, is it not?

Dr. MILLER. Senator Nelson, I think you have stated the case very clearly. We do have criteria for measuring the benefit versus risk when we treat patients. We can measure morbidity, we can measure mortality, and I would like to make here a plea for establishing diabetes registries, registries for any kind of disease in which we can document the amount of illness that this disease is producing, the number of days lost from work, and the mortality. I think it is a crime that we spend $100 billion a year on medical care, but we do not have the kind of cost accounting that any ordinary industry would ask for.

The National Center for Biostatistics has a budget of less than $10 million a year out of a total cost to the medical public of $100 billion, and I would ask and plead that this center be adequately funded, that diabetes registries be set up throughout the country so that we can tell on a total population basis whether the introduction of a new agent does indeed reduce morbidity and mortality.

I think this is an obvious suggestion.

Dr. KLIMT. The Food and Drug Administration has in fact considered using Public Law 480 funds in Yugoslavia to conduct what amounts to a repetition of the UGDP under slightly different conditions, precisely because in Croatia there is a diabetes register available.

Senator NELSON. Did anyone else want to comment on the question of whether or not, in your judgment at least, in light of the studies available, you believe these drugs—the new generation of drugs is in the

same drug class—meet the standard of safety and efficacy pursuant to the statute.

Does anyone else want to comment?

Dr. PROUT. I think one point that was made by Dr. Chalmers should be emphasized again. At the end of his statement he said, we really have not seen the facts. On the basis of our knowledge of this class of drugs, it seems unlikely that they have a use but we do need to see the facts before we prejudge the issue.

Senator NELSON. Do you mean you need to see the adequately controlled studies of the new generation of drugs?

Dr. PROUT. Correct.

Senator NELSON. Well, that is the point I am making. If those studies have not been made——

Dr. PROUT. Then the case for licensing them has not been made.

Senator NELSON. Then they do not qualify, in your judgment, to get into the marketplace at this time until those studies are completed. Is that what you are saying.

Dr. PROUT. Correct.

Senator NELSON. Does everybody agree with that?

Dr. CHALMERS. Yes.

Mr. GORDON. I have one question.

Do the oral hypoglycemic drugs induce weight gain?

Dr. KLIMT. Tolbutamide does not particularly induce weight gain, certainly less than insulin. Phenformin has initially the opposite effect. It has a nauseating taste, a metallic taste, and it usually is connected with a weight loss. This is why in certain groups it has been quite popular, and in the UGDP had unusually low weight gain, but a weight gain or weight loss, we are not talking about incentives here for either one. Insulin, which is the greatest sinner, leading to the greatest weight gain, has no greater mortality than a placebo diet controlled group.

So, this is not the center of this problem.

Dr. PROUT. And to continue that line of thought, diet alone on occasion resulted in the greatest weight loss.

Senator NELSON. Thank you very much, gentlemen, for your very useful, valuable testimony. We appreciate your taking the time to come.

We will resume the hearings tomorrow morning at 10 o'clock in the same hearing room.

[Whereupon, at 1:10 p.m., the subcommittee recessed, to reconvene at 10 a.m., Thursday, September 19, 1974, in room 318, Russell Senate Office Building.]