COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

HEARINGS

BEFORE THE

SUBCOMMITTEE ON MONOPOLY

OF THE

SELECT COMMITTEE ON SMALL BUSINESS

UNITED STATES SENATE

NINETY-FOURTH CONGRESS

FIRST SESSION

ON

PRESENT STATUS OF COMPETITION IN THE PHARMACEUTICAL INDUSTRY

PART 28

JANUARY 31, JULY 9 AND 10, 1975

ORAL HYPOGLYCEMIC DRUGS
[CONTINUED]

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APPENDIX

HEARING DATES

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

(Present Status of Competition in the Pharmaceutical Industry)

FRIDAY, JANUARY 31, 1975

U.S. SENATE,
SUBCOMMITTEE ON MONOPOLY OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to recess, at 10:07 a.m., in room 1114, Dirksen Senate Office Building, Senator Gaylord Nelson (chairman of the full committee) presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist, and Kay Klatt, research assistant.

The CHAIRMAN. Today the Monopoly Subcommittee of the Senate Small Business Committee is resuming its hearings on the oral hypoglycermic drugs initiated on September 18, 19, and 30 of last year.

Our witnesses today will discuss recent studies dealing with the safety, efficacy and usefulness of this class of drugs. The list of witnesses includes four members of the committee selected by the internationally renowned Biometric Society as well as a member of the Mayo Clinic.

Additional witnesses to appear are Mr. Neil Chayet and Dr. Robert Bradley, counsel and chairman respectively of the Committee on the Care of the Diabetic.

Our first witness this morning is Dr. Colin White, professor of public health, Yale University School of Medicine, New Haven, Conn.

Dr. White, your statement will be printed in full in the record, and you may present it however you desire, and extemporize as much as you wish.

Would you identify the organization you represent for the record, or first, for the reporter. Perhaps each of you, starting on my far right, would identify yourself for the reporter, so if you address yourself to some question we shall be able to identify you.

Dr. MEIER. I am Paul Meier, professor of statistics at the University of Chicago.

Dr. RICKETTS. Dr. Ricketts, University of Chicago.

Dr. WHITE. Colin White, professor of public health, Yale University.

Dr. ZELEN. Marvin Zelen, professor of statistical science, State University of New York, Buffalo.

Dr. PALUMBO. Pat Palumbo, Mayo Clinic. [The statements and observations made in this testimony are my own and do not necessarily represent official policy of the Mayo Institution.]

The CHAIRMAN. Thank you, gentlemen, for taking the time from your busy work to come here and testify today.

Now, if each of you, when you speak, would pull the microphone up closely and speak directly into it, we shall be able to hear you.

Go ahead, Dr. White.

STATEMENT OF COLIN WHITE, M.D., PROFESSOR OF PUBLIC HEALTH, DEPARTMENT OF EPIDEMIOLOGY AND PUBLIC HEALTH, YALE UNIVERSITY SCHOOL OF MEDICINE, NEW HAVEN, CONN.

Dr. WHITE. Senator Nelson, I am the chairman of a committee which was appointed by the Biometric Society and funded by the National Institute of Health to carry out the following mission: One, to make an in-depth assessment of the scientific quality of the UGDP study and in particular of the biometric aspects of the design, conduct, and analysis of the trial; two, to make a similar assessment of other controlled trials of oral hypoglycemic agents.

The CHAIRMAN. Would you identify the Biometric Society in at least a brief description so that the record will be clear on that.[1]

Dr. WHITE. The Biometric Society is an international society of people who are interested in the application of statistical data to biological problems.

The CHAIRMAN. Who are the members? That is, what is the eligibility of your membership?

Dr. WHITE. Membership is attained by application and the committee decides the qualifications of those who wish to join. In general, membership is governed by interest in the work of the society.

The CHAIRMAN. Are there any special required scientific qualifications?

Dr. WHITE. I think an expression of interest is all that is necessary.

The CHAIRMAN. Is this an international society?

Dr. WHITE. It is.

The CHAIRMAN. And are you president of this society?

Dr. WHITE. No, I am not. I am chairman of the committee that was appointed by the society for this particular purpose.

The CHAIRMAN. And the society selected the members of the committee of which you are chairman for the purpose of evaluating the UGDP study?

Dr. WHITE. Yes.

The CHAIRMAN. Go ahead, doctor.

Dr. WHITE. The committee consisted of six members: John P. Gilbert, Harvard University; Paul Meier, University of Chicago; Chris L. Rumke, Free University, Amsterdam; Rodolfo Saracci, Pisa, Italy; Marvin Zelen, State University of New York at Buffalo; Colin White, Yale University.

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[1] See Biometric Society study, page 13337.

The full committee met on six occasions over a 2-year period and has completed a report which will be published on February 10 in the Journal of the American Medical Association.

The work of the UGDP is still in progress and I think it is fair to say that diabetologists in general await with interest the findings on the treatment by insulin. There has never been a study of comparable scope and thoroughness on the long-term effects of this agent in subjects with maturity-onset diabetes. In the meanwhile, however, controversy has arisen about the data concerning tolbutamide.

The committee saw as its main task the investigation of the reported excess cardiovascular mortality in the subjects receiving this drug. It is interesting to note that the UGDP presented results on phenformin which are quite comparable to those on tolbutamide: the death rate from cardiovascular causes was approximately the same in the two cases. The findings on phenformin, if one can judge from the absence of criticism, appear to have been accepted by medical scientists, even if they have not so far been translated effectively into medical practice. Yet these findings also were made by the UGDP using the methods that have come under heavy criticism when applied to tolbutamide.

Because of the many factors which influence survivorship in a chronic disease such as maturity-onset diabetes, careful methods of investigation are needed, and, in particular, control groups are essential. Consequently we reviewed only such trials as were controlled. It then became clear that the major study to consider, other than the UGDP, was the study in Bedford England, organized by Dr. H. Abby Keen and Dr. R. J. Jarrett. It should be said at once, however, that the Bedford study, based on 125 patients in each of the two treatment groups was not comparable in size or in detail to the UGDP in which approximately 200 patients were followed on each of five treatments.

The work of the committee appointed by the Biometric Society fell into four sections:

One: Visits were made to the UGDP coordinating center and to two of the cooperating clinical centers to study methods used in the trial. Two: The methods and findings of the UGDP study were discussed with several authors who had written about them, and the Bedford study was discussed with Dr. Keen and Dr. Jarrett. Three: The published criticisms of the UGDP were reviewed in detail. Comparable criticisms of the Bedford study do not exist, though several of the major criticisms made about the UGDP would apply a fortiori to the Bedford study. Four: New analyses were made of the data from the UGDP and Bedford studies, the data being kindly made available by the directors concerned.

Critics have pointed out that in the UGDP study the total mortality was not significantly higher in the tolbutamide group than in the placebo group, even though there was a significant difference in the case of deaths from cardiovascular causes. We consider that this criticism has some weight but is not convincing. Criticisms that have been commonly made but which, in our view, are not correct, are:

One: The finding of excess mortality in the tolbutamide group was due to the data obtained from just a few clinics. These are objections we do not find valid.

Two: The studies of Keen et al. and of Paasikivi contradict the UGDP.

Three: The baseline differences among the treatment groups account for the finding of the adverse effects from tolbutamide. On this point I might remark that none of the criticis, to my knowledge, has given serious consideration to the multiple logistic method that was used by the UGDP to take the effect of baseline risk factors into account. Until they do this they have not carried out an adequate review of the UGDP analysis.

The CHAIRMAN. And your group did do that?

Dr. WHITE. Yes, we did.

Four: The findings on the effect of tolbutamide are flawed by the failure to adapt dosage to individual need.

Five: The evidence was not adequate to justify the discontinuation of the oral drugs.

In our analysis of the UGDP data we have used the same multiple logistic model as was employed by the UGDP investigators, but have taken additional variables into account to allow for the time each subject was under study and for differences between clinics. We confirm the principal finding from the simpler study of failure rates; namely, that the cardiovascular death rate was higher in patients receiving tolbutamide than in those receiving placebo. This difference remains after adjustment for the effect of baseline variables and cardiovascular risk factors.

We have also made an analysis in which the extent of adherence to assigned treatment was taken into account. The highest death rate was found in the tolbutamide group who adhered 100 percent to their treatment and who did not modify the dose.

In an analysis of the data from the Bedford trial we found no difference in death rate between the placebo and the tolbutamide group. As indicated above, we do not interpret this failure to find a difference as a contradiction of the more thorough UGDP study.

The conclusion of the committee is that it remains with the proponents of the oral agents to conduct scientifically adequate studies to justify the continued use of such agents.

The CHAIRMAN. Well, put in different words, are you saying that it is the judgment of the Biometric Society that it was a statistically valid sample, and a scientifically conducted study, and that the results of the study—are the conclusions valid? Is that what you are saying?

Dr. WHITE. Yes. We support the principal findings of the UGDP study. We do make some minor criticisms in the report, but we do, in general, support the main finding.

The CHAIRMAN. And the main finding is what?

Dr. WHITE. That there is an excess mortality in the group receiving tolbutamide as compared with the group on the placebo.

The CHAIRMAN. Well, did you find any evidence at all that the oral hypoglycemic drugs retarded or prevented vascular complications of diabetes?

Dr. WHITE. That aspect of the study is one that we did not undertake. We considered that our main responsibility was to look into

the question of mortality effects. There is evidence still to come in on the long-term effects of the various treatments that were used.

Mr. GORDON. One question.

You say it remains with the proponents of the oral agents to conduct scientifically adequate studies to justify the continued use of such agents.

Now, when we had the UGDP people here before us, they stated that they discontinued the use of these agents because they found it was ethically untenable to keep on giving these drugs to people because they were satisfied that it was causing a lot of harm.

How do you feel about that?

Dr. WHITE. I think that if the group decided that it was ethically untenable, that would settle the question then and there as far as public policy were concerned. If they could persuade a responsible group otherwise, then the only kind of evidence that would be acceptable to us is evidence obtained from a controlled trial.

The CHAIRMAN. Any of you gentlemen may comment on this.

Is my memory correct that the UGDP study then concluded that diet was a better way of managing the problem than by tolbutamide and other oral hypoglycemics? Was that their general conclusion?

Dr. WHITE. Yes. I think that is a question on which Dr. Ricketts would have a more valuable opinion than I have.

Dr. RICKETTS. Well, I suppose it was done because tolbutamide apparently was no better than diet.

The CHAIRMAN. Than diet?

Dr. RICKETTS. Yes. And since it was a little dangerous they would say naturally after a certain number of deaths that they had better stop.

The CHAIRMAN. The general conclusion of the study was that diet was better than tolbutamide or oral hypoglycemics of any kind. Is that correct?

Dr. RICKETTS. Well, I am not quite sure that is the way to put it. I think I just said, and I guess I will have to repeat it, that tolbutamide was no better than diet, and if that is true, and if it looked as if the tolbutamide was rather dangerous, then anybody would say, let us stop tolbutamide and do what we can with the diet.

Does that answer your question?

The CHAIRMAN. Yes.

Dr. MEIER. There is one point I would like to emphasize, and that is that neither our committee, the supporters of the UGDP, nor those who think it was an invalid study, believe that this is a simple question. It is complex, and I do not think it is capable of a simple answer of the form that was suggested, namely: "Here is a drug that is of no value. It is toxic. We ought to abandon it."

There are special subgroups of patients who are not successful with diet, are unable to take insulin, and I think most of the comments before this committee and elsewhere have pointed to such subgroups. For these, tolbutamide may have definite value. But the question of whether it should be used more widely, as it now is, remains difficult also. It is the case that the UGDP investigators themselves were not unanimous about the desirability of dropping tolbutamide from the UGDP study. The discussion that went on there was very well described in a paper by one of the participants,

Dr. Theodore Schwartz.[1] The tension, the pulling and hauling, the major differences of opinion that led to that final decision, must all be taken into account in trying to interpret the meaning of that decision. It was judged likely that tolbutamide was toxic; but the evidence was not considered conclusive.

So I do not think we can say that there is a clear, flat conclusion that comes out of this, and I think reasonable people may come to somewhat different conclusions.

The CHAIRMAN. Clear conclusions about what?

Dr. MEIER. About whether tolbutamide should be abandoned by all physicians in the treatment of diabetes.

The CHAIRMAN. That really is not the issue, is it?

Dr. MEIER. I think the issue is what we ought to do, not whether we have reached a firm conclusion. I do not think we have reached a completely firm conclusion as my statement will show. I deplore the fact that we are not in a position to reach a firmer conclusion than we now have, but I would support the final statement of the Biometric Society committee's report, which suggests that a new study might be conducted. I think it would be ethically legitimate to conduct a new study. I myself think it is not ethically legitimate to continue to use the drug without a new study.

The CHAIRMAN. The issue is not whether you should prohibit its use under any circumstance on any patient in any situation. The question is, as a general proposition, should you use it in those cases where the patient situation can be managed by diet?

For example, Dr. John Davidson said that at the Grady Memorial Hospital it was finally concluded after the study—I think they had some 6,500 patients, which I believe was the largest group in the country—that they would take them off the drug and if my recollection is correct their patients were better managed on diet. He said it was tough medicine to swallow because they had lived with oral hypoglycemics, thought they did well, studied the UGDP study, which, they concluded, was right.

Then, in a more precise answer—I believe I am correct, and if I am not, I will correct the record—he thought that maybe in a very, very small percentage of cases, I think he said it might be 1 percent or less, an oral hypoglycemic would be indicated to be used. He did not state what that case was, so I do not know whether that was an insurance policy statement or not.

But in any event, is that not the question: Not whether you should abolish these drugs, but whether in those cases where diet can manage the problem, it should be used? And is it not the conclusion of the UGDP study, as well as Dr. Davidson at Grady Memorial Hospital—and the doctor from Mayo will address himself to this question also—that there is a very, very small percentage of cases in which it is indicated, but that it is widely used in cases where it is not indicated.

Is that a fair generalization?

Dr. MEIER. I think the question really is whether the evidence is of such overwhelming clarity that the conclusion reached by these gentlemen should be a regulation imposed by law upon the medical

[1] The Tolbutamide Controversy: A Personal Perspective (Annals of Internal Medicine, 75, pp. 803-806, 1971).

community generally. If we were solidly convinced that tolbutamide were poison, there would be no doubt about it, and if the benefit-risk ratio was definitely proved to be unfavorable, then I think we would seek regulation to prevent its general use.

What I am saying is that I do not think the evidence is that clear. I think that some investigators have come to the kind of conclusion that you described, and not being a physician, I have no independent opinion about whether their experience is one that could be generalized to all physicians. I think there is enough room for doubt that I would be hesitant to seek regulation to determine absolutely that the drug may not be used except in that 1 percent of cases. I do think that there is enough evidence against it that even though we might allow the community to use its judgment with relatively little restriction, that it would only be appropriate to do that as long as we are setting about immediately to settle the remaining doubts.

I am sorry that the state of affairs does not lead me to a feeling that we know all the answers. I think there are important answers we do not yet know, and therefore I would be reluctant to go so far as to say that the use of tolbutamide should by law be restricted to the 1 percent subgroup.

The CHAIRMAN. I do not think anyone is dealing in absolutes here, and of course there are all kinds of medicines in the marketplace which are widely used for nonindicated cases. This, it seems to me, from what I have heard from the experts is what we are talking about here.

The conclusions reached at Grady Memorial Hospital was that there was a very, very small number of cases in which the oral hypoglycemics were indicated, that the large percentage was better managed by diet, and that their results after more than 3 years showed that the patients were better than they were before, and this is what the UGDP study indicates.

I assume you agreed that the study was statistically valid although being a scientist I am sure you want to say that nobody can be absolutely sure, which is of course true. Nobody is absolutely sure about anything, but you do endorse the position of the Biometric Society in their evaluation of the UGDP study, is that correct?

Dr. MEIER. Let me say that I wholeheartedly endorse the report that the Biometric Society Committee put out, and I will discuss that further in my statement.

The CHAIRMAN. Dr. Palumbo, did you want to comment?

Dr. PALUMBO. May I?

As a physician and clinician who is involved in the treatment of diabetic patients, I think that we have to make a reasonable judgment on the basis of a randomized clinical trial such as the UGDP as to what we are going to do for the patient who sits in front of us; and the decision here is based upon the first principle that each physician is committed to; and that is—if I may use the Latin phrase, "primum non nocere," which translated means, "do no harm."

And therefore, it has to be clear that our treatment is not doing harm to the patient. Now, we may, under unusual circumstances, elect for a risk-benefit ratio, but I think for the majority of our

practice and the practice in this country that it should be that these agents should be curtailed. The UGDP study's conclusions should be accepted.

Mr. GORDON. Dr. Palumbo, did you people at the Mayo Clinic stop using these drugs?

Dr. PALUMBO. We have stopped using them routinely. We were never very "gung-ho" about them in the first place, but we had used them prior to 1970. When the results of the University Group Diabetes Program came out, we accepted the conclusions and adjusted our practice accordingly.

Subsequent to that, a couple of our members of the department of statistics and epidemiology looked into the matter with a whole group of people with Dr. Cornfield in the group, and they came up with the conclusion in 1971 or 1972 that the studies were valid and that the conclusions were justified despite all of the possible, you know, flaws or criticisms you can point out with any prospective study.

We had accepted these conclusions as valid in 1970 when the results were promulgated. We do not use the agents routinely, only under the unusual circumstance if a patient says, I absolutely refuse to take insulin, then we usually assign them to an oral hypoglycemic agent. I still have this reservation that we are using these agents solely to control blood sugar; and we are not absolutely convinced that the control of blood sugar makes any difference anyway.

In fact, that is one of the findings from the UGDP study that perhaps blood glucose did not have any relationship to complications, and so you are introducing an agent to control blood sugar which of itself may be harmful to the patient.

I think there is no question that this agent has to be curtailed.

The CHAIRMAN. Curtailed, did you say?

Dr. PALUMBO. Curtailed, c-u-r-t-a-i-l-e-d.

The CHAIRMAN. Thank you very much, Doctor.

We will proceed to the next witness, and as I stated a few moments ago, feel free to comment on any question asked or any statement made by other witnesses.

Our next witness is Dr. Henry Ricketts, University of Chicago Medical School, Department of Medicine.

Dr. Ricketts, we are very pleased to have you here this morning. You may present your statement however you desire.

STATEMENT OF HENRY T. RICKETTS, M.D., PROFESSOR OF MEDICINE EMERITUS, UNIVERSITY OF CHICAGO MEDICAL SCHOOL

Dr. RICKETTS. Thank you very much.

I feel a little embarrassed to read the first paragraph, but I suppose I ought to declare myself as to what I am.

I studied—well, first of all, I am emeritus professor at the University of Chicago Medical School. I have studied diabetes and cared for patients with diabetes and conducted researches in this specialty for 34 years. I have been president of the American Diabetes Association and cofounder and president of the Chicago Diabetes Association.

I have served on the study section of endocrinology and metabolism, Grants Division, National Institute of Arthritis and Metabolic Diseases, and have served as a contributor and an associate editor of the journal "Diabetes." I think that is probably enough.

My connection with the Committee of the Biometric Society was that of a consultant diabetologist, and I attended most of the meetings. I was struck by the thoroughness with which the members of the committee made their investigation. I detected no bias for or against the UGDP study. The committee listened to more who criticized the study than to those who were less opposed or favorable. The committee did not hesitate to ask the coordinating center in Baltimore for raw data when a point was in doubt, and members made trips to the center and to several participating clinics to check methods, procedures, and results. No uncertainty was too small to leave unresolved.

I should remind you that the UGDP was set up to determine whether various treatments for diabetes would minimize the mainly vascular complications that notoriously accompany that disease. It is ironic that a full report dealing with complications has not yet been published because, in the third and fourth years of the study, an alarming preponderance of deaths had accumulated in the tolbutamide group. The investigators, then, per force, had to turn their attention to mortality and survival.

I was not a participant of the UGDP study, but I followed it closely. Despite some imperfections, I think that the results and conclusions of the UGDP have shown tolbutamide and phenformin, and probably their cousins, to be dangerous drugs, especially when taken for extended periods of time. I stand by my opinion of 4 years ago, expressed with the help of a committee of the American Diabetes Association in the editorial statement accompanying the first report of the UGDP. I quote: "The UGDP mortality study shows that death rates were essentially the same in the IVAR group"—I suppose I have to explain that.

Mr. GORDON. Is that the insulin variable group?

Dr. RICKETTS. Yes. I will explain that later.

The UGDP mortality study shows that the death rates were essentially the same in the people who had various dosages of insulin and which maintained more nearly normal fasting blood glucose levels than in the more poorly controlled groups of the placebo and the other groups.

This would appear to mean that efforts to establish good control of hypoglycemia in the kind of population studied had no effect on mortality.

The real lesson of the data is that if diet plus insulin does not reduce mortality below that experienced with diet alone, it is highly improbable that oral hypoglycemic agents will do so.

There is indeed no doubt about the reality of the greater number of cardiovascular deaths observed in the TOLB group as compared with all other treatment groups. Inquiry into the reasons for this has been both intensive and extensive. Aside from the most proximate explanation, that tolbutamide may have been directly and solely responsible, the possibility that the tolbutamide population, by chance and despite randomization, entered the study with more or greater risk factors than the other populations had to be scrupulously investigated.

Although this possibility has, in the opinion of the ADA Ad Hoc Editorial and Advisory Committee, not been excluded, the weight of statistical analysis

makes it probable that the excess cardiovascular mortality in TOLB is attributable either to the drug itself or to unconsidered and unknown factors. In the absence of evidence for the latter, suspicion would naturally attach to tolbutamide.

The mortality study is at least suggestive enough to put a damper on what appears to be the indiscriminate use of all oral hypoglycemic agents in the treatment of mild or moderate, adult-onset diabetes. Although tolbutamide, for practical reasons, has been the only sulfonylurea drug investigated by UGDP.

This is 4 years ago.

The chance that other compounds of this family may be similarly involved cannot be dismissed despite differences in molecular structure.

It would not be justifiable at this point, however, to prohibit the manufacture and use of sulfonylurea drugs, for they will probably continue to fill a need in special circumstances.

If these drugs are dangerous, what course should we take? You have just heard that their manufacture of the drug should not be forbidden, and for reason. For example, how do we treat a diabetic patient who ought to be taking insulin but is living alone with a broken, or amputated, or paralyzed arm that prevents him from using a syringe and needle? One who is blind and cannot measure his dose of insulin? One who is old and tremulous? One who is mentally disturbed? And finally, one who refuses to take insulin.

In another vein, there are diabetics who are engaged in hazardous occupations and ought not to take insulin for fear of reactions.

We ought to make allowance for these patients, even though the oral agents are not very effective and, I believe in the long run, may be harmful.

The CHAIRMAN. Does this list of exceptions include most or all of the exceptions that you could think of?

Dr. RICKETTS. Well, I think so, yes. I might think further, but that is quite a number.

The CHAIRMAN. All right, please go ahead.

Dr. RICKETTS. But if we continue to make these agents available, as I think we must, how do we protect other diabetics who would like to use them but should not?

Insulin comes to the patient with a package insert that carries a great deal of information, including certain warnings. The oral agents come to the patient in silence because they have been regarded as innocuous, needing no instructions except the doctor's directions for dosage and timing. This must change.

But it is the physician who should lead the way, and I hope that the report of the Biometric Society will in time convert the many current unbelievers. Meanwhile—and this might seem to be preposterous—it might not be too radical to ask the FDA, under proper authority, to transfer the oral hypoglycemic agents to the circumscribed schedule II of dangerous drugs along with barbiturates, amphetamines, and certain narcotics.

Physicians might learn that the oral agents are not exactly safe, and the requirements of BNDD prescriptions, if for dubious need, might become a salutary nuisance. This arrangement, of course, would have holes in it—and I can see some—but it might have the effect of helping to reduce the use of a product that too many patients could well do without.

The CHAIRMAN. Thank you very much, Doctor. Our next witness is Dr. Paul Meier, Department of Statistics, University of Chicago. Dr. Meier.

STATEMENT OF PAUL MEIER, PH. D., PROFESSOR OF STATISTICS, UNIVERSITY OF CHICAGO, CHICAGO, ILL.

Dr. MEIER. Mr. Chairman, I speak as a member of the Biometric Society Committee on biometric aspects of controlled clinical trials of hypoglycemic agents, which report is under discussion today.

Professor White has outlined our problem and our findings. Professor Zelen will speak about some of the particular criticisms made of the UGDP report. I shall speak a little more generally about the role that I see for clinical trials in guiding our decisions about modes of therapy.

It happens that in March of 1970 I testified before this committee on the subject of risks of thromboembolism due to the use of oral contraceptives. I spoke then of the deplorable lack of prospective controlled clinical studies on the effects of oral contraceptives. I discussed possible reasons for that lack. Let me quote a few lines from that earlier testimony.

I said:

> Frankly, the required research, although important, is not especially appealing to scientists. It is not fundamental and it is not exciting. It is difficult, it is expensive, and it is fraught with the risk of attack from all sides. Who would willingly prepare himself for such a study, make an application to be weighed competitively with others on scientific merit, and risk the loss of support halfway through the study when a review committee with different views or priorities comes to consider renewal of support, all this when he stands to gain so little in scientific recognition or otherwise?
>
> Evidently, for whatever reasons, there is no sound body of scientific studies concerning these possible effects available today, a situation which I regard as scandalous. If we proceed in the future as we have in the past, we will continue to stumble from one tentative and inadequately supported conclusion to another, always relying on data which come to hand, and which were not designed for the purpose. The planning of better studies is difficult, and the recruitment of investigators willing to commit their efforts to these purposes may be more difficult still. I believe both are possible and essential to the public welfare.

At the time those words were written, I had no knowledge of the UGDP, but they could scarcely have been more apt.

Let me interpolate in my prepared statement my warm commendation for the group of physicians and statisticians who undertook the UGDP study. With whatever limitations, this is far and away the best evidence we have to date on tolbutamide toxicity. It is an excellent study. No one study can answer all of the relevant questions, but that is scarcely the fault of these investigators, and I am led to modify my statement about the lack of excitement and interest that such studies could generate.

I think this group has shown us that there is new ground to be broken through some of the work that they have done in the theory of the conduct of controlled clinical trials, and they have also contributed substantial new knowledge to an important medical problem.

I return to my statement.

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

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.

In the latter case, however, I can see no alternative to the initiation of a new clinical trial, conducted by physicians unconvinced by the first one. I should expect, in any event, that both physicians and patients should be made as fully informed about the evidence as is feasible.

I go so far as to hope that the experience to date with oral hypoglycemic drugs may convince us that clinical trials should be a continuing component of drug surveillance for any drug, from the first day of its release, and so long as substantial doubt about the balance of risks and benefits remains.

The CHAIRMAN. I think everybody would agree that your last sentence would state an ideal situation which we would all hope someday would be achieved.

Dr. MEIER. Senator, I would hope that day would be early rather than late. I spoke sentiments like this 5 years ago before this committee. I described in some detail ways in which authority might be given to the FDA, and methods by which the funds could be allocated to such studies. I was pleased to see that in testimony in September Dr. Prout argued along quite similar lines. I do not think I see anything in the line of legislation that would tend to move us in that direction, and I would hope there may be some.

The CHAIRMAN. I do not think we need the legislation, but probably do need the money. But I think there is no doubt that it would be very sound to start good clinical trials once a drug is marketed, because if there is not, we would have to rely upon the reports of physicians' observations around the country. It may take a long time for individual physicians to accumulate enough data to associate with some adverse effect because individual observations would have to be reported through medical journals or to each other, and that would take quite a while. Your recommendation is very sound and I do not believe anyone would disagree with you on that.

Dr. MEIER. I would just like to point out that in this case it depended upon an interested academic group, physicians and statisticians, to decide that it ought to be done and to convince an NIH study section that it ought to be funded, at quite a high price, in NIH terms. That seems to me to be an unacceptable way to operate.

If such a drug is to be marketed, the sales of that drug not simply the taxpayers' money, should contribute to carrying out a study. I think there are proper ways in which that obligation could be laid upon the manufacturers who are selling the product to see that the funds are supplied, not because they feel like it, but because they must do so. And that is the kind of legislation I would hope to see.

The CHAIRMAN. As you might recall if you read the testimony in addition to the testimony you gave yourself 5 years ago, when I raised the question about studies to determine how many micrograms of estrogen could be put into an oral contraceptive and still be effective, the answer was, well, it would be very hard to get volunteers to run that risk. I do not think that is the case. I think there would be plenty of volunteers who are seriously concerned about whether or not they got pregnant now or 6 months later, who would be put into a test to see whether you could dramatically reduce the micrograms of estrogen in the oral contraceptive, and it seems quite

unfortunate that so far as I know, no experiment of that kind has yet been made, and we had 150 microgram pills in the marketplace, while England went ahead with 50. We took testimony from an English scientist.

But you are absolutely right, we have not done the kind of controlled studies we ought to do.

Thank you very much for your testimony.

Our next witness is Dr. Marvin Zelen, Statistical Laboratory, SUNYAB, Amherst, N.Y.

STATEMENT OF MARVIN ZELEN, PH. D., PROFESSOR OF STATISTICAL SCIENCE AND DIRECTOR, STATISTICAL LABORATORY, STATE UNIVERSITY OF NEW YORK AT BUFFALO

Dr. ZELEN. Senator Nelson, thank you for this opportunity to appear before this committee. My general comments will be divided into two parts.

The first topic I wish to comment on is how is it that able and respected clinicians can disagree with the interpretation of the UGDP data? The tolbutamide cardiovascular death rate is more than double compared to other treatments. Yet many clinicians who treat adult onset diabetes find it difficult to accept such a figure. For many of them, this elevated cardiovascular death rate does not appear to have been perceived in the clinic.

I would like to examine other factors which may lead to elevated cardiovascular mortality. According to the UGDP data, the cardiovascular death rate for individuals above the age of 53 is approximately five times that of individuals 53 or younger; people with arterial calcification at time of diagnosis have four times the cardiovascular death rate compared to those without arterial calcification; the initial glucose tolerance test, called GTT, as used by the UGDP investigators, shows that those with a GTT above 723, the median value, have double the rate of cardiovascular deaths compared to those who have a GTT below the median; men have a doubled cardiovascular death rate compared to women. Although the numbers quoted are rounded for simplicity, it is clear that in the clinic there are many factors simultaneously influencing cardiovascular deaths. Several of these have greater or equal effect on the cardiovascular death rate compared to the effect of tolbutamide. As a result it would be difficult for a clinician to perceive an elevated cardiovascular death rate associated with tolbutamide. Such an effect would be almost completely obscured by these other important factors. Only if there is careful and structured recordkeeping on a large number of patients would a changed cardiovascular death rate of two to three be detected. The analysis of such multifaceted data requires more sophisticated data analytic methods than those in common usage by clinicians.

Next, I wish to comment on some features of the Biometrics Society report. A criticism of the original UGDP analysis is that it failed to explore the effects of several factors acting simultaneously on the cardiovascular mortality. Our committee did in fact consider this matter very carefully. We found that when one examines the

group of older women, age greater than 53, the tolbutamide cardiovascular death rate is almost five times that of the placebo group. It is in this group of older women where the tolbutamide excess cardiovascular mortality is most dramatically shown.

Finally, I wish to comment on the problem of planning and analyzing clinical investigations in which patients are expected to be on chronic medications for a period of many years. It is important in planning these long-term studies to allow the clinician to change the medication if it is in the best interests of the patient. This can result in an altered dose or even a change in the medication. The UGDP protocol did allow the clinician this freedom. A protocol which does not allow this flexibility may not be in the best interests of the patients under study.

The CHAIRMAN. In evaluating this study, did you or did you not conclude that the authority of the clinician to alter protocol, which I assume some did, had any adverse effect, or did it prejudice the study in any way?

Dr. ZELEN. No!

In addition to modified or changed medications, patients may, on occasion, not take their medication at all. In the Biometrics Report, these problems were examined in considerable detail. It is our conclusion that the greatest statistically significant difference between tolbutamide and placebo occurs in the group who have taken their prescribed medication in exactly the manner specified in the protocol for the entire period of followup.

To conclude, I wish to state that the interpretation of the data is difficult due to the small number of deaths relative to the total number of patients. In our endeavors we have analyzed the data in many other ways which have not been put in our final report. Our conclusion is that the weight of evidence points to tolbutamide as being responsible for the excess cardiovascular mortality.

If I may, Senator Nelson, I would like to comment on some general aspects of clinical trials that have surfaced during our discussion.

Obtaining scientific evidence using the clinical trial method is the most difficult way of obtaining scientific evidence and should be used only as a last resort. I speak from long experience. My research group, the statistical laboratory at the State University of New York at Buffalo, is involved in over 60 clinical trials at the present time in all areas of cancer treatment. It is very difficult, time consuming, there is a great deal of aggravation arising from the vagaries of the funding agencies.

I think to mount long-term studies, either of oral hypoglycemic agents or anything else, should only be taken after much careful thought and after all other ways of attempting to obtain such evidence have been thoroughly examined. Mounting these trials should not be done very casually.

The CHAIRMAN. Thank you very much.

Our next witness is Dr. Palumbo, the assistant professor of medicine, Mayo Medical School, Rochester, Minn.

You may present your statement however you desire and extemporize on it if you desire.

STATEMENT OF P. J. PALUMBO, M.D., ASSISTANT PROFESSOR OF MEDICINE, MAYO MEDICAL SCHOOL

Dr. PALUMBO. The comparison of treatment for a disorder can only be evaluated through controlled, randomized, clinical trials.

Hints and leads from retrospective studies can be extremely valuable in leading to a new hypothesis and may be the basis of justification of a randomized trial. However, standing alone they cannot form the basis of any firm conclusions concerning treatment effects.

The preliminary analysis of our data of the incidence, prevalence, and mortality of diabetes mellitus in Rochester, Minn., between 1945 and 1970 contains some hints that survivorship may be lower in diabetics on oral antidiabetic agents, and we grouped them all together: These are sulfonylureas and phenformin.

Mr. GORDON. About how many people were you following?

Dr. PALUMBO. We were following over 1,000 [1,090 to be exact] patients with diabetes over that 25-year period. There were only 138 on oral agents out of that group.

Mr. GORDON. How did they fare?

Dr. PALUMBO. Their survivorship was less, but however there are group differences that have to be taken into account, and therefore we cannot make any firm conclusions. Our statisticians are very loath to leave themselves open to the criticism that a retrospective study can lead to firm conclusions [regarding treatment].

All we can say is it suggests or hints that the oral agents plus other factors may affect survivorship of the diabetic. As a clinician—and I am deviating from my statement—as a clinician, I would expect that the oral agent group would be similar to the diet group, the same group, the same ischemic heart disease, the same hypertension, et cetera, and I would have expected them [patients on oral agents] to have the same survival curve as the patients on diet alone; that is, the oral agent group should have been similar to those on diet alone.

However, the survivorship of those patients on oral agents when compared with a group of the general population, similar in age and sex for our midwestern area, the death rate or rather relative survivorship for the group of diabetic patients showed that the oral agent group was much lower.

The CHAIRMAN. Now, wait a minute. You said the death rate and survival. You cannot have it both ways.

Dr. PALUMBO. Their survivorship was lower.

The CHAIRMAN. The higher incidence of death.

Dr. PALUMBO. That is right, and in the first 3 years there was a difference in the death rate for cardiovascular mortality in the oral agent group, or there was a higher death rate from cardiovascular deaths.

The CHAIRMAN. This was retrospective?

Dr. PALUMBO. This was retrospective. The groups are not comparable. The insulin group is younger, has a higher blood sugar, and in our study has a higher percentage of stroke, actually, which should favor a poor survivorship. The oral agent and diet group—

and remember we do not have a placebo to compare this with, so that for the diet-oral agent group, they are pretty comparable with regard to ischemic heart disease. There is less stroke in the oral agent group than the diet group at the time of diagnosis of diabetes, but retinopathy was higher in the oral agent group, and blood pressure was 6 percent higher in the oral agent group.

These are group differences that have to be taken into account. All we can say from our study is that it suggests that the oral agents may be one of the factors that may adversely affect survivorship in the diabetic.

Such an observation—I am returning to my statement now—such an observation would point to the need for controlled, randomized clinical trials to study the possible adverse effect of various treatments on survivorship in the diabetic.

The University Group Diabetes Program was a randomized trial study to evaluate the influence of treatment on diabetic complications. A statistically significant, adverse effect on survivorship was noted after patients had been on tolbutamide and phenformin for 5 or more years. These data have been reviewed by others, and the review was published in the journal, I believe, "Diabetes," by Dr. Cornfield [the journal was JAMA, 1971] and also had been reviewed by our own statisticians, and the conclusions have been found to be sound. I have to rely on their conclusions because I am a clinician and not an epidemologist or statistician.

Was there a question, Senator?

The CHAIRMAN. You concluded that the UGDP study was sound?

Dr. PALUMBO. The conclusions are sound; that is correct. In my opinion as a diabetologist, another randomized trial study of treatment in diabetes is not ethically justified, as the data from the University Group Diabetes Program clearly indicate, from my standpoint, an adverse effect of the oral antidiabetic agents on survivorship in the diabetic. The use of these oral agents, therefore, should be curtailed.

The CHAIRMAN. How long after the UGDP study was published did the Mayo Clinic conclude that they would not use the oral hypoglycemic agents except in special circumstances?

Dr. PALUMBO. There was a meeting of the American Diabetes Association, I believe—and maybe Dr. Ricketts can correct me—in June 1969, was it, that published those results, or maybe it was the following year.

Dr. RICKETTS. 1970, actually.

Dr. PALUMBO. It was 1970, and subsequent to that time we began to inform all patients about the risk involved with the use of the oral agents. We took patients off the oral agents and tried them on diet alone after informing them of the possible risks involved. We have not followed those patients to see how they have done, except that our own clinical impression is, as Dr. Davidson has already reported from his committee, that they do just as well, and I did not feel that a lot of these patients needed to be on oral antidiabetic agents.

When the plasma glucose or their response to treatment to diet has not been satisfactory, we have advised insulin therapy, because we feel insulin at least does no harm. Even if it has been shown not to do any good, at least it does not do harm. It does protect the pa-

tient from the acute complication of ketoacidosis if they are prone to that. We would never have used these oral agents in the ketoacidosis-prone patients anyway, but in any event if I were to err now, I would err on letting the blood sugar drift a little bit upward and not worry so much at keeping it at a certain particular level.

And therefore, our observed policy has been to curtail the use of these agents. I do not use them routinely. I take patients off when they are referred to us. We warn them about the possible hazards, and we transfer them to insulin therapy. We are more a tertiary center than a primary center. We are describing here in the study patients alluded to, our own patients from Rochester, Minn., from a population of about 50,000, so we do provide primary care for that population, but the majority of our patients that we see in the diabetes clinics, which number about 8,000 to 10,000 patients a year would be told exactly the same thing, that the oral agents may be deleterious to their health and that we would recommend, if diet alone does not control their diabetes, that they are placed on insulin therapy.

Most of our patients have been willing to accept this when we have shown them how to administer the insulin. There has been no particular problem.

It certainly would be nice to administer an agent orally and take care of the blood sugar, but unfortunately if the agent has been shown to cause an increased mortality from cardiovascular death, we would be reluctant to use this agent.

As I stated previously, I feel a physician should do no harm.

The CHAIRMAN. Do I understand you are saying that this position is a policy of the clinic?

Dr. PALUMBO. Well, as a member of the diabetes committee of the institution, it is our recommended policy. Obviously, I cannot speak for the 400 or 500 physicians we have on staff. There may be some who might be, but I think we have disseminated the information widely in conferences and through memoranda.

I believe the position is pretty clear that we have accepted the findings of the University Group Diabetes Program, that patients all must be informed about the hazards of these drugs and that only under unusual circumstances would they be prescribed.

There would be very few patients that would not see us in the diabetes clinic, so that it is impossible that a small group of patients might be treated with oral agents. I rather doubt that, since we maintain close contact with all of our colleagues and disseminate information through conferences and memoranda.

The CHAIRMAN. Does anyone on the panel wish to make an observation on any of the points that have been raised thus far in the testimony or on any questions that have been asked.

Dr. RICKETTS. Yes, Senator Nelson, just a rather small point.

It is well known that a great many people, and this is particularly women, are overweight. I mean to say diabetic people. We struggle and preach and do all we can to get them to lose weight, and finally, some of them do. It does not last awfully long but nevertheless they do. And of course if the obesity is controlled, the blood sugar goes down, and this is what we want. And thus it went for a long, long time until tolbutamide came in, and then what happened? Doctors began to give tolbutamide and tell them it is good for them, and

they began to take them. But what did they do? They took their tolbutamide but now they did not think that they needed to diet. And this is very sad. It is a poor outcome of this business we are talking about.

The CHAIRMAN. Thank you.

Dr. Zelen, did you have a comment?

Dr. ZELEN. Yes. There have been some who suggest that another UGDP-like trial be mounted.

The CHAIRMAN. I am sorry. I did not get the first part.

Dr. ZELEN. There have been some individuals who suggest that another UGDP-type trial be mounted. Judging from the experience with this one, it is likely to take 6 to 10 years before any conclusions will be reached.

Furthermore, with the recent change in patient consent, people face the following situation. If an individual comes to a clinician who is participating in such a trial, the physician, by law, has to inform the patient of the risks involved. The scenario would go something like this. The physician would state:

> There are a large group of people in the country who believe that tolbutamide may be dangerous. A study has been completed purporting to show this. However, there is conflicting evidence to believe that the interpretation may be in doubt. Consequently we are going to try again.

Well, I think most people would not like to be part of such a scheme, and it might be very difficult to enlist patient volunteers.

The CHAIRMAN. Well, was there anything in evaluating the UGDP study that would indicate some necessity for repeating the same study?

Dr. ZELEN. In my opinion, no!

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

Dr. MEIER. I would just like to clarify my own position. I have not taken a position on whether there should be restrictions on tolbutamide. What I have said is that if it is to continue to be widely used, then I think it imperative that another study be mounted. I hope I make that clear. It is now being widely used long after the UGDP report was published and discussed. If that situation is to continue, then I would see no ethical choice for those who use it but to mount another study.

Mr. GORDON. But what are they going to do in the meantime? Are they going to keep on using it widely while the 6- or 8- or 10-year study goes on?

Dr. MEIER. That is a matter that I presume the FDA is actively studying right now. The report of the UGDP appeared, received commendation from the ADA and the AMA, but as a matter of fact, the community continued to use the drug. Barring administrative action, I presume they would still continue to use the drug, and I am saying that if there is no action to prevent that, then I think there should be action to further study the matter.

Mr. GORDON. How about the newer drugs that have not been released yet?

Dr. MEIER. I would hope that they would be studied. If they are to be released, I would hope that proper studies would be initiated immediately.

Mr. GORDON. In the Keen study, in the placebo group 30 percent were over 70 years old, and in the tolbutamide group there was 18 percent who were over 70.

According to the Biometric Society report, the difference is statistically significant at the 5-percent level. Do you know the comparable difference in the UGDP? It was much smaller, was it not?

Dr. MEIER. Yes, the UGDP was conducted with very careful randomization, as described in our report. The Keen study used a much more informal kind of allocation scheme, and indeed, in respect to age, the Keen study had a much wider discrepancy between the groups than did the UGDP.

Mr. GORDON. So the baseline characteristics were more similar in the UGDP than they were in the Keen study.

Dr. MEIER. Yes.

Mr. GORDON. I just wanted to clear that up.

The CHAIRMAN. Is there any other observation any of you gentlemen have on any aspect of this?

Well, the committee wants to thank you very much for taking the time to come here and present the results of your study for the record of this committee. We appreciate it very much. Thank you.

If you have anything supplementary that occurs to you that you think will be useful for the record, the record will be opened for another 2 weeks and you may submit it for printing in the record.

Our next witnesses will be Dr. Robert Bradley, chairman of the Committee on the Care of the Diabetic, Joslin Clinic, Boston, Mass., and Mr. Neil Chayet, counsel.

The committee appreciates you gentlemen taking the time to appear before the committee. You may present your statement however you desire. It will be printed in full in the record.[1]

STATEMENT OF NEIL L. CHAYET, COUNSEL, ACCOMPANIED BY ROBERT F. BRADLEY, M.D., CHAIRMAN, COMMITTEE FOR THE CARE OF THE DIABETIC, JOSLIN CLINIC, BOSTON, MASS.

Mr. CHAYET. Thank you very much, Senator.

My name is Neil L. Chayet. I am a member of the law firm of Chayet & Sonnenreich, and I appear as counsel for the Committee on the Care of the Diabetic.

The CHAIRMAN. Counsel for whom?

Mr. CHAYET. The Committee on the Care of the Diabetic.

The CHAIRMAN. Are you also counsel for the Medical Tribune?

Mr. CHAYET. I would be glad, Senator, to submit it, a list of all my clients, if you care to subpena it. I still believe, however, in the concept of attorney-client privilege and the confidentiality of that relationship, which I know does not mean that much around here anymore, but I still value it very highly.

If you care to subpena a list of my clients, I would be glad to provide it. We have many clients and represent many groups, individuals, publications, and others.

The CHAIRMAN. You are the first witness we have had who is embarrassed about whom he represented.

[1] See prepared statement, page 13620.

Mr. CHAYET. I am not embarrassed at all. As I said to you, I am willing to provide it under a proper subpena. I believe in confidentiality and that is my response to that question.

May I continue, sir?

The CHAIRMAN. Go ahead.

Mr. CHAYET. Thank you.

With me is Dr. Robert Bradley, who is director of Joslin Clinic and who is also the chairman of the Committee on the Care of the Diabetic.

I have a written statement which I would like to submit and ask that it be printed in full in the record.

The CHAIRMAN. It will be printed in full in the record as though read and you may present extemporaneously whatever you desire.

Mr. CHAYET. Thank you very much, sir.

This matter has continued now for nearly 5 years and the Committee for the Care of the Diabetic as well as physicians and scientists throughout the country have been engaged fully in this controversy. When my involvement began, it was solely as a lawyer for a client. I now have another interest in this matter which I would like to disclose to the committee at this time.

Since I began handling this matter in 1971 my mother has been diagnosed as a diabetic, and she has become very severely ill and crippled by this disease; and so while I still function as an attorney here, I also have a personal interest in this matter because of this situation.

The Committee for the Care of the Diabetic is a group of leading diabetologists from all over the United States which was formed in November of 1970. It initially sought to deal with the Government administratively before seeking legal counsel.

The CHAIRMAN. Are you saying this was the year that the Committee for the Care of the Diabetic was created?

Mr. CHAYET. Yes, sir. It was created shortly after the results of the UGDP were first brought forth; I did not become counsel until about a year later. It is clear from the record that there was extensive correspondence between Dr. Bradley and the Committee and the FDA in an attempt to settle this matter administratively. These are not litigious individuals. They chose the courts only as a last resort because there was simply no place else to turn.

When I first reviewed this matter from a legal point of view it concerned me that if a doctor continued to prescribe this medication in the face of a package insert which indicated there was an increased risk of cardiovascular disease, it appeared to me, having looked at some recent cases, that such physician could well be sued for malpractice. I have found several cases where the package insert was introduced as expert testimony into evidence. That was my initial concern from the legal point of view; there is, however, a far greater concern, and that is the impact that this entire matter has had on millions of patients throughout the country; it is the fear and the panic that has been caused by a combination of governmental action and the press, and by the great confusion that has swirled around this issue that has really done the damage.

And while the issue of potential malpractice actions is still present, it is now much more a question of how patients react when they

read press reports of deaths allegedly caused by oral hypoglycemic agents. How can they retain any confidence in their physician in light of such reports? We are concerned with not only the protection of the physician from a malpractice action, but of equal importance, the protection of his patient from the actions that have occurred again this very week; actions similar to what occurred in 1970, when premature press releases again heralded this a biased view of controversy. It is most unfortunate, Senator.

The CHAIRMAN. Well, I guess you have made it clear. You are referring to what you believe to be confusion and doubts which have resulted from stories respecting the UGDP study.

Is that what you are saying?

Mr. CHAYET. Is there any question about that Senator? For example, I will quote a UPI report in the Boston Globe, Tuesday, January 2, 1975. The report is pathetically inaccurate: "An international scientific jury has supported the much debated view that the oral diabetes drug used by 1.5 million Americans are probably killing 10,000 to 15,000 of them yearly."

And the inaccuracy is not the fault of the press. It is the fault of those who are giving the releases and the fault of those who have written and released the editorial statement which accompanied the Biometric Report which reviewed the UGDP study.

The Biometric Study, in many ways is a very scholarly study, but what was done with it is most unfortunate. And that is where the problem lies. It is a repeating pattern by those who seek to stifle and muzzle the controversy which nobody can any longer deny.

The CHAIRMAN. I have not seen all of those stories, but the stories I have seen were based upon an editorial that is appearing, apparently, in support of the UGDP study, in the Journal of the American Medical Society. Then the stories were written from that. Now, I have not seen what the journal said, but if the journal story was exaggerated, that would be a matter of whoever reported the story, I guess.

Mr. CHAYET. Well, that is the problem, Senator. It is one exaggeration on top of another. You have the Biometric Study, then someone writes an editorial and refers to "possibly some 10,000 to 15,000 deaths"—no statement of which appeared in the Biometric Study—and then the press reports that an international blue-ribbon jury found 10,000 to 15,000 deaths a year. And I think we are well aware of the political process to know that this is the way it goes; and we in the legal and scientific communities have to take steps to prevent this from occurring. And those steps were never taken in this situation, and I regret that.

The CHAIRMAN. I understand what you are saying. I have been in politics for many, many years, and have been "done in" many, many times. But I have not suggested that we abolish the freedom of the press.

Mr. CHAYET. I guess when we get done in, Senator, we at least have the risk of that because of our public position. But the millions of people out there do not take that risk, and that is why I am concerned about it. That is the point. It is not the press which should be restricted but those who provide the erroneous information to the press.

As for the UGDP study itself, I am not at this point going to discuss its scientific flaws in detail. Although I am a lawyer, not a scientist, I would emphasize, however, something which strikes me as very important; and it is the final paragraph of the UGDP study, which reads: "It should be noted that any conclusion reached in this study pertains only to the type of patients studied"—and a very particular group of people were studied—"and only to the specific hypoglycemic agents used. Extrapolation of findings obtained in the UGDP to other dosage schedules of the same drug"—and dosage schedules other than those used in clinical practice were used in that study—"or to other chemically related hypoglycemic agents not included in this study, must be made on a judgmental and nonstatistical basis."

Now, those are the words of the study itself. And yet, in spite of these words, we see an unfortunate extrapolation contrary to the very words of the UGDP study; and I would only say, Senator, that questions of——

The CHAIRMAN. May I say, just a moment? I was looking at the final paragraph, and the final paragraph, as it reads to me, is: "In conclusion,"—this is the——

Mr. CHAYET. Excuse me, Senator; it is the next-to-last paragraph at page 814 of the study. I am sorry.

The CHAIRMAN. Well, let me say this, so they juxtapose. "In conclusion, we consider, in the light of the UGDP findings, it remains with the proponents of the oral hypoglycemic to conduct scientifically adequate studies to justify the continued use of such agents."

Mr. CHAYET. Unfortunately, you are reading from the wrong study, Senator.

The CHQLRMAN. This is the Biometric Society Study.

Mr. CHAYET. I know. I am not talking about that, sir. What I said very clearly is that I am talking about the UGDP study. You see, this is how it goes.

The CHAIRMAN. I misunderstood.

Mr. CHAYET. This is how the confusion escalates.

The CHAIRMAN. I am sorry I misunderstood you. We will put the two together, so that everybody can read them. Go ahead with your testimony.

Mr. CHAYET. That will be fine, Senator.

As I said, I am not going to concentrate on the UGDP study itself, or even the specifics of the Biometric Study. I only want to make one point, and I would like to make it as clearly as I can. There is great controversy in this situation, and it is not going to go away. It does not matter how many people are lined up on either side—and I am perfectly cognizant of the fact that the press releases describe the blue-ribbon jury of experts who are for the UGDP, and when anybody on the other side is mentioned, they are referred to as a group of practicing physicians. I realize these are subtleties, but they are subtleties that have resulted from the fact that the Government has made a fundamental error in this situation; that is, it has tried to muzzle a controversy, which has been put forth in good faith by very eminent, very learned, and qualified people.

Now, I know that $8 million and 10 years is a long time, and a lot of money, and criticism is difficult. It is not to be given or taken

lightly. But that is the way it is; nothing is going to make this study free from controversy. Nothing thus far has settled this controversy, and Dr. Chalmers can write editorials entitled "Settling the UGDP Study" as long as he wants, and it is not going to resolve the issue. I would like to now move on and state exactly what the Committee on the Care of the Diabetic is seeking to accomplish.

First of all, may I state that, when I began this matter I sought to restrict the UGDP findings on the label. I thought the study was so flawed, based on what I had learned from the physicians I represent that it should not appear on the labeling. However, I later filed an amended complaint in the Federal court, because there is the possibility that the study has some merit even though it is flawed. We are not saying that these drugs absolutely do not cause certain problems because we do not know. But the UGDP study did not give us the answer, and pretending it did does not help us at all.

What we are seeking is a label which reflects fair balance, which reflects the fact that there may be a problem with the drugs, which indicates the study results and the controversy surrounding them. There have been many eminent people supporting both sides. The evidence which has been presented clearly points up the existence of conflict and controversy which now must be admitted by all. To fail to indicate such controversy on the label is most inappropriate.

At this point, I would like to discuss the lawsuit, Senator. I believe that the action is unprecedented. It is the first time, to my knowledge, that a group of physicians and patients—and I emphasize that the plaintiffs include patients—in a class action representing all physicians and patients similarly situated—have sued the Government and the manufacturers to prevent the Government from forcing the label change along the biased lines that it sought and the manufacturers from buckling under to FDA pressures, for a variety of reasons, and voluntarily changing the label. It is on the basis of that lawsuit that we secured, in November of 1973, a preliminary injunction halting the Government from ordering the label change and halting the companies from voluntarily altering it. We have not sought to hold up labeling, and I do not understand why it has taken so long for the FDA to move forward with labeling. This case was before the court of appeals on July 31, 1973. Why is it that 18 months later, we still have no revised labeling? One reason may be the unrealistic expectation that the Biometric Study would settle the matter once and for all and then the labeling could proceed.

Well, that has not happened. And the Committee for the Care of the Diabetic will go back to court, and will take every step it has to take, to prevent a onesided, biased label from emerging; and the Biometric Society Study does not alter our resolve. I might add that we have had less than 2 days to review the Biometric Report. Why did we only have 2 days? Why was it not made available to men like Dr. Bradley, and the other members of the Committee on the Care of the Diabetic? I asked the AMA why it was not, and they said they could not allow this because the Biometric Society said not to release it to anyone; anyone except Dr. Chalmers, that is.

Why was the Biometric Society so secretive about this document? I would very much like you to find out, Senator; the answer probably is that NIH insisted on secrecy. The result is that a document is going

to be printed in a journal in 2 weeks, a document which is not given to others for review despite the known controversy which exists. Then the AMA calls a prepublication press conference, and announces an article that is to be printed in 2 weeks, and the result is a headline which appears in papers throughout the country which speaks of 15,000 people dying each year, which has nothing whatsoever to do with any of the material to be published. I think it is irresponsible, and I am extremely disappointed that the AMA has seen fit to take this measure; I can only ascribe it to some naivete, they never should have functioned in this manner.

The CHAIRMAN. I have not, by the way, seen either the editorial, nor have I yet seen the report of the Biometric Society.

Mr. CHAYET. You ought to read it. It is most interesting, particularly the editorial.

The CHAIRMAN. Well, I have not seen it.

Mr. CHAYET. Senator, I am sorry to go on for so long, but you said something previously about the legal aspects involved in this matter, and you referred to the Food, Drug and Cosmetic Act. I would like to address myself to this aspect of this very important question.

We have depended on a regulation of the FDA itself, which reads as follows:

> The existence of a difference of opinion among experts qualified by training and experience, as to the truth of a representation made or suggested in the labeling is a fact the failure to reveal which may render the labeling misleading, if there is a material weight of opinion contrary to such representations.

What this means is, if a manufacturer seeks an NDA and he knows that there is controversy over his product, he has a duty to come forward, if there is a material weight of opinion against his drug, and inform the FDA. Why does not the Government have a similar obligation to inform physicians that there is a material weight of opinion contrary to its findings? Why has the Government sought to repeal this regulation when the case was returned to the agency by the court of appeals? Does this principle exist only for the manufacturers? If there is material weight of opinion against a position why is it stifled and not reflected—just because it is the Government position? That is my question. I have not yet received an appropriate answer.

The CHAIRMAN. Well, just let me say—if we are addressing ourselves to the same thing—that I carry no brief for everything the FDA does, but, as a matter of fact, they have in a very massive way done exactly what you say they have not done. In accordance with the 1962 amendments to the Kefauver Act, the FDA contracted with the National Academy of Sciences-National Research Council which set up panels on all kinds of drugs. These panels evaluated thousands of drugs and then made recommendations. And the FDA took very positive action on a large number of drugs, perhaps as many as 6,000 of them.

Mr. CHAYET. That is true.

The CHAIRMAN. Informing the public about their deficiencies.

Mr. CHAYET. I do not want to imply that the FDA does not do anything proper at all. The FDA has done a great deal of fine, very valuable, very important work, and I never want to deprecate that

for a moment. But in this case—and I do not know why, but—in this case, the process has broken down irretrievably. The FDA is not living up to its mandate in this case; it has not, and it is not at the present time. And what its mandate is, it seems to me, is to present information, but to do so fairly and impartially; and it is not doing so.

Let me explain what I mean by this. When one applies for an NDA, the substantial evidence test is applied. The thrust of implementation of the Food, Drug and Cosmetic Act has been to do away with clinical opinion insomuch as possible, and reduce it to controlled, statistical studies. That may be a very laudable goal in some cases, but in other cases, it can lead to great difficulty, as in this case. There is substantial evidence of efficacy of these drugs—as they do lower the blood sugar—and that is the efficacy which is claimed. The question is, what is the result of lowering blood sugar, and how dangerous are these drugs. This is where one gets into difficulty.

There is a question as to whether the UGDP study can be considered substantial evidence, as it appears to be so flawed. I think that the study is reflective of a great deal of effort and, in many ways, it was a very complicated and very sophisticated study. It is indeed unfortunate that improper extrapolation has caused it to reach this result.

Let us assume, then, that the UGDP constitutes substantial evidence. It is important to realize that we are dealing with a warning which is to appear on the label. If a drug is approved for efficacy and is being marketed and a problem develops with the drug, I think that problem ought to be reflected on the labeling, and in this case, it should be so indicated as to the oral hypoglycemic drugs.

So, what does one do? Let us say substantial evidence is not in issue but, rather, someone comes up with a clinical opinion that there is a problem here. That controversy should be adequately reflected on the label. Where there is great controversy about findings such as UGDP, we want to have the FDA indicate such controversy on the label, even if they are not exactly sure that it is a final or totally correct warning.

The fact that there is controversy about a particular finding, and there is no final answer does not mean that you ignore the controversy. Where you do a substantial evidence study that costs $8 million, and lasts 9 years, and it is wrong, you are confronted with a major problem. You are in serious trouble. You cannot replicate it, because it is going to take another 10 years, if you can find the $8 million to do it. So you have a problem—and I hope the Government is not going to say that, just because we have a study that cost $8 million and lasted 9 years, therefore, that is substantial evidence and it cannot be wrong; because, as I say in my statement, there have been mistakes made—very costly mistakes made—in research, as in all human endeavor, and there will be again in the future. For this reason, I feel that the FDA regulation itself should be applied in this particular situation. We have already filed comments against the suggestion by FDA that this regulation be repealed. And we will go back to court, if we have to, to prevent this regulation from being repealed in this particular case. We believe the UGDP study has

such severe inherent problems that, unless the controversy is indicated, it will be misleading to the public and to the physicians who are responsible for treating this problem.

I mentioned this article in the Globe. Dr. Bradley will tell you how many people have called the Joslin Clinic in the last few days, and have been so upset. I have heard similar statements from other physicians, telling me how many of their patients become upset by the press releases which have occurred. I do not blame the Biometric Society. They said things such as the following—I am reading now from the Biometric Society: "There remains the question whether tolbutamide, although ineffective in a fixed-dose regimen, might be an effective therapy as ordinarily used." That is right in the Biometric Report, Senator. In other words, if they used the drug properly, maybe it would be effective therapy. Very interesting—that is why I say, it is not these reports per se that are causing the problem for the public. It is what people are doing with these reports.

The CHAIRMAN. I think it should be known you are reading excerpts.

The fact of the matter is that the members who did the study agreed with the UGDP study results. The fact is that one of the greatest clinics in the world, the Mayo Clinic, has accepted the report. It is accepted at Grady Memorial Hospital in Atlanta. Those were two of the witnesses.

So sure, there are scientific disputes, but this society which was independently chosen of very distinguished people, have concluded that it was a valid statistical study, but the record is clear on that, anyway.

Mr. CHAYET. The record is not that clear, I would like in closing to summarize my position for the record if I may, Senator.

The CHAIRMAN. Sure.

Mr. CHAYET. I think we need new labeling right away. I would like to dispel any doubts at all that we are standing in the way of new labeling. We need it, and I am sorry we do not have it up to this particular point, and I hope we will have it soon.

I also——

The CHAIRMAN. Excuse me for interrupting. The committee counsel tells me that the FDA is going to testify very soon on the question of labeling. I did not realize it was already scheduled.

Mr. CHAYET. Fine.

But I think we need this labeling very badly, by that I mean labeling that will be fairly balanced and indicate the scientific controversy. This raises the question of what do we do about the controversy. Although I heard what the doctors said before about the difficulty of launching another study like this, I really do not see any way of avoiding it, unfortunately, at the present time, because what we have at the moment does not answer the critical and crucial questions raised. Regardless of an additional study, I think there ought to be balanced labeling so that doctors will use this drug properly and be aware of the controversy while, as quickly as possible, we ought to have additional studies. I would say, Senator, there ought to be at least one study that is as lengthy and as fully

funded as this, and we ought to stop putting money into trying to justify a flawed study. Instead we ought to try to correct it, come up with a better study, and come up with the answer which really is of such importance to millions of people throughout the country.

I thank you very much, Senator.

Dr. Bradley?

The CHAIRMAN. You are an articulate advocate, and I appreciate your testimony.

Mr. CHAYET. Thank you, sir.

The CHAIRMAN. Doctor, we are glad to have you back again.

Is there anything you would like to add?

Dr. BRADLEY. Yes. I would like to make a few comments, Senator Nelson. I would like to start, if I may, with a slight anecodote, and this just to change the pace a little bit. Yesterday one of my associates came up to me proudly and said I want you to meet Mr. X. He now is down to his ideal weight of 150 pounds. A little over a year ago he weighed 275 pounds, and at that time was taking 80 units of insulin. Now he weighs down to his ideal weight, and his glucose tolerance test is normal, so that this is an illustration, I think, of the benefits of weight loss and of diet. One of the first things I want to affirm is that the idea of diet as treatment for diabetics did not originate with Dr. Davidson, or with the UGDP or with Dr. Ricketts. As a matter of fact, one of the reasons the Joslin Clinic has been criticized over the years is that they have so rigidly insisted upon diet as primary treatment, whether people are on just diet alone, or whether they are taking insulin or pills. This continues to be the case and has been so all along.

So if you will pardon my digression, I would like to come back to the other issue if I may. I think Mr. Chayet quite rightly has emphasized that the controversy remains, but I would like to approach it along three or four lines with you briefly, if I may.

First of all, the Biometric Study, I think most of us realized, would, to a certain degree, be moderately supportive, and I think those words appear in the study of the UGDP experiment. We did not expect anything different. I would not have been here just because I knew the Biometric Study Report was going to appear, because it does not answer the fundamental questions in this whole issue.

They did not address themselves specifically to two questions which I have raised all along, and now I realize I must send you a publication that has appeared within the last year or so which I prepared for "Controversies in Medicine," and I would be happy to send you copies of that if you wish for the record.

The CHAIRMAN. Thank you.

Dr. BRADLEY. And without going into much detail, these relate to unknowns, if you will, and they are what clinicians, those people taking care of people with diabetes, are more aware of, perhaps a little more humble about than others looking at it from a purely scientific standpoint. There could be unknowns that we have no way of knowing about, but there can be two specific unknowns that come to mind, and these are critical, really, and they are as follows: First, the level of coronary heart disease, the condition of the heart in the diabetics at baseline was not known. I emphasized this in my

previous testimony. The tools for evaluating these were crude. There was some knowledge about it, but not enough was known so that one could really say these treatment groups were the same.

Second, and this is crucial to the whole thing, they did not really know how long diabetes had been present. Now, diabetes is a risk factor in all of the patients in all of the groups of the study. Most clinicians know quite well nowadays, and there is good statistical evidence to back it up, that the major effect of diabetes on vascular disease relates to how long one has it—its duration. And unfortunately, in adults it is very difficult to know how long diabetes has been present.

We have a little clue from the study. I think Dr. Zelen or one of the other witnesses referred to the glucose tolerance tests. The clue is a very interesting one in that when one looks at the glucose tolerance test in the group on tolbutamide, there were more people in the tolbutamide groups who had higher fasting blood sugars, and I think, more at every interval of the glucose tolerance tests, than in any other of the treatment groups, certainly more than was the case of placebo.

This means, then, two things. Subgroup (1): Their diabetes was somewhat more severe as a group at baseline; and (2) they may have had diabetes longer.

Now, we have no way of proving or disproving it. We can present evidence on both sides, but it raises the same kind of uncertainty about the hardness of the UGDP, and I think I gained this from Dr. Meier's testimony, a lack of hardness. He was not quite willing to say that this was a very hard kind of decision. I think this is where we have to be very careful in accepting these results hook, line, and sinker.

Now, we have a further hint that there may have been more risk in that when you add up the numerators of the various risk factors in the patients on tolbutamide, they were somewhat more.

The key issue here is, again, that this does not prove that tolbutamide and phenformin are not hazardous. They may still be. And our problem is how do we resolve this. Sir, if I may, I would like to make a few more suggestions that might help us all come to a solution of the problem.

First: I think the role of Government has unfortunately gotten to be a little bit too strong here. Mr. Chayet has referred to this, and it is alluded to in our statement. But I will focus specifically on the FDA.

We have been concerned all along that the FDA has not gone ahead with labeling which was reasonably balanced. That was all we wanted, something that acknowledged the fact that true controversy existed, that would not lay undue concern upon the minds of physicians and their patients, yet enough so that they would be careful, but also allow us to get about our business of educating physicians and patients. This is what has fallen terribly behind and is the reason these drugs are being used altogether too much today in diabetic patients of this type throughout the country.

I will come back to that in a moment.

Now, you asked a very important question, and that is about the benefits. In my original statement in September I indicated that

these drugs are not oral hypoglycemic drugs. This is a semantic error on the part of Dr. Palumbo, who may be here to defend himself. They really are oral blood sugar lowering drugs. They may produce hypoglycemia, but that is not their blood sugar lowering agents, and they do this very clearly. No scientist in his right mind would argue with this, that they do it very clearly in selected patients, not all of the patients of the type that were studied in the UGDP, but in a majority of them. The problem is they do not continue to do it.

And second: There may be a hazard from a cardiovascular standpoint, so they are suspect in two areas.

Now, in terms of other kinds of benefits which the UGDP study was set up to evaluate, I do not believe they were set up to evaluate cardiovascular mortality. They wanted to see, did these patients have more diabetic neuropathy after a period of time? Did they have retinopathy, involvement of the eyes? Did they have more kidney involvement? Did they have more cataracts? Did they have more infectious disease?

I think the end point was listed as vascular complications in general, as a mixed bag, but they really were looking for those complications which are more specifically related to diabetes.

At the moment we do not have data relative to such end points in terms of effectiveness, long term effectiveness. The only data we have is relative to the blood sugar. If these drugs do not lower the blood sugar, no thoughtful diabetologist would continue to use them.

Now, certainly if he does not believe that lowering the blood sugar might protect from these complications, he would not use these drugs. So at the moment we must deal in terms of blood sugar lowering and maintaining it.

Now, what I would like to see happen, I would hope from these hearings, is that we would get away from this controversy. Frankly, I think it is ridiculous. I think the people who suffer from this potentially are patients. The controversy has held up our getting together and trying to approach the problem not by governmental fiat, not by Dr. National Institutes of Health or by Dr. FDA, but by the appropriate cooperative statements of objectives in terms of treatment of patients. And if we cannot agree on objectives, maybe we will have more controversy. But I think we should agree on objectives that relate to using these drugs, if they are going to be used at all, in such a way that the one effect we know about, namely, lowering of blood sugar, is indeed guaranteed in patients. If we do not do that, I think patients either will be stopped because of governmental fiat, and a law forbidding them, or a policy, or else physicians will go on using it in patients. And if there is a hazard, then obviously they are being exposed to it.

I think we must realize there may be a hazard. There is no question about it. And our committee has never tried to say that this was not a possibility. All we wanted to do was to be sure that the situation was put in balance. That is all.

Thank you.

The CHAIRMAN. Well, thank you very much, Dr. Bradley. I appreciate your taking the time from your busy schedule to come here and testify today.

Well, thank you very much, gentlemen.

Mr. CHAYET. Thank you.

The CHAIRMAN. Did any of the members of the biometrics panel wish to comment for the record on any of the statements made by Dr. Bradley?

All right. Thank you very much.

[Whereupon, at 12:08 p.m., the subcommittee adjourned, subject to the call of the Chair.]

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

(Present Status of Competition in the Pharmaceutical Industry)

WEDNESDAY, JULY 9, 1975

U.S. SENATE,
SUBCOMMITTEE ON MONOPOLY OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to notice, at 10:15 a.m. in room 318, Russell Senate Office Building, Senator Gaylord Nelson (chairman of the full committee) presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist, and Kay Klatt, research assistant.

The CHAIRMAN. Today the Monopoly Subcommittee of the Senate Small Business Committee resumes its hearings on the safety, efficacy, and use of oral blood-sugar-lowering drugs, which are taken by diabetics.

Well-controlled studies showed that users of these drugs are 2½ to 3 times more apt to die from heart problems than those who depend solely on diet or diet and insulin. According to expert testimony, these drugs also have limited uses, and Dr. John Davidson, the director of the largest university-based diabetes clinic in this country, estimated that more than 99 percent of the people using these drugs should not be using them.

In early 1974 the FDA moved to change the labeling of the blood sugar lowering drugs to reflect the latest scientific evidence about their dangers and lack of efficacy, but the agency's efforts were blocked by a court order. Nevertheless, recent additional studies confirming the dangers of these drugs have made a change in the labeling imperative, and the Commissioner of the Food and Drug Administration is here today to discuss the new labeling of the oral blood-sugar-lowering agents as well as the recent human and animal studies that confirm the need for prescribing physicians to be informed in the clearest terms possible of the latest knowledge in the field.

The new labeling—as well as other aspects of these drugs—will be discussed tomorrow by a number of medical experts.

Dr. Schmidt, you may present your testimony however you desire. The statement will be printed in full in the record.[1]

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[1] See prepared statement, page 13697.

STATEMENT OF ALEXANDER M. SCHMIDT, M.D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY RICHARD MERRILL, CHIEF COUNSEL, FOOD AND DRUG ADMINISTRATION; J. RICHARD CROUT, M.D., DIRECTOR, BUREAU OF DRUGS, FOOD AND DRUG ADMINISTRATION; JAMES M. BILSTAD, M.D., GROUP LEADER, DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS, BUREAU OF DRUGS, FOOD AND DRUG ADMINISTRATION; AND ROBERT WETHERELL, DIRECTOR, OFFICE OF LEGISLATIVE SERVICES, FOOD AND DRUG ADMINISTRATION

Dr. SCHMIDT. Thank you, Mr. Chairman.

Because the statement I have is relatively brief, I thought I would go through it. I am accompanied this morning by Dr. Richard Crout, Director of the Bureau of Drugs, on my right and your left, and Mr. Richard Merrill, Chief Counsel of the Food and Drug Administration, behind me. To my left is Mr. Robert Wetherell, Director of our Office of Legislative Services, and to my right, Dr. Bilstad, our Group Leader of the Division of Metabolism and Endocrine Drug Products. We are pleased to be here this morning to discuss our current actions regarding the oral hypoglycemic drugs.

As you are well aware, labeling for this class of drugs has been the subject of extended public controversy and legal challenge for a number of years. The Agency has now published a proposed regulation providing new labeling for this class of drugs. The proposal appeared in the Federal Register on July 7, 1975, and asked for comment on the labeling. It also announced a public hearing to be held on August 20, of this year to afford interested persons a further opportunity to comment.

Last September, I summarized before this subcommittee the actions of the FDA that followed the report in 1970 of the results of the university group diabetes program study. Today I will review the events that have taken place since my previous testimony and will discuss, in some detail, of course, aspects of the proposed labeling.

Mr. GORDON. May I interrupt you for just a second, Dr. Schmidt?

As I understand it, new labeling was originally proposed by the FDA in 1972. Is that correct?

Dr. SCHMIDT. That is correct.

Mr. GORDON. So, you have already had comments on that labeling. You stated in your statement which appeared in the Federal Register, that you did not expect any major new information. In fact, it is on page 15 of the Federal Register insertion. You have the results of other studies including animal studies which support the UGDP study.

Why do you, then, have to go through the same long procedures again, that is, proposing changes, having 60 days for comments, having administrative hearings, and so on? Is that for legal purposes?

Dr. SCHMIDT. Well, we spent a considerable amount of time discussing and deciding on the best procedure to use in going ahead with the labeling change and quite deliberately chose the formal rulemaking procedure which in effect this is. And I think the reason the rulemaking procedure is clearly the best way to go is that the goals

that we have in this whole process include not only the revision of the labeling but the dissemination of information, the education of the great number of people, physicians and others, who are interested in this subject.

We are interested in educating everyone as to our firm beliefs in this area and the rulemaking procedure allows public discussion, public debate, public comment, a process through which many people can become informed and become educated, and we think the benefits of this in this area are obvious and all to the good.

Second, we would wish to avoid further litigation, if that is possible, and one can perhaps avoid litigation by achieving consensus and one of the best ways of achieving consensus is through public debate and discussion.

We further think that the rulemaking procedure done formally could strengthen any court case that might evolve. And I could ask Mr. Merrill to comment on that.

Mr. MERRILL. Senator Nelson, Mr. Gordon, there is a second reason behind the way we are proceeding now. Nothing would please us more than to avoid reinstitution of that lawsuit in the Court of Appeals in the first circuit. But it is our belief that we should follow the regular rulemaking route prescribed by our procedures in the Administrative Procedures Act.

We strengthen ourselves in any subsequent court challenge of this labeling. It forces the court to, in effect, conclude that we were demonstrably wrong. It puts the burden on any challenge or to establish that we were arbitrary and capricious on the basis of the evidence and information that we assembled in this administrative proceeding.

The CHAIRMAN. Go ahead.

Dr. SCHMIDT. Because of the controversy among physicians concerning the UGDP study on the oral hypoglycemic labeling previously proposed by us based on the use of the UGDP study, we decided the publication of the proposed labeling in the Federal Register should await completion of the detailed study of the UGDP study by the Biometric Society.

The report of the society was published in the February 10, 1975, issue of the Journal of the American Medical Association. In testimony before the subcommittee last January by the members of the society who conducted the review, a review of their conclusions was provided for you. The Biometric Society committee assessed the scientific quality of the UGDP study, particularly the design, conduct, and analysis of the trial.

And, as well, the committee evaluated other controlled trials involving oral hypoglycemic agents. The committee discussed in detail criticisms of the UGDP study and concluded that they found, "most of the criticisms unpersuasive."

Specifically, the Biometric Society committee concluded that first, the criticism that patient selection was inappropriate, was "largely irrelevant" to the validity of the evidence for the toxicity of the oral agents.

Second, the criticism that total mortality in the tolbutamide was not significantly different from that in the placebo group had some weight and "the toxic effect of the oral hypoglycemics cannot be affirmed with the certainty that would be present if total mortality were significantly different."

Third, excess mortality in tolbutamide-treated patients was not confined to a few clinics, as critics have claimed.

Fourth, although there was a "puzzling anomaly" concerning the distribution of sexes to the treatment groups within clinics, they could find an assignable cause for this distribution and have no reason to think that this study had been compromised by a breakdown in the randomization of patients to the treatment groups.

The committee particularly analyzed the criticism that there were important differences in baseline cardiovascular variables among the groups and concluded that there was no evidence that the baseline differences arising from the randomization contributed in any important way to the finding of adverse effect from tolbutamide.

Another conclusion was that the criticism that oral hypoglycemic drugs were given in fixed dosage was not relevant to the question of whether the drugs were toxic.

The committee also noted that the fixed dose given was about equal to average recommended dose. They further concluded that although it would have been easier to interpret findings were there more data on mortality, that is if the study had been carried out longer, they did not criticize the UGDP investigators for having made the decision when they did. The committee said:

> Nevertheless, the result of that decision is to leave us with some residual uncertainty about the meaning of the findings, a point that is well understood by the UGDP investigators themselves.

And last, the committee said that other studies said to contradict the findings of the UGDP study do not in fact do so.

The CHAIRMAN. Dr. Schmidt, yesterday and today—yesterday in the New York Times, today in the Washington Post—there is a story referring to a letter that was written early this year by Dr. James Sammons, executive vice president of the AMA to the Upjohn Co. in which, as I read the story, he is critical of the UGDP study and the evaluation by the Biometric Society of that study. Among other things his letter states: "A considerable body of expert scientific opinion contradicts these published findings." Then the letter was sent to the State medical societies and county medical societies, and 1,100 of detail men of Upjohn were furnished copies of the letter.

Obviously, it attacks the findings of the UGDP and as well the evaluation of the Biometric Society of those findings, which appeared in the Journal of the American Medical Association.

My question is, the UGDA study extended over 10 years; is that correct?

Dr. SCHMIDT. The study began in 1961, and the evaluation of it is still going on now.

The CHAIRMAN. It started in 1961. On page 4 of your prepared statement you quote from the Biometric Society report that other studies said to contradict the findings of the UGDP study do not in fact do so.

Are you aware of any carefully designed scientific studies that have been conducted that refute the findings of the UGDP?

Dr. SCHMIDT. No, sir, we are not.

The CHAIRMAN. So, as far as the Food and Drug Administration is concerned, you are not aware of any scientific studies that contradict the UGDP findings?

Dr. SCHMIDT. No well-designed studies; no, sir.

The CHAIRMAN. Well, I will not ask you what you think the motivation of Dr. Sammons is because I think everybody knows.

Go ahead, I will print in the record this article from the New York Times as well as the Washington Post on this subject at the appropriate place in the record.[1]

Dr. SCHMIDT. In addition to evaluating criticisms of the UGDP study, the Biometric Society conducted extensive new analyses of the UGDP data, taking into account the effect of various baseline variables and cardiovascular risk factors. These analyses confirmed that cardiovascular mortality was increased in the tolbutamide group. This increase was statistically significant for the patient population taken as a whole and in the subgroup of females, especially in women over the age of 53, but not in the male subgroup. This does not mean that the studies show that the drug carries less risk in males. On this point, the committee concluded:

The data do not support the same conclusions for men, but one possible reason is that the smaller number of patients in the male group results in a lack of sensitivity to detect differences of moderate magnitude.

An important finding was that the highest death rate occurred in the group of patients who adhered most closely to the tolbutamide regimen and did not have their dose modified. Also, when the analysis was conducted according to an approach called the survival modeling method, which takes into account the proportion of time each patient received the assigned medication, women in the tolbutamide group had a statistically significant increase in both cardiovascular and total mortality.

The Biometric Society committee summarized its conclusions in the final sections of its report as follows—and I need to point out that all of page 5 on my copy is, in effect, taken from the conclusions of the committee. And they said:

On the question of cardiovascular mortality due to tolbutamide and phenformin, we consider that the UGDP trial has raised suspicions that cannot be dismissed on the basis of other evidence presently available.

It further went on:

We find most of the criticisms levelled against the UGDP findings on this point unpersuasive. The possibility that deaths may have been allocated to cardiovascular causes preferentially in the groups receiving oral therapy exists, and, in view of the "nonsignificance" of differences in total mortality, some reservations about the conclusion that the oral hypoglycemics are toxic must remain. Nonetheless, we consider the evidence of harmfulness moderately strong. The risk is clearly seen in the group of older women. Whether it affects all subgroups of patients cannot be decided on the basis of the available data, owing to the small number of deaths involved in these subgroups.

In conclusion—

They went on:

We consider that in the light of the UGDP findings, it remains with the proponents of the oral hypoglycemics to conduct scientifically adequate studies to justify the continued use of such agents.

Mr. GORDON. You stated before to the chairman that they have not come up with these scientific studies.

[1] See pages 13413 and 13439.

Dr. SCHMIDT. That is correct. The committee concluded that there were no data that refuted the principal conclusions of the UGDP study, and we agree with that.

Mr. GORDON. But setting aside, for the moment, the cardiovascular deaths, have the opponents of your proposed labeling supplied substantial evidence—as required by law—that the oral hypoglycemic agents have a beneficial effect on the long-term vascular complications of diabetes? In other words, I am talking about efficacy in treating diabetes.

Dr. SCHMIDT. Yes, I see; I have a little problem with your question because it implies that what is required by law would be that these drugs would have a beneficial effect on the long-term vascular complications of diabetes. And in fact, we have no substantial evidence on that point.

Mr. GORDON. But, that is required by law, is it not?

Dr. SCHMIDT. Well, no, because it depends upon the claims made and if the claim for these drugs was that they influence the long-term mortality, then they would indeed need substantial evidence. But, if the claim is that they lower blood sugar or relieve symptoms—in other words, if they have that effect and there is substantial evidence for that, then that is what is required by law for that labeling. And we do have substantial evidence that these drugs lower blood sugar and that they relieve symptoms.

Mr. GORDON. Well, does it state that the purpose is merely to relieve symptoms and that is all?

Dr. SCHMIDT. Well, no, but you see, what you are doing is two things: one is you are pointing out the need for revised labeling, and we firmly agreed with this. In times past, as I believe I said last time I was here, it was believed by most physicians that lowering the blood sugar in the diabetic would have a beneficial effect upon the long-term mortality figures of diabetic patients. We analogized this to the idea that lowering blood pressure would prolong the life of individuals with hypertension. And what we are determining by some substantial evidence is that lowering blood pressure in hypertensives does prolong lives in those individuals that have high blood pressure.

We are learning things about the lowering of the blood sugar in diabetics that surprise us. And so we are in a different position now than we were in the past when the labels may have been silent on the issue of whether or not lowering glucose prolongs the life of a diabetic.

We may have applied this cause and effect relationship. What we need to do now is to separate out now clearly the treatment of people in order to relieve symptoms, which is very important.

I have taken care of many diabetics. And you can be sick if you are a diabetic. You can feel terrible when you are a diabetic. And in symptomatic diabetics, the normalization of blood sugar, which relieves symptoms as it does in some, is a very important thing. But we have to separate that and substantial evidence for that and that claim from the effect that that might or might not have on longevity of individuals with diabetes.

Mr. GORDON. Now, even if the results of the UGDP study were not conclusive—let's assume they are not conclusive—but are likely,

or even suggestive, would not the absence of the beneficial effect on the long-term complications of diabetes mean that the benefit-to-risk ratio for these drugs is unfavorable.

Dr. SCHMIDT. Well this comes back again to that same point of separating out treatment of the symptomatic diabetic who cannot take insulin, or who is not normalized by diet, that small group of people. Clearly, the benefit-risk ratio for that small group of individuals is such that we believe the drugs are safe and effective for them and should be available for their treatment.

Mr. GORDON. Only for lowering blood sugar—is that right?

Dr. SCHMIDT. That's right.

Mr. GORDON. And for a limited period of time?

Dr. SCHMIDT. And for symptomatic patients. Now if you are talking about asymptomatic patients, then my belief is that the drugs simply should not be used.

Dr. CROUT. I would agree with Dr. Schmidt as a physician. On the other hand, the asymptomatic patient is what the argument, the true argument, is all about. So, I think when you see estimates, or hear estimates of whether the oral drugs should be used in 1 percent, or 10 percent or 20 percnt or 50 percent of the people now taking them, what you are hearing are differences of medical opinion on whether or not the lowering of the blood sugar in asymptomatic patients may stave off long-term cardiovascular disease.

And I think an important point to realize is that we do not view the UGDP study as conclusive on that point. Nor did the biometric study review the study on that point. The point we feel considerably more secure about is the evidence that the drugs may increase cardiovascular mortality. Whether the lowering of blood sugar staves off such mortality and is a compensating benefit for these drugs is an unanswered question, and the labeling reflects that point.

The CHAIRMAN. Is it not also correct that the study concludes that the purpose can be accomplished by diet better than the use of the drug—except for that rare small number you are making reference to?

Dr. CROUT. I think a number of physicians, including ourselves, would draw that interpretation from the study.

Your question was, did the study per se show that? And the answer is, not precisely. But that would be the conclusion people would draw from the study and it is an important point. Because the question has been asked, if usage of these drugs goes down, does that mean that usage of insulin will automatically go up? And in our opinion, and I think in the opinion of a number of physicians, the answer to that is no.

The best alternative therapy for the great majority of patients now on these drugs is diet. We believe that the changes in the practice of medicine that ought to occur at this point in time will focus more on the value of diet than on replacement of oral hypoglycemic drugs with insulin.

The CHAIRMAN. Dr. Davidson at Grady Memorial Hospital said in his testimony [1] that he thought perhaps the oral hypoglycemics

[1] See testimony of John K. Davidson, M.D., Ph. D., director, Diabetes Unit, Emory School of Medicine and Grady Memorial Hospital, in hearings "Competitive Problems in the Drug Industry," part 25, pages 10838–10854.

were indicated in about 1 percent of the cases.

I have a note here that Dr. Bradley thought 20 percent and Dr. Weingrad 10 percent. I believe Dr. Davidson testified that they had the largest university based diabetes clinic in the country. Is that your memory?

Dr. CROUT. As far as I know, yes.

The CHAIRMAN. I think that was his testimony. You may recall he testified that since they used the oral hypoglycemics for many, many years, it was hard for them to conclude that they have been wrong, but they concluded they were. And he testified that they had taken everybody off the drugs. As I recall, he said they got better results by managing his patients with diet alone than when they were using the oral hypoglycemics.

Do you remember that testimony?

Dr. CROUT. Yes.

The CHAIRMAN. Are you aware of whether or not that is the experience in other clinics?

Dr. CROUT. I think that is a common opinion among many good diabetologists. And I think that actually Dr. Bradley would harbor the same opinion, I believe, and you could confirm this with him, that his figure of 20 percent represents his opinion of the number of diabetics who might need drugs if greater emphasis were given to diet. So we do not contest those figures at all.

I would point out that nobody to my knowledge, including Dr. Davidson, has ever published in the medical literature sharp studies on this issue. Dr. Davidson's views are largely in testimony before this committee, not in the medical literature. So real studies to define 1 percent, 10 percent, 20 percent are not available either.

Mr. GORDON. I think Dr. Davidson also publishd an article in the journal of the American Medical Association recently, did he not?

Here it is: May 26, this year.

Dr. CROUT. I think it was a comment. But to really present the data that were presented before this committee in a full published form has not occurred to my knowledge.

The CHAIRMAN. Go ahead Doctor.

Dr. SCHMIDT. In addition to the Biometric Society report, other information has recently become available. First, the UGDP has published recently their detailed report of the results of the phenformin study. In addition to reporting that cardiovascular mortality and total mortality were greater in the phenformin-treated group than in the other treatment groups, the report presented evidence that phenformin therapy resulted in increased blood pressure and heart rate, thus suggesting possible mechanisms by which this drug might influence cardiovascular mortality.

Mr. GORDON. Dr. Schmidt, are you saying here that the benefit-to-risk ratio of phenformin is even more unfavorable than for the other oral hypoglycemics?

Dr. SCHMIDT. Yes, that would be the conclusion one would draw from this study, yes.

Mr. GORDON. In a study published in a book called "Controversy in Internal Medicine" by Winegrad, Clements and Morrison, University of Pennsylvania School of Medicine, Dr. Allan Winegrad,

with whom, I am sure, you are acquainted as being an eminent scientist and clinician, and others stated that phenformin has no role in the treatment of diabetes mellitus. Do you agree with Dr. Winegrad?

Dr. SCHMIDT. Well, Dr. Crout and I have been discussing this for some time. And with your permission, I will let him describe our feelings on this.

Dr. CROUT. Let me wear two hats. The first hat is as a physician. And I agree with him. The second hat, Director of the Bureau of Drugs, where we have to deal with the issue of action on that point.

Let me state the reason why the benefit to risk for phenformin is less than for the other drugs. This drug may cause lactic acidosis, a potentially fatal complication in patients who take it. So, there is a clear added hazard, in addition to what it does to cardiovascular mortality.

Now, the incidence of that lactic acidosis has in the past been thought to be quite low. As more and more information comes along, it looks like it is higher than we had anticipated. And that issue of lactic acidosis was brought before our Metabolic and Endocrine Advisory Committee more than a year ago.

At that time they recommended that a warning be placed on the drug, but that it stay on the market. We are going to take the issue back to that committee and take up that issue again. But, it is a separate issue, it is a separate issue from the labeling on cardiovascular mortality. On that, as far as we know, phenformin is the same as the sulfonylureas. We are dealing here with two adverse effects. And it is the sum of those two that I think is the important issue.

Mr. GORDON. As a medical scientist, could you tell us what the medical justification is for having this drug on the market?

Dr. CROUT. What my personal opinion is?

Mr. GORDON. Yes.

Dr. CROUT. I would support Dr. Winegrad. I personally would not use the drug.

Mr. GORDON. Then you see no reason for this drug to be on the market. Is that correct?

Dr. CROUT. You are asking me as a medical scientist?

Mr. GORDON. As a medical scientist.

Dr. CROUT. As a medical scientist, yes, I don't see any such reason.

Mr. GORDON. Well, then, why is it not being taken off the market? Why aren't steps going to be taken to take it off if there is no medical justification? After all, is that not the purpose?

Dr. CROUT. As I point out, we will take that back to our advisory committee. It is hardly a universal opinion. And neither I nor anybody else in the Federal Government that I am aware of has the power to simply exercise his personal opinion in the drug regulation business.

If I may wear that hat of the Director of the Bureau of Drugs, we will take that back to our advisory committee. We will attempt to see what support there is for a position that phenformin should not be marketed. We will take appropriate action after that.

That is a separate issue from this labeling.

Mr. MERRILL. Mr. Gordon, Dr. Crout makes a point that is too important not to reemphasize. And we have been spending a lot of time in the Food and Drug Administration trying to insist that drug manufacturers back up their claims with adequate and well-controlled clinical studies—scientific evidence and not on opinion. And for the very same reason we are reluctant to rely upon our own instinctive judgments. We would like the backing of the scientific community, and strong scientific evidence. We think it is obtainable. But we want to be sure.

The CHAIRMAN. Go ahead Doctor.

Dr. SCHMIDT. At hearings before this subcommittee this past January, Dr. P. J. Palumbo reported that a retrospective study of diabetic patients treated at the Mayo Clinic suggests that survival was lower in those patients treated with hypoglycemic agents compared to those patients treated with either insulin or diet. Dr. Palumbo's full study has not yet been published.[1]

Another study, a retrospective study of patients treated at the Joslin Clinic reported in a doctoral thesis by P. Kanarek, can be interpreted as providing results that are consistent with those of the UGDP. Although we have seen this study, it has not yet been subjected to a full review by statistical and epidemiological experts.[2]

At this point we can say that certain subgroups of insulin-treated patients appear to have better survival rates than tolbutamide-treated patients with comparable glucose abnormalities. Studies of this type, however, always present problems in interpretation because of doubts regarding comparability of treatment groups and because treatments are not randomly allocated. Thus, although the retrospective studies of Palumbo and Kanarek may or may not, when fully analyzed, add support to the UGDP findings, the prospective UGDP study must be accorded far greater weight and is alone a sufficient basis for our proposed actions.

Doctors Tan, Bradley, Gleason and Soeldner have reported on the long-term effects—4 years—of hypoglycemic agents on the oral glucose tolerance test and blood lipids in chemical diabetics at the annual meeting of the American Diabetes Association, in 1973—abstract in "Diabetes" 22 (suppl. 1): 290, 1973. The investigators' abstract reported there was no significant difference in the improvement in glucose tolerance between patients receiving oral hypoglycemic agents and patients receiving a placebo. The full report of this study has not yet been published, but it appears that the investigators studied glucose tolerance on the day following discontinuation of the drugs. Their findings thus would indicate only that the oral agents do not lead to improved glucose tolerance in the absence of continued use of the drug.

In another study, Dr. R. W. Wissler, in an FDA-supported investigation, examined the chronic effects of tolbutamide in the rhesus monkey. He found that coronary artery lesions were almost two times more ferquent and three times more severe in the tolbutamide-treated animals than in the control animals. FDA recently received

[1] Hearings before the Subcommittee on Monopoly, Select Committee on Small Business, U.S. Senate, 94th Congress, 1st Session, on Safety, Efficacy, and Use of Antibiotics—Clindamycin and Lincomycin, January 28, 29, and July 8, 1975, Part 27.

[2] See study by P. Kanarek, page 13393.

the final report on this study, which has not yet been published in the literature. FDA, at Dr. Wissler's request, is supporting further study of the pathologic findings by several independent pathologists.

Dr. D. F. Wu, et al., reported on the effects of tolbutamide on heart function in dogs, with chemically induced diabetes, at the meeting of the American Federation for Clinical Research this past May. The investigators reported that after 1 year of treatment with tolbutamide the left ventricular function was reduced and cardiac morphology altered compared to control groups.

The animal studies do not necessarily bear directly on the excess cardiovascular mortality seen in tolbutamide-treated humans in the UGDP study, but they do suggest overall mechanisms by which this might have occurred.

Now, as you know, Mr. Chairman, it has been the view of the FDA since 1970, that the findings of the UGDP study should be reflected in a warning in the labeling for oral hypoglycemic drugs and in turn, in the use by physicians of these drugs. Let me emphasize that this view does not require that we conclude the study provides absolute proof of hazard. The UGDP study is an adequate and well-controlled study—by far the most extensive and best examination of the long-term effects of oral hypoglycemic agents yet ever undertaken.

The finding of an increased cardiovascular mortality in tolbutamide and in phenformin-treated patients cannot be attributed to any shortcomings of study design or execution. This finding, despite any residual uncertainty that may remain, requires a clear warning to physicians. Prudence dictates that a warning be issued whenever there is sufficient evidence to believe that a drug may be hazardous or carry a risk, and that such a warning is necessary for the safe and effective use of the drug by physicians and patients. Enough time has now passed for interested persons to have studied the Biometric Society report and the recent detailed UGDP report on phenformin. The Agency has, therefore, published for comment a regulation proposing new labeling for the oral hypoglycemic labeling. Interested persons may comment on the proposal by September 5, 1975, and a public hearing will be held on August 20, 1975. Final labeling regulations will not be published until after all comments and materials have been considered.

Our proposed labeling has two sections of particular importance; a boxed warning stating that there may be an increased risk of cardiovascular death associated with the use of oral hypoglycemic drugs and a new indications section that limits use of these drugs to patients whose symptoms or blood glucose abnormalities cannot be controlled by diet alone and who cannot take insulin for one of a number of specified reasons.

Now, I would like to discuss both of these sections in greater detail. And they are both reproduced in full in an attachment to the statement. The warning describes the UGDP study and its findings. It has been contended that certain studies said not to support the findings of the UGDP study should be mentioned in the warning section to provide the "fair balance." We have concluded, however, and made clear in revised regualtions that if scientific data exist to support a warning, the warning must be presented in unambiguous

terms without disclaimers or qualifications that would undermine or destroy its usefulness. There is, therefore, no mention in the proposed warning of other studies involving the oral hypoglycemic drugs. The mention of studies in which increased cardiovascular mortality was not found would serve only to encumber the warning.

Mr. GORDON. Dr. Schmidt, you say that the warning must be stated in vigorous terms without disclaimers. Why, then, does the warning include—you do not have it in your statement, but it is included in the Federal Register statement—"that, despite the controversy regarding the interpretation of these results, the findings of the UGDP study provide adequate scientific basis for this warning"? Is it not true that the presence of controversy about the need for the wording is irrelevant and is distracting? Is that not an encumbrance, in a way?

Dr. SCHMIDT. No. We definitely do not feel it is an encumbrance, and I personally feel that it is absolutely necessary to the creditibility of warning that we state that the UGDP study, despite this controversy, provides sufficient evidence for the warning. I think that were we to remain silent, or to ignore the fact that many physicians and many experts have said, in effect, forget the UGDP study—if we were to remain silent on that, it would be so obvious, cause so many questions, make people wonder why we were in a sense trying to finesse the issue, that it is to me absolutely necessary in order to have a credible statement that we say that very clearly. The UGDP study is sufficient to provide a sound basis for this warning, and the controversy does not controvert the fact that the study provides that avenue.

Mr. GORDON. Well, I thought that it is not just the UGDP study that you are basing the label on. It is the UGDP study, the Biometric Society study; you referred to the Wissler study, the Wu studies, the Tan studies.

Dr. SCHMIDT. No, I did just now in the statement. The warning is based on the UGDP study.

Mr. GORDON. Solely?

Dr. SCHMIDT. Yes, sir. I can make a couple of other points. The first is that the encumbrance of other studies is not present, and I think that the warning statement is much better for another reason; it relates to credibility. It makes the statement believable, and it renders it, I think, much less subject to attack and discredit. As I said early on, one of our goals here is to achieve a professional concensus about the use of these drugs. So I just strongly believe that the warning, stated as it is, makes a much better statement.

Mr. MERRILL. May I inject one comment? Your question, Mr. Gordon, is one that will be asked of us again. I have no doubt, that the charge will be made that we are speaking out of both sides of our mouth in these very two documents. In one it will be argued we say there can be no encumbrance of the warning, and in the other we seek to encumber it. That is not true. In the context of this warning, the statement that the administration of oral hypoglycemic drugs may be associated with increased cardiovascular mortalities as compared to treatment with diet alone and diet with insulin is two full paragraphs away from the line you just quoted. In addition, the

reference is to the controversy about the interpretation of the UGDP study, and says nothing about the significance of the warning. So I do not have any difficulty at all reconciling the two statements.

Mr. GORDON. One other thing. You also proposed a boxed warning at the beginning of the warning section of the labeling. Is that not correct?

Dr. SCHMIDT. Yes, in the proposal. That is where it is put.

Mr. GORDON. Why not put the boxed warning at the beginning of the labeling, as with chloramphenicol and lincomycin and clindamycin?

Dr. SCHMIDT. Speaking only for myself, when I went through it, its location was logical. It was at the beginning of the warning section, where many are, and the thought did not cross my mind that it could be or should be or might be removed from the warning thing, and stuck at the beginning. I think that it is an interesting suggestion, a valuable comment, and is one that we will evaluate, reevaluate. There is certainly no—it need not stay where it is.

The CHAIRMAN. With respect to the UGDP study, if my memory serves me correctly, it was reviewed at the request of Dr. Marstan, the then Director at NIH, by Dr. Chalmers, who at that time was at NIH. It was reviewed by somebody else prior to calling upon the Biometric Society to evaluate it, was it not?

Dr. CROUT. It was reviewed by a number of people, and it was reviewed by our own staff. It was reviewed by people at the NIH. It was reviewed also by critics. So, rather simultaneously, there were several reviews that appeared in early- to mid-1871. It was reviewed by Dr. Seltzer. Dr. Schor and Professor Cornfield also had detailed reviews of it.

The CHAIRMAN. Well, what were the conclusions of the other groups that reviewed it?

Dr. CROUT. The major conclusions of Dr. Seltzer and Dr. Schor were that the study had flaws in its fundamental design and execution to the extent that it was worthless, and that was the beginning of the controversy. Dr. Cornfield then felt that those criticisms, while correct in certain respects, were insufficient to negate the study. I must also say Dr. Alvin Feinstein also had a very critical review. So, the major critical reviews were those of Schor, Feinstein, and Seltzer. The major supporting review has been the Biometric Society, and the review by Cornfield.

In our opinion, the review by the Biometric Society was in far greater detail, far greater depth, than any of the others, and is again the overriding review of the study.

The CHAIRMAN. The Biometric Society was a review for the purpose of evaluating the validity of the studies. Is that correct?

Dr. CROUT. That is correct, and it is the only review conducted, in a sense, by a third party. You see, the controversy was begun by Dr. Feinstein, Dr. Seltzer, and Dr. Schor; and, in a sense, they were parties to one side of the controversy. Dr. Cornfield was a consultant to the study, and in defending it was, in a sense, on the UGDP side. So the Biometric Society review was, in our opinion, not only the most detailed and thorough, but it also was by a third party. All the people were previously involved in the controversy.

That is really why we waited so long for that report, and believe it is so important.

The CHAIRMAN. Go ahead.

Dr. SCHMIDT. Our warning also points out that, although only one sulfonylurea and one biguanide were included in the UGDP study, it is prudent from a safety standpoint, in view of the similarities in chemical structure and mode of action of drugs within each of these two categories, to consider that the UGDP findings may apply to the other drugs in each category. The warning has thus been applied to all sulfonylurea drugs, and the one biguanide drug marketed in this country.

Finally, the warning section states that the clear implication of the finding that tolbutamide and phenformin may carry a risk not associated with insulin; the drug, the label will state: "Should be used in preference to insulin only in patients with maturity onset diabetes whose symptoms or blood-glucose level cannot be controlled by diet alone and only when the advantages in the individual patient justify the potential risk (see Indications). The patient should be informed of the advantages and potential risks of the (drug) and of alternative modes of therapy and should participate in the decision to use this drug."

We have concluded that a patient population exists for which these drugs, properly labeled, can be considered safe and effective. We have also concluded, however, that this patient population is a limited one.

The CHAIRMAN. This is part of the warning, is it?

Dr. SCHMIDT. Yes, sir.

The CHAIRMAN. The label states that the patient should be informed of the advantages and so on, and should participate in the decision to use the drug. I am wondering what you are getting at there. If in fact you have a patient, who cannot manage it for whatever reason, psychologically, mentally, physically, or what have you; could not use insulin or could not be kept on a diet, and the doctor concludes you should reduce the blood sugar level, that is a case for which, I would assume, there is general agreement that an oral hypoglycemic would be indicated. Is that correct?

Dr. SCHMIDT. Yes, sir.

The CHAIRMAN. Well, now, then, when you say they should participate in the decision to use one of the drugs, are you then talking about that very large number of people whose problem can be handled effectively by diet? Are you saying to the physician that before you put them on an oral hypoglycemic, they must be notified it is the belief of the physician that their problem can be handled by diet; that it would be better to use the diet, and that the doctor should attempt to persuade him to do so, and understand that the use of the drug may have adverse effects, and that the patient would be better off on a diet. Is that what you are talking about?

Dr. SCHMIDT. No. I think that this is really quite explicit. The warning says that the drug should be used in preference to insulin only in patients with maturity-onset diabetes, who cannot be controlled by diet alone, and only when the advantages in the individual patient justify the potential risk. Now, this narrows it down to that

very small group of patients we have talked about before, who for whatever reason cannot be controlled by diet or cannot take insulin. So first of all, we are talking about just this small group, and then second, we are saying that the patient must be knowledgeable. Good medical practice dictates that the patient is knowledgeable about the options of control by diet, control by insulin, and if the choice by the physician is to be the oral hypoglycemic agent, we are saying that the patient should be knowledgeable about the risks of this drug to which he may be subjected.

Now, I could use another analogy that may help a little bit. If one has hypertension, he really ought to avoid salt. Now, I do not know if you have ever tried a salt-free diet, but a salt-free diet or low-salt diet is an extremely difficult, and in many respects uncomfortable sort of trial. When drugs came along that increased the renal excretion of sodium, there was a very strong tendency on the part of the patients to say, this solves my problem. I can now eat salt again, and have tasty food, and take the drug, and everything is fine. I will be just as well off as I was when I was on a salt-free diet. Physicians found it much easier to prescribe a pill than it was to fight—and believe me, it is a constant struggle with patients to keep them on a salt-free diet, or to control a diabetic by diet. So, taking the pill was really kind of a step toward the brave new world.

Now, when I used to inform my patients that, yes, they could lower their sodium with this drug, and not be as strict about their diet; but when they took a drug, they were running these risks. Sometimes for the first time, I got compliance on the part of my patients with this sodium-free diet, the low sodium diet. Now, what I am talking about is simply good medical practice that would be accepted as good medical practice by anyone. And we are saying, in this labeling, that patients, for the reasons I just illustrated with my analogy, must be informed of this possibility of increased risks; and as part of their management, they must know the options of insulin and of their using dietary control.

The CHAIRMAN. Well, then, if I understand the whole paragraph quoted there, it is addressed to a very narrow spectrum of patients.

Dr. SCHMIDT. Quite so, yes.

The CHAIRMAN. And, if I interpret it right, you are saying that if, as a practical matter, the patient's blood sugar can be controlled by diet, the doctor should not give him the drug.

Dr. SCHMIDT. That is our opinion, yes. But, as I indicated, we do believe that there is a small patient population for which these drugs, properly labeled, can be considered safe and effective, and we have also concluded though that this patient population is quite limited.

The CHAIRMAN. I have forgotten the figure of the estimate of the number of patients per year that were receiving prescriptions for oral hypoglycemics? Was it 1.5 million?

Dr. SCHMIDT. About 1½ million patients is a rough estimate.

The CHAIRMAN. You testified a few months ago that there has not been any careful studies to show what percentage of those receiving oral hypoglycemics are receiving them for properly indicated reasons.

If the figure is 1 million and a half and if you take even Dr. Bradley's estimate of only 20 percent, Dr. Bradley is saying that 80 percent of a million and a half people—about 1,200,000—should not be using them. In the view of Dr. Davidson, only 1 percent should be taking them which means that almost the whole million and a half are exposed to needless risks. Only 150,000 diabetics are taking them for proper indications. Is that correct?

Dr. SCHMIDT. It would be hard for me to believe that anymore than, say, one out of five or two out of five, at the absolute outside, of people who are now getting these drugs by these indications should get them.

The CHAIRMAN. Well, if you go above one out of five you are above Dr. Bradley, who has been one of the most vocal critics of the UGDP study.

Dr. SCHMIDT. I have really no sound basis on which to pick a number.

Dr. CROUT. I seem to think you are emphasizing the importance of this relabeling and what it means to the practice of medicine. I would also emphasize that we are talking about the United States and point out that these drugs are used worldwide. No country has yet, to my knowledge, put a warning of this type on the labeling, and, yet, we do know that when the Food and Drug Administration of the United States does something it tends to cascade worldwide. These drugs are used enormously in Europe. I am told, for example, that the number one selling prescription drug in Germany is not a tranquilizer as it is in the United States, but an oral hypoglycemic drug. So this particular action will, I think, have world impact, and we are sensitive to that. It is also why it is so terribly important to the drug industry because it is multinational.

Mr. GORDON. In an article in the Journal of the American Medical Association, Dr. John Davidson stated:

> There has been a striking increase in death rate and decrease in life expectancy in maturity onset diabetics in America, Europe, Asia, Africa, and Australia during the last 20 years. These changes have paralleled the increasingly widespread neglected diet therapy and the almost unbridled enthusiasm among many physicians and patients for the use of sulfonylureas and treatments of choice. They seem to parallel the rise and the uses and increase in these drugs and increase in the death rate and the decrease in life expectancy among diabetics.

Do you have any comments to make on that?

Dr. CROUT. We have not reviewed that situation, and I would not want to engage in the sensationalization of putting those two things together. That statement may be true or not true. I do not know.

The CHAIRMAN. Go ahead.

Dr. SCHMIDT. The limitation of the treatment population to patients on whom insulin cannot be used has been opposed in the past on the ground that it has interfered with the practice of medicine. We recognize that drug labeling has an impact upon the practice of medicine, and I think it should for this reason. The Food and Drug Administration has an obligation to ensure that drug labeling is as correct and accurate as possible. It must, moreover, meet the statutory standard of describing the conditions and use under which

the drug may be considered safe and effective. If a known hazard and potential risk leads to the conclusion that a drug may be used safely only on certain patients, this limitation on use must be expressed in labeling.

The indications section, in addition to describing the population in whom these drugs is indicated, points out that "in considering the use of (drug) in asymptomatic patients, it should be recognized that whether or not controlling the blood glucose is effective in preventing the long-term cardiovascular or neural complications of diabetes is an unanswered scientific question." This emphasizes the different benefit-risk considerations that obtain in the symptomatic patient who needs alternative treatment if insulin cannot be used, and the asymptomatic patient, whose need for alternative treatment is debatable. I think we have discussed this point at some length previously.

You asked that I comment on the promotion of these drugs. We cannot conclude that advertising for these products has been generally violative. It has, however, been based upon labeling that is in need of modification. It is clear that promotional materials must change radically to reflect the new warning and restricted indications. You can be assured that we will be monitoring the advertising of these products closely after the new labeling becomes final to see that they do, indeed, do so.

The CHAIRMAN. Do you permit reminder advertising, and how do you handle them?

Dr. SCHMIDT. Well, we permit reminder ads, yes.

The CHAIRMAN. With no claim?

Mr. MERRILL. This drug, Senator, carried a boxed warning. We have in preparation a final order that is responsive to a notice of proposed rulemaking published last year that would prohibit the use of reminder ads for any drug that carries a boxed warning.

The CHAIRMAN. I see, so any advertising would include the box.

Mr. MERRILL. It would include a brief summary—the full range of information.

The CHAIRMAN. I see, go ahead.

Dr. SCHMIDT. It is important to realize that the use of these oral hypoglycemics remains widespread despite the UGDP study and despite the rather limited ability of the drugs after a few years of use, even to lower the blood sugar. Total prescriptions for this class, according to the National Prescription Audit, have been stable between 19 million and 21 million since 1967 (except for an apparent dip in 1969.)

The CHAIRMAN. That is per year?

Dr. SCHMIDT. Yes.

The CHAIRMAN. What does that prescription mean in this context?

Dr. SCHMIDT. Well, any one individual would during the year receive more than one prescription.

The CHAIRMAN. Well, if 1½ million people were getting it, of course, it would not always necessarily be the same person.

Dr. SCHMIDT. Well, if these figures are accurate what that means is the average person would receive over 15 prescriptions or one prescription a month. I will not put my career on the line toward the

accuracy of those figures, though. Generally, physicians control when they see patients by writing prescriptions, though, and I used, for example, to be sure that I would see a patient at such and such a time by being sure that he ran out of medicine and had to come in, so that it is not unusual for indications of this kind to have more prescriptions than some others.

But the point of these relatively high figures is that there is a great deal of common practice to overcome before use of the oral agents will proceed to what we would consider to be proper levels.

It is anticipated that publicity attendant upon publication of proposed labeling by FDA and the announcement of the upcoming public hearing, as well as publicity relating to today's hearing, will bring the new labeling to the attention of physicians, as we begin the long process of persuading them that the UGDP findings should change the way they treat diabetics.

In addition we plan to issue a drug bulletin when the labeling for these drugs is made final. We will monitor the use of these drugs and will take additional measures as necessary to publicize the labeling.

This concludes my formal statement. I will be happy to respond to additional questions.

The CHAIRMAN. Thank you, Doctor. I note your comment that there is a great deal of common practice to overcome before the use of oral agents would recede to its proper levels. I think you face a formidable task, considering that you have Dr. Sammons of the AMA writing to all the State medical and county medical societies in the country and then Upjohn Co., using his letter. We received a letter from Dr. Max Miller, who, as you know, is director of the UGDP study. He sent along a copy of the letter that was sent to him by a doctor reporting on what the Upjohn salesman said to this doctor about the study. Dr. Miller did not wish that the doctor's name who wrote to him be disclosed, but he did not object to his own name being used.

This doctor wrote to Dr. Miller and said, "Dear Max, Here is a summary of what the Upjohn salesman said to me in his visit yesterday: (1) there is no cause-and-effect relationship revealed in the study between the use of Orinase and the incidents of coronary disease; (2) the statistics are so complicated that only a student of statistics can evaluate them; (3) 2½ less coronaries in the study would not change the results; (4) 35 diabetologists do not accept the results of the study; (5) the director of the study in Cincinnati does not accept the results; (6) two other men in the study do not accept the results; (7) Dr. Kent of Cleveland does not accept the results of the study; (8) Cincinnati added patients from its cardiac unit to fill its quota of diabetic patients; (9) most of the coronaries came from two centers; (10) there was no follow-up on five patients in the study; (11) the dose of Orinase was fixed so, therefore, it was not a correct dose for many patients; (12) the Joslin Clinic and other diabetes clinics have reviewed their cases in their clinics, and the result cannot support the results of the university study; and (13) the FDA will probably modify the ruling on Orinase. During the interview he had a copy"—that is the Upjohn representative—"of the Medical Tribune in his hand which he referred to from time to time."

So, considering that Upjohn has 1,100 detail men and other efforts by the industry, you have a long battle ahead of you to achieve a standard of rational prescribing of oral hypoglycemics despite the fact that there are no scientific studies refuting the careful studies done by the UGDP or the Biometric Society's evaluation. As is clear from here, the Biometric Society refuted charges that are made by the detail men. I would have this printed in full in the record.

Dr. SCHMIDT. I would sincerely hope that the medical profession, itself, and particularly the diabetologists would respond to what to me is a clear challenge in all of this and would be able to separate out the principal issue and that is the following: For whom, for what group of individuals, are these drugs suitable, given the UGDP study? And as I have indicated earlier in many, many conversations I have had with the most vigorous opponents of the UGDP study, there is an agreement that these drugs are grossly overused. Once there is agreement to that, that identifies a very serious problem, which is, in essence then, apart from the controversy of the UGDP study. And if 80 percent of these drugs are misused, that identifies a problem to which the medical profession itself must respond, and I will be bitterly disappointed if it does not.

Mr. GORDON. Doctor, suppose you are disappointed and use does not go down? That is a possibility. What do you think of the idea—I brought this up yesterday with respect to lincomycin and clindamycin—about having corrective advertising with surveys by the FDA and continuation of the corrective advertising, as in the FTC's *Hawaiian Punch* case, until the use actually drops?

Dr. SCHMIDT. We will, as I indicated, monitor the use of these drugs. We will certainly monitor the advertising, and we will see if, indeed, these drugs do become in effect unsafe and this can be shown, then I would probably have a long talk with Mr. Merrill, but I do not know. It is hard for me to hypothesize.

Mr. GORDON. May we get periodic reports on the use of these drugs as you get them?

Dr. SCHMIDT. Certainly. I would be happy to.

The CHAIRMAN. You get reports monthly?

Dr. SCHMIDT. Well, we follow certain surveys that are done, such as the prescription audit survey that I mentioned and others. There are some commercial sources of data and others that we follow that can give at least an estimation of the use of the drugs. We can also undertake surveys of our own.

Mr. MERRILL. Our information is not as good about drugs in this class as it would about antibiotics, which are certified, of course, and thus, we know how much is being produced. But we have access to pretty good numbers.

The CHAIRMAN. Thank you very much, Dr. Schmidt, for your very valuable testimony today. The hearings will open tomorrow morning at 10 o'clock in the same room. Senator Abourezk will preside as I have hearings starting on the energy legislation in the Finance Committee that has come over from the House. Thank you.

[Whereupon, at 11:35 a.m., the subcommittee recessed to reconvene at 10 a.m., the next day.]

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

(Present Status of Competition in the Pharmaceutical Industry)

THURSDAY, JULY 10, 1975

U.S. SENATE,
SUBCOMMITTEE ON MONOPOLY OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to notice, at 10:05 a.m., in room 318, Russell Senate Office Building, Senator James Abourezk presiding.

Present: Senator Abourezk.

Also present: Benjamin Gordon, staff economist, and Kay Klatt, research assistant.

Senator ABOUREZK. The hearings will come to order.

Part of the panel is here this morning, Dr. Sims and Dr. Chester. Is that right? Dr. Felig and Dr. Larner will be here soon.

Unfortunately, I have to run over to the Senate Democratic Caucus for a few minutes. I am going to open the hearings now, and you can begin your testimony. I shall ask Benjamin Gordon, our staff economist to receive your testimony until I come back, so that we do not interrupt the hearings. I shall be back as soon as I can.

So, if you are ready to begin your testimony, we are ready to receive it.[1]

STATEMENT OF EDWARD M. CHESTER, M.D., PROFESSOR OF MEDICINE, CASE WESTERN RESERVE UNIVERSITY, AND DIRECTOR, AMBULATORY MEDICINE TEACHING CLINIC, CLEVELAND METROPOLITAN GENERAL HOSPITAL

Dr. CHESTER. Mr. Chairman, I am pleased to respond to the invitation to testify concerning the use of oral hypoglycemic agents in the treatment of diabetes mellitus.

I am a professor of medicine at Case Western Reserve University and director of the ambulatory medicine teaching clinic at Cleveland Metropolitan General Hospital. A large segment of my time is devoted to teaching 3- and 4-year medical students during their clinical clerkships.

My research efforts have been directed toward an understanding of the eye changes which are associated with diabetes mellitus. For

[1] See prepared statement, page 13643.

the past 16 years I have been active in the direction of the diabetes clinic at Cleveland Metropolitan General Hospital. Prior to 1959, when I joined the full-time faculty of Case Western Reserve University at Cleveland Metropolitan General Hospital I had been engaged in the practice of internal medicine for 18 years in a suburban area of Cleveland. My practice dealt chiefly with patients who suffered from cardiovascular disease and/or diabetes mellitus. During the years of practice I served as a part-time teacher at Case Western Reserve University at Cleveland Metropolitan General Hospital.

The diabetes clinic at Cleveland Metropolitan General Hospital provides care to approximately 500 patients with diabetes mellitus per year. This totals approximately 2,000 patient visits per year. Approximately 80 percent of the patients have the maturity onset form of the disease. Prior to 1973, the majority of this group of patients were treated with oral hypoglycemic agents with a limited degree of success. Although dietary instruction was provided for the patients, there was little compliance.

When the results of the UGDP study were issued in 1970, we became concerned with our use of the oral hypoglycemic agents. We urged the physicians who cared for patients with diabetes in the clinic and hospital to pay heed to the results of the above study and to reevaluate their treatment of the maturity onset group of patients. In an attempt to learn the extent of the use of oral hypoglycemic agents and their cost, the amounts of these medications dispensed by our staff were recorded from 1968 to early 1972, and I would refer you to table I. Review of these data disclosed an alarming increase in the use of these agents from 1968 through 1970. Response to the recommendations of the UGDP study was reflected by a modest decrease in the use of the oral agents during 1971 and 1972. Because we believed that the use of these agents was still excessive, the following letter was dispatched to the chairman, pharmacy committee of the hospital on May 24, 1973.

The results of the University Group Diabetes Program, UGDP, Diabetes, 19, Supplement 2, 747–830, 1970, allows one to develop the following conclusions concerning the safety and effectiveness of the oral hypoglycemic drugs, specifically the sulonylurea group, Tolbutamide and Chlorpropamide. (1) In the group treated with Tolbutamide there was a significant increase in deaths from cardiovascular disease, as compared with those treated with either insulin or strict adherence to a calculated diet. (2) That Tolbutamide was not as effective as either insulin or strict adherence to an isocaloric diet in the control of levels of blood sugar.

The UGDP study subsequently reported comparable results with the use of Phenformin, J.A.M.A., 217 No. 777–784, 1971.

It is only fair to point out that there are skeptics who do not accept the results of the above study.

I accept the results of the study and believe that the use of Sulfonylureas, Tolbutamide and Chlorpropamide, and the Biguanides, Phenoformin, should be restricted because they appear to be hazardous to health and are far less effective and more expensive than insulin.

I suggest that we implement a form of control which would restrict the use of Sulfonylurea drugs, Tolbutamide and Chlorpropamide, and Phenformin with the following exceptions:

One, patients who cannot administer insulin to themselves because of severe visual impairment or other physical handicaps such as neurologic disorders which impair use of arms and hands.

Two, patients who refuse to use insulin.

In order to accomplish such control, the department of medicine would provide a list of physicians who could authorize the use of the drugs under discussion. Other services may wish to provide a similar mechanism.

In 1972, $30,000 were expended for Tolbutamide, Phenformin, and Chlorpropamide. Substitution of insulin would be less costly.

The results of this educational reminder and form of control produced the results noted in table I.

Table II indirectly indicates that many of the patients previously receiving oral agents were started on insulin therapy. I would like to add that if we totaled the cost of the oral agents in 1970, it reached $56,000. By 1974, this was reduced 55 percent (sic) to $9,676. That information is not recorded on the table.

Continuous review of the use of the oral agents is in progress with the intent of further decreasing their use except under the circumstances noted in the letter of May 24, 1973. It is apparent that restriction of the use of these medications in a hospital can be accomplished by education of patients and physicians and by providing a method for control. The problem is unfortunately not as simple for a variety of reasons when one attempts to achieve similar results with patients who are under the care of private physicians. Among these reasons are: One, that the conclusions of the UGDP study are not accepted by some diabetologists.

Mr. GORDON. May I interrupt for just a moment?

Even the critics of the UGDP study admit that it is the best study conducted in this field. Other studies, including animal studies, have confirmed the validity of its conclusions.

Why, then, have some physicians—even some with prestigious names in the diabetes field—continued to attack these studies, even though they acknowledge lack of effectiveness of these drugs?

Dr. CHESTER. Mr. Gordon, this is extremely difficult to understand. I can envision that some of them believe that lowering the blood sugar may prevent the vascular disease. However, there is no evidence to support that contention.

Mr. GORDON. Would any other witnesses care to comment?

Dr. SIMS. Would you be willing, Dr. Chester, to add as a qualifying phrase in this group of noninsulin dependent, predominantly overweight diabetics? In other words, I am asking you, would you make the same statement for the juvenile diabetics?

Dr. CHESTER. Would I make a different statement for the juvenile diabetics? No.

I think that there are no data to support the concept that the control of diabetes, as we measure it, namely levels of blood sugar and quantities of sugar in the urine, will prevent the development of the vascular diseases that we see in the coronary arteries, the peripheral vessels, and in the eye.

Mr. GORDON. Dr. Felig, would you care to comment?

Dr. FELIG. I agree with Dr. Chester's remarks.

I think that the kinds of treatments available to us, be it insulin, oral agents, or diet, are such that we do not fully restore the patient's metabolism to normal, and I think that we can at least explain why we might not see the improvement in prevention of vascular disease.

I might comment on the point that you raised as to why people in the face of evidence of lack of effectiveness still criticize the UGDP.

It should be recognized that some of the most vocal critics of the UGDP have raised issues regarding experimental design, statistical methodology, and some basic aspects of the approach to clinical trials without necessarily tending to promote the use of the oral agents, as such. But, this has then been misinterpreted as a validation of the oral agents. Specifically, one of my own colleagues at Yale, Dr. Albert Feinstein, has been a notable critic of the UGDP study. Dr. Feinstein is an outstanding biostatician, clinical epidemiologist, as well as internist. The basis of his criticism is not directed at trying to promote the use of the oral agents; but he has looked upon this particular study and has raised some statistical questions. Others have unfortunately used his objections as evidence for the perpetuation of a treatment which they themselves say is hardly effective.

Mr. GORDON. Dr. Feinstein, as I understand it, has never made that clear, that he is not really pushing the drugs.

Dr. FELIG. Well, while this may not be clear from his public statements, knowing him well and having worked closely with him, and since we both have appeared on panels on this issue in New Haven, it is quite clear that he does not particularly favor the utilization of these agents; but, he is merely raising questions of experimental design.

Dr. SIMS. If I could just add a word.

I do agree with Dr. Felig that, as ordinarily carried out, the partial regulation of blood glucose has not had demonstrable effect in preventing gross cardiovascular lesions in the group of largely overweight people in the UGDP, most of whom did not actually need insulin.

I do believe, however, and Dr. Crout made this point yesterday, that we do not have the evidence from the UGDP to justify extending a spirit of therapeutic nihilism with respect to blood sugar regulation to all types of lesions and in all types of diabetes.

I do feel that with Dr. Felig, that has ordinarily accomplished the regulation of blood glucose, it is not altering the cardiovascular effects from all the measurements we have up to now in the group of overweight people who do not actually need insulin anyway.

I do feel, and I think Dr. Crout made the point yesterday, that we do not have the evidence on that study to extend the therapeutic nihilism in applying it to all parts of the body.

Would you agree with that?

Dr. FELIG. I would agree.

Mr. GORDON. Dr. Chester, please proceed.

Dr. CHESTER. Two, that education of physicians lags well behind the knowledge developed through research. Unfortunately, drug company literature provides the major source of information for many physicians.

Three, the lack of adequate patient education in their understanding of diabetes and the hazards of oral hypoglycemic agents.

Four, the failure adequately to impress the patients with sufficient understanding of the importance of a calculated isocaloric diet and their failure to comply in this respect.

Five, the case of using oral medication compared with the injection of insulin.

The UGDP study clearly demonstrated that standard doses of oral hypoglycemic agents did not effectively reduce levels of blood

sugar over a 5-year period. These data confirmed previous studies which disclosed that the success rate in managing diabetes with tolbutamide at the end of 5 years was only 13 percent.

Mr. GORDON. Dr. Chester, what precisely does the 13 percent represent? Does it mean that in only 13 percent of the cases was the tolbutamide successful in lowering blood sugar at the end of 5 years?

Dr. CHESTER. At the end of 5 years. There may be early success if one measures levels of blood sugar. This is called primary failure. That is, there is no response within 1 month. In effect blood sugar levels are not at the range that one desires within that period. Then there are secondary failures in patients who initially appear to respond. Again, this is determined by levels of blood sugar. Subsequently, over each year there are more and more called secondary failures, so that by the time the 5-year period arrives, at least in this study, only 13 percent were still responding.

Therefore, we have a drug with limited effectiveness that progressively loses its effectiveness.

Mr. GORDON. Well, there is no evidence that lowering blood sugar prevents the vascular complications resulting from diabetes. Is that not correct?

Dr. CHESTER. Yes.

Mr. GORDON. Then, what are we actually accomplishing when we lower blood sugar?

Dr. CHESTER. Well, we do accomplish a variety of things. If the blood sugar level becomes excessive, then the amount of urine, salt, et cetera, are passed out into the urine, and the patient not only loses tremendous amounts of water and becomes dehydrated, but may suffer from some of the loss of the electrolytes.

Second, continuation of poorly controlled diabetes, again measured by levels of blood sugar, may be followed by a variety of very serious manifestations. One is diabetic ketoacidosis, where presumably, because of lack of insulin and other factors, large amounts of the fat are broken down, mobilized, converted to a number of substances known as ketone bodies. As these substances accumulate, the patient may become unconscious and death may follow.

There is a comparable state in which the blood sugar reaches extremely high levels, perhaps in the range of 1,000 or above, where extreme loss of water becomes critical. These patients may become unconscious and die within a relatively short period of time if not treated adequately.

There is also the question of whether or not keeping blood sugar at given levels will prevent infection. This is difficult to document. What we do know, however, is that the individual with diabetes who develops infection, unless we treat the diabetes vigorously and simultaneously treat the infection, the patient is likely to suffer and may die.

So, there are reasons to try to reach given levels of blood sugar. The difficulty is that in general no one of us knows what the optimum level may be. It is extremely difficult to restore the blood sugar levels to those that supposedly normal people would carry throughout the day without the risk of developing extremely low blood sugar or hypoglycemia, which in turn may damage the brain and cause other problems.

Mr. GORDON. Would any of the other witnesses care to comment?

Dr. SIMS. I think that it is fair to say that insulin as we now administer it to a patient, particularly one with a high degree of insulin resistance, falls far short of reproducing the elegance of control that the normal body accomplishes. So we have to keep a reservation in our minds as to whether, when and if the day comes when we can more precisely regulate insulin administration through an artificial pancreas, multiple injections, or some such, the results with respect to vascular disease might not be quite different. I am just arguing against a general attitude and nihilism that might lead to some of the complications that Dr. Chester mentioned.

Mr. GORDON. Any other comments?

Dr. Chester, please proceed.

Dr. CHESTER. These data confirm previous studies that disclose that the success rate in managing diabetes with tolbutamides at the end of 5 years was only 13 percent. Relapse or secondary failure is recorded as 22 percent within 5 years. After 6 to 7 years of therapy with oral hypoglycemic agents, only 6 to 12 percent remain well controlled. Yet, despite the ineffectiveness of these hypoglycemic agents and their demonstrated relationship to increased mortality from cardiovascular disease, these drugs are still widely used in the treatment of maturity-onset diabetes. I have noted previously the reasons for the failure on the part of physicians and patients to heed the warning of the hazards and ineffectiveness of this group of drugs.

There appear to be three approaches to this problem. These include an immediate restriction of their use through firm warning and labeling via the FDA, a long-term educational process, and the development of more rigid drug testing requirements.

Mr. GORDON. May I interrupt at this point?

Is it your opinion that warnings and strong labeling by the FDA will have an effect on the use of these drugs?

Dr. CHESTER. I would say yes, provided the labeling is done on the patient's drug box or bottle. Although I think it is fair to say that the insert in the drug package should have these warnings, by and large physicians and certainly patients do not see them.

Mr. GORDON. In the light of previous experience, do you not think that something stronger and more dramatic might be more effective?

Dr. CHESTER. Yes. I would put a label right on the box or bottle that the patient has, indicating that this is a hazardous drug.

Mr. GORDON. Maybe a skull and crossbones?

Dr. CHESTER. Yes. I would put on a skull and crossbones.

Mr. GORDON. I am kidding, by the way. Are you serious about that?

Dr. CHESTER. Well, something close to it.

Mr. GORDON. In the light of what you know about these drugs, and if the drug firms were only now seeking approval to market them, would you approve them as being safe and effective for the purposes claimed?

Dr. CHESTER. No. If they are related to the sulfonylurea group or to the biguanides, I can not see that any modifications in the drug or prolonging their half-life, or making them more potent, will resolve this problem.

Mr. GORDON. So, those drugs that are now in the NDA process, which are now being considered by the Food and Drug Administra-

tion, the glyburides, the glibenclamides, and others—if you would not approve the ones that are on the market now, you certainly, if I understand it, would not approve the other ones.

Is that a correct assumption?

Dr. CHESTER. That is correct.

Mr. GORDON. If, as you state, the oral hypoglycemics are a potential hazard to health, and if we are not sure that they are effective, what is the sense of using them?

Dr. CHESTER. Well, there are people who, for reasons mentioned, refuse to take insulin, or are too handicapped to use it. But parenthetically, we have been faced with the handicapped patient for many years before we had the oral agents. There are ways to administer insulin in the handicapped if its use is indicated.

For example, there are syringes for the administration of insulin that can be used by people with extremely limited vision. They come under a variety of trade names. Essentially they consist of an insulin syringe in which you can lock the plunger so that it cannot go beyond a given dose; so that if a patient were to receive 20 units of insulin, for example, you could set the plunger at that level. Even with limited vision the patient can withdraw the insulin from the vial and can inject it into the thigh with little difficulty.

I think the other thing that we must consider, and this is particularly true in large clinics such as ours, that we frequently do not have good contact with relatives who might be willing to learn this technique. Unfortunately, not enough effort is made to do this. The practicing physician has an advantage. He often knows the family well, and I might state parenthetically, that while in practice, this was no problem. I was able to get family members to learn how to administer insulin.

Agencies in our communities can often provide such help. For example, we have a Visiting Nurse Association in Cleveland that will perform such service.

Mr. GORDON. What puzzles me is if these drugs are harmful to nonhandicapped people, aren't they equally harmful to people who are handicapped or blind?

Dr. CHESTER. Yes, they are, and I would say that any time we use them, there is a calculated risk. The patient and the family should be aware of this risk.

Mr. GORDON. In other words, being handicapped or being blind does not make you immune to the risks.

Dr. CHESTER. That is correct.

Mr. GORDON. Doctor, go ahead.

Dr. CHESTER. Recommendations: One: Immediate warning to all physicians of the hazards by a bulletin from the FDA stating the following: (a) A suitably calculated isocaloric diet serves as the cornerstone for the treatment of maturity onset diabetes; (b) a suitable trial of dietary management for several weeks should be instituted first; (c) if adequate levels of blood sugar cannot be obtained with this regimen, even in the absence of symptoms associated with diabetes, insulin therapy should be instituted; (d) the oral hypoglycemic agents are a potential hazard to health and should be used, after the patient has been advised of this fact, with caution only

under the following circumstances: One; If the patient is handicapped by serious visual loss or other physically incapacitating disorders; and two, if the patient refuses to use insulin.

The drug companies should be required to include the above facts on the package inserts of medication, despite the fact that physicians infrequently read them. Some method of identifying these medications as hazardous must be developed for patient protection.

Two: Long-term educational effort. Medical school educators, clinicians who care for patients in university and community hospitals must emphasize the facts known about these drugs to medical students, house officers, and physicians in practice. Efforts should be made to reach the last mentioned through post-graduate courses and through the development of self-educational units in an attempt to provide more reliable and scientifically based information to counteract the biased and often inaccurate statements issued by pharmaceutical companies and the throw away pseudomedical periodicals.

A vital step in the educational process is the need to encourage and support the young investigator. Greater availability of research and training grants through the National Institutes of Health or other Government agencies should be encouraged. For, it is through the development of such investigators and teachers that the many problems related to diabetes may be resolved.

Three: Adequate long-term trials before drugs are released for use. Most drugs, and this applies to the oral hypoglycemic agents, were initially tested for their ability to lower levels of blood sugar in animals. Search for toxicity was made as well. These studies were short in duration. After short-term trials in man were made by able investigators and clinicians, the drugs were released. Subsequent long-term studies of these drugs were retrospective and dealt only with their ability to alter levels of blood sugar and lipids. The UGDP study was the first well-controlled prospective study and was designed to determine the role of these drugs in the development of vascular disease. Thus, many years elapsed before medications, which were commonly used, were found to be hazardous to health and to possess very limited effectiveness. Standards for long-term studies must be developed by the FDA to insure adequate clinical trials of drugs before their release.

The steps indicated above are likely to be met with severe outcry and resistance by pharmaceutical companies and scientists and clinicians who do not accept the conclusions of the UGDP study. Continued support of the medical societies, particularly the American Diabetes Association, would be essential.

Restriction in the use of the oral hypoglycemic agents would significantly alter modes of care for the patient with diabetes. To begin, it would needfully provide a great emphasis on the importance of dietary management. In many instances with adherence to diet, adequate reduction of blood sugar and removal of symptoms would follow. Physicians or their assistants would have to instruct patients in the use of insulin when diet alone did not suffice. Thus, more teaching would be needed for each patient. Perhaps more teaching related to mechanisms involved in the production of the disease, the need for preventing infection, manifestations of hypoglycemia, and

other measures would be taught as well. Since the cost of insulin is considerably less per patient than oral hypoglycemic agents, there would be a decrease in total cost.

The issue of the clinical use of research information is exemplified by the mixed reception of the results and recommendations of the UGDP study. Why, one may ask, are there delays in the transmission of research data to its clinical applications?

There are several reasons: One: Early research data may be presented initially to select groups in research societies and published in journals which are read by only highly trained specialists. In addition, most articles are not published for at least 6 months after they have been submitted. Two: Further delay occurs because of the need for clinical testing. Three: When the information is finally released, there are varying degrees of receptivity and understanding. Here we deal with a number of variables which include initial training and continuing education of physicians. Medical educators, both basic scientists and clinicians, and medical societies must play an important role in narrowing the gap between delivery of research information and its clinical application.

Corrective measures in this regard are most likely to be effective if medical students, fellows, and house officers in training are adequately prepared to receive and evaluate research data. This requires improvement in the teaching of basic science, biostatistics, and clinical pharmacology during medical school and postgraduate training programs. As a teacher of students and physicians in training during their formative years, one is aware of the need to stimulate them to share in the joy of learning. Such an effect develops and fosters intellectual curiosity, critical thinking, and the self-discipline required for continued intellectual development throughout their careers.

During their period of formal training, they will recognize the need to continue their education once they embark upon their careers as practitioners. Reading current literature, attending medical meetings, utilization of self-educational material, and attending specific postgraduate courses are effective approaches. Physicians should be urged, if practicing in groups, to exchange information and ideas with peers. Journal clubs and conferences could be developed. As a former practitioner, I found that becoming a part-time teacher at a university affiliated hospital was an excellent learning experience and a considerable stimulus to encourage my own intellectual development. Medical schools should encourage suitably trained physicians to participate in clinical teaching.

The task of communicating with the well-established practitioner is more difficult. Those who are well trained in various major specialities generally keep abreast of new developments in their area of interest and expertise through many of the educational methods previously mentioned. Unfortunately, there is another group of physicians who, because they are either overworked or inadequately trained, find or take little time to read or attend educational meetings, and rely upon ill-informed pharmaceutical company representatives and medical throwaways for their sources of information. Many of them observe that because of their lack of scientific background and the tremendous

burst of new information that they cannot understand and profit from current medical literature. They are thus poorly prepared to accept new research data which are clinically applicable. As a result, they are not equipped to be critical of some of the claims by drug companies of the effectiveness of various forms of therapy.

It is difficult for me to envision major corrective measures for this group. Obviously they should be urged to attend postgraduate courses in which efforts would be made to bring them abreast of current understanding of disease and therapy. The Academy of General Practice has made efforts to promote such courses. Medical schools, medical societies at local and national levels must share in this educational process.

Thank you.

Mr. GORDON. Thank you very much, Dr. Chester.

There is one more question I would like to ask you, but I think I shall save it for later because I think that the four of you may wish to discuss it. The next question is: Have you read the proposed labeling and what are your comments on it?

But I shall wait, and maybe we can talk about it as a group.

Dr. Felig, would you please give your statement?

STATEMENT OF PHILIP FELIG, M.D., PROFESSOR AND VICE CHAIRMAN, DEPARTMENT OF INTERNAL MEDICINE, YALE UNIVERSITY SCHOOL OF MEDICINE

Dr. FELIG. I am pleased to have this opportunity to participate in these hearings on the oral hypoglycemic drugs. Over 5 years have now elapsed since the initial presentation of the findings of the University Group Diabetes Program indicating an increased risk of death from cardiovascular disease in patients treated with tolbutamide or phenformin. Since that time, there has been considerable debate and controversy in the medical profession as to the validity of these findings and their implications with respect to the treatment of diabetic patients.

My discussion will focus on the following areas: One, those aspects of the pharmacology and clinical applications of the oral hypoglycemic agents in which there is fairly uniform agreement among proponents as well as opponents of the UGDP study; two, the impact which the findings of the UGDP study have had on medical practice; and three, the mechanisms by which the prescribing habits of physicians may be altered.

Virtually all experts in the field of diabetes agree that the oral hypoglycemic agents are drugs of convenience. They are convenient because they may be taken orally as opposed to the injections of insulin. More importantly, they are convenient because they do not require the self-discipline and compliance inherent in a weight-reducing dietary regimen. In contrast to the effects of insulin in the patient with diabetic coma, the oral hypoglycemic agents are not lifesaving drugs. Furthermore, no convincing evidence is available which indicates that regulation of blood sugar by oral agents retards or prevents the long-term degenerative complications of diabetes which may affect the eyes, kidney, or nervous system.

Mr. GORDON. You say that there is no convincing evidence that controlling blood sugar prevents or retards the vascular complications resulting from diabetes.

In that case, then, is there any sense in using drugs that are harmful to accomplish something that we don't know is helpful?

Dr. FELIG. Patients may derive some benefit from oral agents by virtue of their effects on the acute or short-term consequences of the high blood sugar. When the blood sugar rises to the point of causing excessive urination, as Dr. Chester has indicated, the depletion of certain essential body minerals, electrolytes, is harmful. In that circumstance, there are patients who, because of their total unwillingness to use insulin, could benefit from the oral drugs in the sense that they could have symptomatic relief. So, in that short-term or limited sense, one could ascribe a therapeutic benefit from these drugs. Whether or not that outweighs the consequence or the potential risk is something that is the essence of clinical judgment.

Mr. GORDON. We have asked Dr. John Davidson, who is director of the diabetics clinic in Atlanta, Ga., what percentage of the people using these drugs should actually be using them. He stated that maybe 1 percent of the people who are using them should be using them; or, 99 percent should not be using them. We asked Dr. Bradley who is one of the proponents of the use of this drug—or at least so he seems to be—the same question. He said that about 80 percent of the people who were using them should not be using them. Then I asked Dr. Winegrad the same question on the telephone, and he estimated about 90 percent of the people. So, you see, you have from 80 percent to 99 percent of those who are using them that should not be using them.

Would you gentlemen care to make any estimates, given your experience, given the fact that maybe 1½ million people are using these drugs?

Dr. FELIG. I am firmly convinced that there is overutilization, and we think that the figure of 80 percent represents a very conservative estimate of overutilization. We estimate that probably somewhere in the neighborhood of 90 percent should be treated with means other than the oral agents.

Mr. GORDON. Would the others agree with you?

Dr. CHESTER. I would.

Dr. LARNER. I would think 90 percent or more.

Dr. SIMS. I think it is a game of selecting a figure. But it is worth emphasizing that, if there is a minute percent in which the drug is indicated and the drugs are allowed to remain on the market for that reason, the realities are that it will continue to be used on many more patients. I believe it is for that reason that the FDA and others have to play an active role in education, as was emphasized at the hearing yesterday.

Mr. GORDON. Dr. Felig, please proceed.

Dr. FELIG. It is thus clear, I think, from what the other experts here have said, as well as from what is generally recognized, that these drugs are useful in a very limited number of patients with adult-onset diabetes; namely, those with symptoms due to an elevated blood sugar in whom dietary measures have failed and in whom insulin is impractical or refused by the patient. While some

experts would include patients with an elevated blood sugar who are asymptomatic, there is universal agreement that these drugs are overprescribed in the United States.

All of the above was in fact well recognized before the UGDP study was reported. The effect of the UGDP has been to add evidence of a relationship between oral agents and increased cardiovascular mortality. This relationship has been considered conclusive by some, persuasive by others, and at the least possible by all, including the most severe critics of the UGDP. Given the fact that: One, these agents are drugs of convenience; two, they are overprescribed; three, they may increase cardiovascular mortality; and four, that the practice of medicine is usually governed by the axiom "Primum non nocere"—"above all, do no harm"—one may question whether the findings of the UGDP study have resulted in a change in the clinical treatment of diabetes. Unfortunately, the answer is very definitely no. The most recently available data reveal that the total prescriptions for oral hypoglycemic agents increased 5.5 percent between 1972 and 1973. This represents a total of over 19 million prescriptions costing over $100 million and involving over 1½ million patients.

Mr. GORDON. Can you explain why the use of these drugs has increased in the face of the known results of recent studies—human and animal—that show that these drugs are harmful?

Dr. FELIG. I think it is difficult for me to assign a specific factor or factors. I think that what we are dealing with has been an overridding tendency to use a convenient method which both the physician and the patient are likely to be more willing to tolerate or to follow. In addition, we have the influence of a very vocal group which has been so severely critical of the UGDP that the effect has been to totally mute any of their own concerns regarding the overprescription of these drugs. So, I think what we have is the practicing physician faced with a choice between different methods, one of which is more convenient than others; and, he is being bombarded with information that could be reassuring regarding his convenient method because the data suggesting that this may be hazardous is constantly being attacked.

Mr. GORDON. How about advertising?

Dr. FELIG. I think when we talk about the data being attacked, it becomes difficult to separate the constant criticism of the UGDP by those who attack it from a seemingly scientific viewpoint and fail to point out that it is overprescribed on the one hand, from those who are actually advertising the drugs. Given the profusion of literature to which the physician is subjected, much of which is not really scientific but a pseudoscience, one can appreciate the quandary of the practicing physician. He may not have the opportunity or perhaps does not avail himself of a more dispassionate form of instruction, so as to make adequate or appropriate decisions.

Since all agree that these agents are overprescribed and, at the least, possibly toxic, it is apparent that the experts in the field of diabetes have failed to appropriately influence the clinical management of this disorder. To rectify this situation, I would propose the following:

One: Leading proponents as well as critics of the UGDP study should meet for the purpose of issuing a joint statement in which the primacy of diet and the obvious need for restriction in the use of oral hypoglycemic agents is clearly spelled out.

Mr. GORDON. What kind of a joint statement?

To whom would it be directed?

Dr. FELIG. I think we have witnessed, now, for the last 5 years, since the report of the UGDP study, that physicians who had been very critical of this have tended to band together and release statements as the Committee for the Care of the Diabetic Patient, et cetera. This group, I think, would be one which is so clearly identified as critical of the UGDP, that I would hope they would be part of a joint statement together with other individuals who have been proponents of the UGDP, or who have not attacked it, so as to come to some joint statement regarding the overall situations in which these agents should be prescribed.

It is interesting that in the criticism of the UGDP, the severe critics do not generally raise an argument as to the situations in which the drug is indicated, but restrict their argument to the question of whether there is absolutely incontrovertible data that these agents will be harmful. They should in fact be addressing themselves to the facts before us; namely, that we have a situation in this country in which a potentially toxic drug is being widely overprescribed. If one assumes to be, or in any way is willing to be called an expert in the field, he has a responsibility which goes with that designation; namely, to influence the prescribing habits and over-all practice of medicine by his colleagues. I think this is where the field of diabetes has been remiss, and in particular those who have been critical of the UGDP. They have failed, as I think all medicine has failed, to rectify a situation which all agree is not optimal from the standpoint of the patient.

Mr. GORDON. When Dr. Bradley testified here, he acknowledged that these drugs are vastly overused. I do not know whether he used the word vastly, but I am putting that in.

Nevertheless, it appears that in his attacks on the UGDP study, he is essentially promoting the use of these drugs.

Is that a correct conclusion from what you have stated?

Dr. FELIG. I would think that any group or statement that tends to accentuate the criticism of the UGDP and is not accompanied at the same time at least by an equally forcible statement indicating that these drugs are overprescribed, will have the effect of perpetuating the use of the agents; or, probably more likely, they would promote their utilization.

So, it becomes very difficult to divorce comments from such critics of the UGDP from an effect which is very similar to that which would occur with a drug promotional type of statement.

Mr. GORDON. I conclude from what you state—and I ask you if this is a valid conclusion—that it is really the responsibility of the critics of the UGDP to insure that there is some rectification in prescribing habits of physicians today.

Dr. FELIG. I think it is the responsibility of all experts in the field. That responsibility becomes that much more manifest and incumbent

upon us to exercise when we make statements which can be interpreted by others or would have the effect of promoting these drugs.

So, in that sense their responsibility goes beyond those of others who have been critical of the use of these agents and who have been proponents of the UGDP conclusion.

Such a statement can be divorced entirely from the UGDP study. It should be noted in this regard that the critics of the UGDP study often emphasize the limited indications and rarity with which they employ oral agents in their own practices. However, so long as such statements are immediately followed by a statement attacking or discrediting the UGDP, the end result is a perpetuation or exaggeration of the abuse of these agents which characterizes current medical practice.

Two: Emphasis should be placed on dietary management rather than oral agents in the instruction of medical students and in postgraduate medical courses on the treatment of diabetes.

Three: Research should be undertaken on developing improved methods of assuring patient compliance and success in adhering to weight-reducing diets.

Four: Most importantly, the labeling of oral hypoglycemics should be changed to include: (*a*) a warning that evidence has been reported that these agents may increase cardiovascular mortality; and (*b*) that use of these agents should be restricted to adult-onset diabetes in whom dietary measures have failed and insulin is refused or impractical.

I might just digress for a moment to indicate that the question of the patient's refusal becomes a difficult one. It is almost analogous to the question of informed consent. It has been said that any physician can probably convince any patient to do anything. In the same way, I am quite certain that every patient I see would refuse to take insulin depending on the way in which I present the alternatives. If I say, would you like these nice tablets or this medicine that has to be injected with a needle, I think we can all predict what proportion would refuse having to take a painful injection every day. So, I think we have to couple with this the clear implication of the physician's responsibility to advise the patient in the context of that decision of the implications of the findings of the UGDP study. Only in that way can we have patient refusal that represents a decision on both the physician's and the patient's part which is made from some knowledge.

Mr. GORDON. The Commissioner of the Food and Drug Administration stated, and I think it is also in the proposed labeling, that the patient should participate, that the physician should inform the patient of the side effects, and so forth. The patient should participate in the prescribing and use of these drugs.

Now, what do you think of the idea of having a document for getting informed consent? The form, which would be signed by the patient, would state that he had been told what the risks are, the advantages, if any, that he is aware of all this, and he wants to use the drug.

What do you think of that idea?

Dr. FELIG. I would be concerned about going to a mechanism of informed consent with respect to a particular drug, lest we have a situation in which we find ourselves having to get informed consent before any drug can be used.

My own feeling has been that the physician should document in the record of that patient, be it an outpatient record, his own office record or a hospital chart, that he has in fact discussed this matter with the patient, and the patient has been apprised of the problems, and the decision of the patient based on that. I would be concerned in terms of the overall practice of medicine, if we were to go to a situation where informed written consent were required for any particular drug that is available on the market. I think that the precedent exists for our having informed consent in a situation of experimental use. There are drugs which we administer which are potentially quite toxic, and I think that we might be faced with a situation where innumerable patients in a variety of circumstances would have to provide written consent for their treatment to be undertaken.

Mr. GORDON. Would this not be a protection both for the patient and the doctor? The doctor will have a written statement that he has already informed the patient.

Dr. FELIG. Yes, it could have a productive benefit. I would be concerned about it becoming a requirement for the practice of medicine, lest we find ourselves in a situation where we are so enmeshed with certain bureaucratic aspects of treatment that it would interfere. In other words, I am concerned with the widespread application of that type of situation. But I think it is incumbent upon the physician to make written note that this has been discussed with the patient as an added measure of being certain that such discussion has taken place.

Mr. GORDON. Would not this also be another way of cutting down on the use of these drugs?

Dr. FELIG. It would. But I think that one would run the risk—if we were to have such a situation of written informed consent as a requirement for a particular drug, I think we would run a severe risk of it interfering with treatment in other circumstances totally unrelated to the oral agents; where, for example, a potentially toxic antibiotic could be administered or is considered appropriate treatment for a particular infection. One might find a situation where treatment is interferred with because of the need to obtain informed consent.

Mr. GORDON. Any other comments?

Dr. LARNER. I feel the same way. I think that it would be very good from the point of view of minimizing the use of the drug, but it would be very difficult from the point of view of the generality of the situation if it were applied across the board. How would you decide which drugs to apply this to, and which ones not?

Mr. GORDON. Well, it could be used in certain drugs which are known to be toxic. For example, such drugs as chloramphenicol, which is also vastly overused, or clindamycin, or lincomycin, which are vastly overused. The fact that you apply them to a few drugs or some drugs does not mean necessarily that it is going to be applied to every drug.

Dr. LARNER. This would, I think, present a difficult choice situation. I mean, what would you do with—all drugs are potentially toxic, and what would you do in the case of digitalis where——

Mr. GORDON. But the benefits may outweigh the risks. It may be toxic, but the numerator representing the benefits is such that for the purposes claimed, digitalis has a favorable ratio. Now, for these drugs, I do not know. Clindamycin, as you know, is on the line. These drugs are vastly overused. Some drugs may not be vastly overused. I do not know.

Dr. Sims?

Dr. SIMS. I think it would be more consistent with the whole idea of peer review, which is prominent today, to have a physician simply justify in the record use of the particular agent under the circumstances. I am reminded of an informed consent form that appeared in Science, years ago, by Greenberg, I think it was, for a hernia operation. He listed all of the possible, horrible things that could happen, and indicated it would have to be signed by the patient's lawyer and mother-in-law as well. I believe that if informed consent was required for everything, we would end up in a difficult situation.

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

Dr. FELIG. There has been much discussion in the lay press and medical journals of the need to maintain the physician's freedom of choice in the treatment of his or her patients. I believe that our overriding concern as physicians is to do no harm. As experts in the field of diabetes, our primary obligation should be to improve the lot of our patients by influencing current treatment practices rather than perpetuating a situation which is at the least wasteful and at worst causing an unnecessary shortening of lifespan in adult-onset diabetics.

Mr. GORDON. Thank you very much.

Dr. Larner, would you proceed with your statement?

STATEMENT OF JOSEPH LARNER, M.D., PH. D., PROFESSOR AND CHAIRMAN, DEPARTMENT OF PHARMACOLOGY, AND DIRECTOR OF THE DIABETES AND ENDOCRINOLOGY CENTER, UNIVERSITY OF VIRGINIA SCHOOL OF MEDICINE

Dr. LARNER. I am responding to five points which Senator Nelson wrote in his letter of June 19, as follows: Point number one, the proper labeling of the oral hypoglycemic drugs in the light of the studies recently conducted with these drugs.

Having reviewed the literature, I have come to the following conclusion which is quoted from chapter 71, written by myself and R. C. Haynes, Jr., of a standard textbook in pharmacology, Goodman and Gilman's textbook, fifth edition, to appear in September 1975.

> The sulfonylureas should be used only in subjects with diabetes of the maturity-onset type who cannot be treated with diet alone or who are unwilling or unable to take insulin if weight reduction and dietary control fail. The physician must realize that he is using these agents only to control symptoms associated with hyperglycemia and that dietary control with or without insulin is more effective for this purpose.

The major complications and life-threatening disorders associated with diabetes are heart disease, kidney disease, blindness, and limb gangrene. There is no evidence that sulfonylureas ameliorate or prevent these disorders. While in many instances in medicine the physician must prescribe for overt symptoms, we all prefer to correct the underlying problem if possible. Unfortunately, this is not presently possible with diabetes without additional basic and clinical investigation. There is no evidence that sulfonylureas will assist in the underlying problem. Since these agents would appear to relieve primarily the symptoms of hypoglycemia, one should restrict their use until less costly and perhaps safer measures have been used—diet with or without insulin.

For this reason, I feel that there should be stronger labeling of the oral hypoglycemic drugs in the package insert. With regard to the nature of the labeling, I feel that the stronger 1972 FDA draft is preferable to the weaker 1974 draft for the reasons just discussed.

Mr. GORDON. Dr. Larner, this is a question actually for the panel rather than for you alone, but I would like you to take the lead in this.

Yesterday the Commissioner of the Food and Drug Administration acknowledged that phenformin has even a more unfavorable benefit to risk ratio than the other oral hypoglycemics. In an article that appeared in Controversy in Internal Medicine Dr. Albert Winegrad and two others wrote that the biguanides have no role in the treatment of diabetes mellitus. In addition, the Director of the Bureau of Drugs, Dr. Crout, yesterday could see no justification for this drug to be on the market. That's phenformin.

How do you feel about this?

Do you find any medical justification for that particular drug to be on the market?

Dr. LARNER. Well, I would generally agree that probably there is no—at the present time—medical indication for phenformin that I can think of. That would be my feeling.

I do not see any justification for phenformin being prescribed at all.

Mr. GORDON. Dr. Chester?

Dr. CHESTER. I would agree. It is not only hazardous, but it is almost totally ineffective.

Mr. GORDON. Dr. Sims?

Dr. SIMS. I think that first of all we ought to speak specifically about phenformin and not the biguanides as a group.

Mr. GORDON. I am talking about phenformin, which is the only biguanide on the market now.

Dr. SIMS. There is a tendency to condemn the whole group. Phenformin does some very interesting things and some of them resemble the effects of exercise lowering insulin, and whatnot. Further research may develop new drugs of this class which will do what one wants without the side reactions. So, I would not say that it should be a blanket condemnation of all of that type of drug. But, on the other hand, my own feeling about phenformin is that the labeling should be shortened to four words: Not for internal use.

Mr. GORDON. In other words, take it off the market.

Dr. SIMS. Right.

Mr. GORDON. Dr. Felig?

Dr. FELIG. I agree with the other speakers. The usefulness of phenformin is extremely limited, if it exists at all. I think there is no question that the risks exceed those that we have with any other form of antidiabetic treatment. I do not think it would be any loss if this were removed from the market.

Mr. GORDON. And you agree with Dr. Crout that the drug should be removed from the market—is that correct?

Dr. FELIG. I agree with its extremely limited usefulness.

Mr. GORDON. Would the record show that four witnesses agree with Dr. Crout.

Dr. Larner, please proceed with your statement.

Dr. LARNER. Two, the effect of these studies on medical practice.

To my knowledge these studies have had a variety of effects on medical practice. The total utilization of this group of agents, however, has not seemed to change much. For example, when the results of the studies were initially announced, some physicians changed their patients to other sulfonylurea analogs not realizing that the fundamental pharmacology should be quite similar to the drugs studied. This obviously demonstrates the need for additional postgraduate training and education of some of the medical community. Some physicians accepted the results of the study and some questioned the design and control nature of the experiment. This controversy has undoubtedly been apparent to this committee. On the whole, these studies indicate that the use of oral hypoglycemic agents should be limited to the small percentage of patients with diabetes for whom other therapies have proven impossible to carry out.

Three, the availability of scientific evidence, if any, which demonstrates the benefits of oral hypoglycemics.

I know of no evidence that directly demonstrates that the oral hypoglycemics are life-saving or life-prolonging in the therapy of diabetic patients.

The major therapeutic problem in diabetes is no longer the acute ketoacidosis which used to be the cause of death before the introduction of insulin. Rather, it is the long term or chronic vascular complications of the disease. In other words, the major problem now is the well recognized thickening and other damage to the blood vessels throughout the body leading to kidney disease, heart disease, blindness, and gangrene in the limbs. We still do not know the answer to the following fundamental question, "If the blood glucose level in the diabetic patient could be controlled as precisely as that of a nondiabetic through the use of an insulin delivery system yet to be developed, would there still be vascular complications?" In other words, we are dealing with a situation here, where there is a fluctuation as a result of three meals per day of the amount of insulin delivered from—in a very regulated manner, and, to date, we have not been able to duplicate this situation in the diabetic patient, such as it exists in the normal. And the

question is if we could duplicate it theoretically, could we prevent the vascular complications.

The second part to this is, alternatively, is there some factor or factors involved other than proper insulin delivery which leads to these harmful effects on the blood vessels? Basic and clinical investigators are working on this question with respect to insulin at present.

Mr. GORDON. Can you give us some more information about the kinds of research being conducted in this area?

Dr. LARNER. Yes, very simply, for example, the question that is now being investigated in diabetic humans is whether to return to the early methods of therapy, using several injections of rapidly acting insulin, for example three injections of the rapidly acting insulin, coordinated with meals, leads to a better situation with regard to the prevention of thickening of the blood vessels and the vascular complications.

In other words, biopsy studies are being done to investigate whether an insulin delivery system of three injections or multiple injections of rapidly acting insulin, rather than a single injection or several injections, or slower acting insulin are more effective in preventing the vascular complications than the therapy with long-acting insulins.

Now, this type of questioning is being done in humans and analogous and even more sophisticated experiments are being done in animal systems. So, my point is, we don't yet have the answer to that question with insulin. And, insulin is itself a direct hormone replacement therapy. And for this reason, if we don't have the answer with insulin yet, we certainly don't have the answer with the sulfonylurea drugs.

What we need is accelerated research in this area to answer this question. Fortunately, we have enough information now to be able to phrase the question in a sound way as an either/or type of question. Either it is the insulin delivery system, or it is not. And we should be able to get a yes/no answer on this situation. Until we do, we can't go forth, in terms of other applications, until we understand the theory.

For this reason, I feel there is no direct evidence that these oral agents are beneficial, that is, in the sense of life saving or life preserving.

Mr. GORDON. You seem to emphasize "directly." Is there any indirect evidence, whatever that means?

Dr. LARNER. Neither direct or indirect. I didn't mean to distinguish between them.

Number four, the problems of translating the results of basic research developed by medical scientists to the practice of medicine.

This is a very broad question, and we could spend a great deal of time discussing it. Briefly, I am of the opinion that scientists today are more aware than ever before of the importance of applying their fundamental studies to the practice of medicine.

For example, in my own field, pharmacology, there has been a strong development in the area of clinical pharmacology which addresses itself to this problem: Namely, the application of fundamental

laboratory findings to the patient in order to understand and treat the disease process.

For example, the sulfonylureas have been used clinically for about 20 years, yet a great deal of information regarding these compounds is still lacking. The metabolism of these compounds in patients and their precise mechanism of action are still very poorly known. These have been complicated problems and require additional studies in both animal systems as well as patients.

Scientists are very interested in coordinating such diverse efforts and studies. I feel that clinical research work in this area should be further nurtured, but that it must be balanced by a broad base in fundamental animal research as well.

And other aspects of the subject which you think might be helpful to the subcommittee.

I feel strongly that the time has come in terms of the oral hypoglycemic agents to restudy their efforts in animals and patients. It is my feeling that since recent animal studies are proving of considerable interest in terms of the actions of these drugs on organs such as the heart, adrenal glands, and liver, it would be wise to restudy these compounds in animal systems during the time their clinical use is reevaluated in order to see whether we can gain an understanding of the mechanism of the cardiovascular deaths or even reproduce them in animals.

Here I note with particular interest two recent pieces of data in animals: One, the summary statement of the work of Wissler et al. which states that in rhesus monkey fed an average American diet for 74 weeks containing 20 milligrams per kilogram tolbutamide, there were present in the coronary arteries two times more frequent and three times more severe atheromatous changes than in the coronary arteries of control monkeys; two, the work of Hsu et al. from our Department of Pharmacology at Virginia which demonstrates that in heart, adrenal medulla, and other organs, sulfonylureas inhibited catecholamine release from the nerve endings of the antonomic nerves. Thus the function of the autonomic nervous system, which provides the involuntary control for many of the organs of the body, is significantly influenced by these drugs.

Therefore, I feel that it is time to caution physicians about the use of these drugs, and to restudy them in the clinical and basic laboratory much more extensively.

Mr. GORDON. Dr. Larner, thank you very much.

With respect to the Wissler study in rhesus monkeys, what conclusions can be drawn from this for humans?

Dr. LARNER. Well, I think, the obvious warning can be put on that these may be potentially harmful drugs, that they may affect selectively, the coronary arteries, that these changes in the artery, may lead to malfunction and difficulty in the heart.

I think the warning is obvious. I think that more studies need to be done, both of anatomical nature, and of a functional nature. These studies reported here were of an anatomical nature, in which the structural changes were pointed out. And I think they must also be accompanied by studies in which the function of the heart is also studied, so that we will have some more information.

But I definitely think that, since these were done in primates, a species which is closer to human species than the rodents and so forth, they definitely should be taken seriously and considered seriously.

Mr. GORDON. Thank you very much.

Dr. Sims, would you proceed with your statement? [1]

STATEMENT OF ETHAN A. H. SIMS, M.D., PROFESSOR OF MEDICINE, COLLEGE OF MEDICINE, UNIVERSITY OF VERMONT, BURLINGTON, VT.[2]

Dr. SIMS. Mr. Gordon and members of the committee a ritual of hornblowing seems to be in order at the beginning of these statements, so I will mention that I have had experience with a number of diabetic patients over a considerable period at Yale New Haven Hospital and in Vermont, though not as many as has Dr. Chester. I am a member of the workshop on obesity of the National Diabetes Commission and of the advisory and editorial group for the Fogarty International Center conferences on obesity. The background of a lot that I have to say is contained in the volume from the centers based on the last conference, which is to be released this summer by the Government Printing Office. I do not claim to be an expert in anything except in our research work persuading volunteers to gain weight.

I would like to acknowledge a major contribution to my written statement of my wife Dorothea, who is a Fellow in Health Care of the Radcliffe Institute, and is working on diabetes education, and also of my son Nat, who has been writing a history of the UGDP as his undergraduate thesis at Harvard. They have both been doing their best to educate me.

I have included a brief summary at the beginning of my written statement, but instead of that I will read a restatement of some of the points which I believe should be emphasized. To my knowledge they have not been emphasized at these hearings before.

I would like just to list the main points, which I want to be sure to get over. To my knowledge, they have not been emphasized in these hearings previously.

One: Obesity is now recognized as a factor predisposing to non-insulin dependent diabetes in those who are genetically susceptible. Untreated obesity represents a long-term risk in relation to cardiovascular and also other diseases.

Two: Insulin, in addition to its well-known action of lowering blood sugar, is a hormone which promotes the deposition of fat.

Three: The intense preoccupation with one aspect of the UGDP, the cardiovascular mortality, and the accompanying sometimes acrimonious debate has blurred our perception of the fact that at least 50 percent of the maturity onset diabetes in the study were overweight and underexercised and that both the sulfonylureas and insulin work to make them fatter. This is a threat to their well-being,

[1] See prepared statement, page 13676.

[2] Dr. Sims on sabbatical leave at the Endocrine Division Tufts-N. E. Medical Center, Boston, Mass.

and it increases a well established risk factor for cardiovascular and other diseases.

Mr. GORDON. Dr. Sims, can you explain how both insulin and the oral hypoglycemics promote obesity? You have just said that they do, is that right?

Dr. SIMS. Even in small amounts insulin turns off the release of fatty acids from the fat deposits in both experimental and spontaneous obesity. By providing excess insulin, either by injection or by giving sulfonylureas which stimulate insulin release, weight gain is enhanced. I will go into this in a few minutes in a bit more detail.

With all due respect to Dr. Max Miller, who is here today in the audience, I would like to say that the treatment options selected for the UGDP, which represented the prevailing options of 1960, are out of date now. They do not include exercise or intensive education, or several other newer methods of management, some of which can actually reverse the overt diabetic state.

We must conclude that neither sulfonylureas, since they increase the secretion of insulin, nor insulin itself are indicated for the treatment of the overweight and I emphasize overweight, maturity-onset diabetic.

Four: Much of the problem of maturity-onset diabetes is a consequence of our American affluent post-World War II lifestyle. Altering this may frequently reverse the diabetic state, whereas prolonged use of the sulfonylureas will not.

Five: Exercise or increased level of physical activity is a means of prevention and treatment which has been sadly ignored at these hearings. I suggest that whenever diet is mentioned, as in the proposed package labeling for the oral agents, it should be as diet and exercise or diet and increased physical activity. This is because one is always dealing with both the input and also the energy output side of the problem when working with the diabetic patient.

After giving this brief outline, I would now like to elaborate a bit.

Diabetes incurs in two forms: First of all there is the insulin lacking, lean, hungry type of diabetic, usually young; the second is the non-insulin-dependent type, typical of the majority of the 1½ million people receiving oral agents today. They are usually overweight—53 percent of those in the UGDP were over 25 percent above accepted normal weight. And I think, Dr. Chester, did you not give us a figure of 80 percent overweight in your Cleveland group?

In this non-insulin-dependent there is a resistance to the action of insulin of both muscle and the fat. The insulin in the blood is actually increased, but it is inadequate in the face of the resistance for the normal metabolism of food. This produces a stress on the pancreatic islets, which may ultimately be followed by failure and development of insulin-dependent diabetes.

In treating a patient, we have to know where he is with respect to the natural history of the disorder. And we also have to know whether he is overweight. We know from our work in Vermont with normal volunteers, who have no family history of diabetes or obesity, and who have agreed to deliberately gain weight, that this insulin resistance may develop secondarily to the obesity and overeating. It is also completely reversible.

We also know from the studies of others that if overweight patients are reduced, their insulin resistance also is reversed. It is thus illogical to do anything which will increase the obesity and in turn to add to the insulin resistance of our patient.

The UGDP studies showed clearly that that actually is what happened in the group given tolbutamide and in the two given insulin. In all of the five groups there was a loss of about 3 percent of the body weight initially, as a result of the moderate dietary restriction which they were all given. The placebo group and the phenformin group, maintained this loss throughout this study. But, in this, the phenformin group was actually no better than the placebo. On the other hand, patients in both the tolbutamide and the two insulin groups, not only regained the weight initially lost, but gained well above their original baseline. So, there is a considerable difference in the study between the weight of those receiving insulin or sulfonylureas as opposed to the placebo group.

What are the other options available to us in 1975. And I see them as follows:

First, in the September 18 hearing before this committee last fall, Dr. John Davidson gave his experience in withdrawing oral agents from 1,500 patients at the Grady Hospital in Atlanta. As you heard yesterday, he has reported further on his experience in the May 26 issue of the Journal of American Medical Association, and I suggest that this article be part of the record of this hearing. By a comprehensive and rigorous regimen which included 25 hours of education per patient, he has been able to achieve substantial weight reduction in 50 to 90 percent of the patients and has essentially reversed their overt diabetic state. This is something quite different from the token prescription of a diabetic diet of which most of us have been guilty. He maintains that all diabetic patients who are overweight when they present themselves can be controlled without use of insulin, if they are given such a regimen, and, remember that this constitutes 50–80 percent of the group of maturity-onset diabetes that we are talking about.

Yesterday somebody asked me, well, if insulin is so contraindicated in this group of patients, shouldn't we have a package warning for insulin as well, against its use in the overweight diabetic? If you think about it, there really should be such a warning. So, perhaps, when Commissioner Schmidt gets done with the oral agents, he can rewrite the package label for insulin.

Second, there are more rigorous means of achieving weight loss. Dr. Davidson and others have sometimes initiated therapy of the seriously obese diabetic with brief fasting. There are now new techniques of modified, so-called protein sparing starvation that can accomplish weight loss without a damaging loss of body protein. These regimens sometimes very dramatically reverse the overt diabetic state as well. They have been proven in early pilot work to be a useful adjunct for initial weight loss. I would emphasize that must be done under supervision and we have much more to learn about them.

Third, there is a whole new field of behavioral self-modification as applied to both eating and physical activity, which can help a patient modify his basic lifestyle. Parenthetically the blame for

many of the problems ought not to go to the physician working with the limited resources he may have available or to the pharmaceutical house. A lot of our current problem is a reflection simply of our American lifestyle.

Mr. GORDON. May I interrupt for just a second? Do I understand what you are saying is that an additional danger of these oral hypoglycemic agents—I mean their very presence has been a danger—because it has taken the attention of the doctor and the patient away from the essentials of diet and exercise to a much less rigorous regimen of just taking pills?

Dr. SIMS. Thank you for stating it so well. That is precisely what I mean. The presence of this option over the 20 years that it has been available has been undesirable just for that reason. In the preinsulin days, when Dr. Allan did not have that particular option, he did very well with diet in this type of patient. I am pleased also to see that you mentioned exercise. That is about the fourth time the word has been mentioned in any of these hearings.

Mr. GORDON. And one other point: Am I also correct in that you are also saying—I am trying to summarize this in my own words—that insulin and the oral hypoglycemic agents are really treating or at least being used to treat symptoms and not the basic problem which would require a change in lifestyle, which would include diet and considerable exercise?

Dr. SIMS. Precisely. Consider the problem, say, of a relatively young housewife who has had a couple of babies and gained a lot of weight. Unfortunately she has selected the wrong parents, who are both diabetic, and her grandmother was obese. If she develops glucosuria, the odds are that the average dietary effort in the busy physician's office will not correct it. She is already running an elevated blood insulin and has an increased insulin response. If then we give her a shot of insulin every day, we are instituting a regimen that will just progressively make her gain more and more. And ultimately the increased weight is going to interfere with her well-being and probably will have a greater negative impact on her survival than might the toxicity of the oral agents itself had she been given them.

Now, the fourth option is exercise. I emphasize it as a potent means of treating a patient, although I am well aware that the patient applying to a large hospital clinic, elderly or far advanced in his disease, is not going to join the squash team.

Mr. GORDON. Dr. Sims, I might point out to you that there are certain hazards in exercise, too. One being the broken bone that I have in my foot. That is the result of playing tennis.

Dr. SIMS. Perhaps, Mr. Gordon, if you should have been exercising more, maybe your metatarsal bone would have stood up under the strain.

To resume, support for the use of exercise is given by some work by a Dr. Bjorntorp in Sweden, who measured the insulin response in obese, middle-aged men before and after a course of physical training, even though he urged them not to lose weight. The insulin response to glucose was markedly reduced. In other words, exercise alone did much to decrease the insulin resistance which is a major problem, in the maturity onset diabetic. The effect of exercise is

something that every insulin-dependent diabetic knows well. A lot of formerly overweight patients have learned to rely on physical activity to maintain their weight loss.

I believe that these options should be emphasized in the package labeling for the sulfonylureas. And on page 9 of my full statement I have written out a suggestion for altered labeling.

Mr. GORDON. That will be included in the record. All your statements will be put into the record.

Dr. SIMS. I would like, finally, to say that what we have been talking about is changing people's lifestyle, which is a very difficult thing. Some may say it simply cannot be accomplished. But I suggest that our lifestyles have been reversed once, largely as a result of advertising, and they might be reversed again by education. And I was very pleased yesterday to see the degree to which Dr. Schmidt and the staff of the FDA are concerned with this aspect of their responsibility.

Thank you very much for the opportunity to emphasize these points.

Mr. GORDON. Thank you very much, Dr. Sims.

I must say that exercise was one aspect that was really not emphasized in our previous hearings. I brought up the subject of exercise when Dr. Schmidt was testifying some time in September, but I do not think that we spent very much time talking about it.

Dr. SIMS. I remember that you mentioned Dr. Jesse Roth's suggestion that exercise actually did have some long-term effects, and that Dr. Schmidt demolished the idea.

I think that one of the problems with evaluating exercise as a modality of treatment, is that it is hard to measure, and also it cannot just be prescribed like a dose of an oral agent. But I think that we have the techniques now to run a prospective study, perhaps another UGDP study, which will include the variables of exercise and of vigorous weight reduction like that produced in the Grady Hospital program. I think that we would see results which would make the meager benefits achieved for the patients in the various groups of the UGDP seem insignificant.

Mr. GORDON. Is this being emphasized at the University of Vermont?

Dr. SIMS. We say and do a lot about it, yes.

Mr. GORDON. I have just one more question. This is a question about the labeling. It is addressed to the four of you. And that is: Have you read the proposed labeling and what are your comments on it?

We can start with Dr. Felig and go from left to right.

Dr. FELIG. I am pleased to see, in terms of labeling, that the FDA is apparently making a stand to change the labeling, and I do believe there has been some change, as regards to previous suggestions with regard to the labeling; namely, that this would apply to the entire group of oral hypoglycemic agents rather than be restricted to phenformin and tolbutamide, but also the other sulfonylureaic agents.

I am concerned about the question of the indication in diabetic patients without qualifying the fact that it should be restricted, mainly of symptomatic diabetic patients. I recognize that there are

those that would believe that the regulation of blood sugar, in the absence of symptoms, might be an indication. But I would prefer to see, based on the available evidence, a comment in the labeling that this would be primarily for the symptomatic diabetic patient, because it is only in that circumstance that we really have evidence of the benefits. There is a lot of evidence of the risk, but we are concerned with risk-benefit ratios and we ought to emphasize the utilization of these drugs only in situations where one can provide evidence of benefits. Symptomatic relief would be considered a benefit, without any question, and that is why I would favor a labeling which emphasizes the importance of restricted utilization to the symptomatic diabetic patient—clearly, where diet has failed and where insulin is refused by the patient.

Mr. GORDON. Incidentally, we will send a copy of your comments to the Food and Drug Administration to be included in their record before they issue the final order.

Dr. Larner?

Dr. LARNER. Well, in general, I am very pleased that the movement to insert the labeling is now going on, and it presumably will be consummated, and I, in general, agree with the labeling as it is written up.

I would feel a little bit more comfortable if perhaps something specific could be said in the labeling about warning physicians administering these agents to patients who have demonstrated cardiac problems, for example, with abnormal electrocardiagrams and so forth. I would like to see a little bit more of that type of warning.

Mr. GORDON. Dr. Chester.

Dr. CHESTER. I agree in general, but there are two things that disturb me, and one, on page 29, the very first sentence: "The Commissioner also concludes that a patient population exists for which these drugs, properly labeled, can be considered as safe and effective."

I would take issue with "safe" and would indicate that the effectiveness is limited.

And the other thing that bothers me—and I cannot find in this document—is how the patient will ever see the label. Will it be on the bottle with a skull and crossbones?

Mr. GORDON. Maybe that should be made more explicit in the proposal.

Dr. CHESTER. I would think so.

Mr. GORDON. We shall send that on to the FDA.

Dr. Sims?

Dr. SIMS. I have already described some ways in which the labeling could be modified to include mention of other preferable options for treatment. The question has been raised as to whether the FDA has the right to dictate to the physician how he will manage his particular patient. Another question is whether, if specific priorities and options are outlined, the physician would then become medico legally liable to suit if he does not follow them. I believe that these fears are a distortion. The FDA, in section 505 of the Food and Drug and Cosmetic Legislation, is given the responsibility to determine, to insure, rather, the efficacy of a drug. Now, efficacy is a relative thing, and if there are other options which are better, the drug

no longer can be considered efficacious. So, I think it is appropriate for the FDA to list the options. Also, regardless of any warning that is issued, the physician is in the ultimate position to say, "I am aware of your warning; it does not apply to my particular patient, because of such-and-such condition." He can write that on the record and will not be vulnerable for legal suit, if his reasoning is valid.

So that I think that the two fears are not grounded, and I think that furthermore, we all have the problem of educating patients and getting them to go along with this. I think we could regard an appropriate warning as a useful adjunct in our own education of the patient. I think that the package labeling should be written in a form and language that the patient is able to understand. We are entering an era where patients with chronic diseases are no longer satisfied to be passive sheep waiting on the word of the doctor. Rather, they are assuming more the role of a client of the physician working together with him toward the management of their lifelong problem.

Mr. GORDON. On behalf of the chairman, Senator Nelson, Senator Abourezk, and myself, I want to thank you very much for coming here and for your very informative contribution to our record.

Thank you very much, gentlemen.

The hearing is recessed, subject to the call of the Chair.

[Whereupon, at 11:50 a.m., the hearing was recessed, to reconvene subject to the call of the Chair.]

APPENDIX

EXHIBITS PROVIDED FOR THE HEARING RECORD BY THE SUBCOMMITTEE ON MONOPOLY

[From the Journal of the American Medical Association]

REPORT OF THE COMMITTEE FOR THE ASSESSMENT OF BIOMETRIC ASPECTS OF CONTROLLED TRIALS OF HYPOGLYCEMIC AGENTS

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1. INTRODUCTION

In a report that was published as a supplement to the November 1970 issue of *Diabetes*, The University Group Diabetes Program (UGDP) concluded that in patients with adult-onset diabetes, "talbutamide and diet may be less effective [in prolonging life] than diet alone . . . at least insofar as cardiovascular mortality is concerned." (*1, 2*) Of the subjects treated with tolbutamide, 12.7% died from cardiovascular causes, as compared with 6.2% or fewer in the other treatment groups. As a result of these findings, the Food and Drug Administration (FDA) recommended that tolbutamide should be used only in patients who had adult-onset, stable diabetes that could not be controlled by diet alone, and who, for some good reason, could not be treated with insulin.

The findings of the UGDP and the action of the FDA had a dramatic impact. Tolbutamide had been in general use in the treatment of diabetes since about 1956 and was thought to be a safe and effective drug. The UGDP report was carefully scrutinized by many, and, though defended by some, was severely and exhaustively criticized by others. A group of the critics started legal action to enjoin the FDA from issuing a labeling order that would discourage the use of tolbutamide.

In 1971 the UGDP reported that treatment with phenformin hydrochloride also resulted in an excess cardiovascular death rate and indeed, an excess overall death rate. (*3*) These findings have not been widely discussed, and their impact on the treatment of diabetes is unclear.

The UGDP study is the largest controlled clinical trial of oral hypoglycemic agents to date. Other studies of these agents are in progress, with preliminary results, however, that appear to differ from those of the UGDP. The National Institutes of Health (NIH), which has funded the UGDP, felt the need of a review of evidence available in all the trials. Accordingly, on June 9, 1972, the director of the NIH at that time, Robert Q. Marston, MD, wrote as follows to the chairman of the group presenting this report:

References at end of article.

At my request, on September 14, 1971, Dr. Thomas Chalmers, Associate Director of NIH for Clinical Care, invited the President of the Biometric Society, Professor B. Schneider, to appoint a committee to consider the biometric aspects of controlled trials of oral hypoglycemic agents. I am informed that the committee has now been appointed and that you have agreed to act as its Chairman.

The interest of NIH in this matter arises from the fact that approximately four million Americans have diabetes, as defined by an abnormal hyperglycemia and that seventy-five percent of these die of cardiovascular causes. Over 1.5 million diabetics are currently being treated with oral hypoglycemic agents. It is now about two years since the University Group Diabetes Program first reported that some oral hypoglycemic agents might increase the death rate from cardiovascular causes. Because of the wide clinical use of these drugs in the treatment of diabetes, it is important that the scientific aspects of the evidence concerning these agents be subjected to careful review.

Since the conclusion of the UGDP study depends in great measure on the biometric aspects of the investigation, I charge your Committee

1. to make an in-depth assessment of the scientific quality of the UGDP study and in particular of the biometric aspects of the design, conduct, and analysis of the trial;

2. to make a similar assessment of other controlled trials of oral hypoglycemic agents.

The committee is urged to utilize all the resources it needs to arrive at a satisfactory answer, and to prepare a report for publication. The Committee should feel free to obtain expert help in preparing this report and to call on representatives of pertinent disciplines as consultants. Although no prior approval by the NIH is required, we shall expect to be kept informed of the conclusions as they develop.

The committee was appointed by the President of the Biometric Society and now reports its findings.

The full committee met on six occasions during the period from August 1972 to October 1974. In addition, the European members met once as a group, and the US members did likewise. In the course of these meetings, discussions were held with others who are familiar with the clinical trials of oral hypoglycemic agents. Owing to limitations of time, the committee was able to hear only a few of the people who are knowledgeable in this field. It wishes to record special thanks for help given by Robert F. Bradley, MD, Jerome Cornfield; Alvan Feinstein, MD; R. J. Jarrett, MA, MD; Harry Keen, MD, FRCP; John B. O'Sullivan, MD; Stanley Schor, PhD; and Holbrooke Seltzer, MD.

The full committee visited the Coordinating Center of the UGDP at Baltimore and a subcommittee made a further visit to review the processes used in randomizing the allocation of treatments. Christian R. Klimt, MD, DrPH, the director of the Coordinating Center, and his staff provided extensive tabulations and original data of the UGDP trial. Harry Keen, MD, FRCP, also kindly made data available from the study that he and his colleagues conducted.

Subcommittee visits were paid to the centers at Boston and Cincinnati that participated in the UGDP trial.

Since the work of the UGDP is still in progress, it is not possible to assess the final outcome of the trial. In particular, much of the data on nonfatal events still remain unpublished. The committee saw as its main task the investigation of the excess cardiovascular mortality in the subjects who had received tolbutamide. It reviewed in detail reports of the UGDP on the design, methods, baseline data, and mortality results (*1, 2*); the original data on which these reports were based; and the commentary that has appeared in the literature up to the end of March 1973. The mortality data covered a period of approximately 8.5 years ending in October 1969; the committee has seen later overall figures, but since they were not final, the detailed data on which they were based were not studied. The preliminary report on phenformin (*3*), was considered in September 1973, but in view of the fact that the final report on that subject was still unpublished, the committee did not request the basic data on the effects of this treatment. For a similar reason it has given only limited attention to the findings on nonfatal events in the tolbutamide study. (*4*)

The committee has reviewed the published evidence available at the end of 1972 on other controlled trials of oral hypoglycemic agents. Some reference is made to all of these, but the main emphasis of this report is on the study by the UGDP and the Bedford study organized by Keen. (*5, 6*)

References at end of article.

2. CLINICAL TRIALS IN GENERAL

The evidence considered by the committee was almost wholly derived from randomized clinical trials, and it is appropriate to begin with some general remarks about this type of study.

The effects of drugs, whether beneficial or adverse, can be assessed in various ways. A traditional approach is to present a small number of case reports that are judged against other clinical experience. This kind of comparison between a few observations on a new treatment and a larger experience on standard treatments, may be convincing when the new drug has a clear-cut effect. More often, though, a new treatment produces a small improvement as compared with the standard treatment, or there is a relatively large number of variables that affect the outcome of therapy. In such situations, case studies, however carefully carried out, do not provide clear evidence of the improvement. What is needed is a controlled study using groups of explicitly defined patients who are comparable in all relevant respects, or whose potential lack of comparability can be allowed for in the analysis of the data.

Serious attempts to conduct large-scale controlled trials can be traced back to the 19th century or earlier.(7). The essential ingredients of present-day trials, however, are found notably in those planned during and after World War II, particularly those for the treatment of tuberculosis and cancer, and for prophylaxis against infectious diseases.(*8–12*) We may identify for special comment three aspects of a clinical trial to which much thought has been given; the assignment of treatments to patients, the assessment of the outcome for each patient, and the analysis and interpretation of the results.

It is very desirable that assignment of treatments to patients be done by a random mechanism, the most convenient form of which is a table of random numbers. Randomization ensures that groups are unlikely to differ materially in any prognostic factor, known or unknown. More specifically, it enables the investigator to determine the probability that observed differences in outcome between groups are due to sampling fluctuations rather than to real differences in treatment effects. Only when this probability is small can we feel confident that the treatment effects are really different. Without randomization there is no guarantee that differences in outcome are not due to the investigator's tendency to assign certain treatments predominantly to patients who have a poorer than average prognosis—a tendency of which he might be quite unaware. A further advantage of randomization is that it facilitates the use of methods for maintaining "blind" assessment, although it does not necessarily ensure their success.

If the response to treatment is thought to be influenced by one or more qualitative variables—such as sex, clinic, or stage of disease—a stratified system of allocation may be used to ensure that the treatment groups are balanced for these variables. Alternatively, simple random allocation may be relied on to produce near-equality of the groups for these particular variables, with a post hoc adjustment of the treatment comparisons in the subsequent analysis.

Experience has shown that the assessment of the response of a patient to a specific treatment may sometimes be influenced when either the patient or the investigator knows which treatment is being given. Even if such influence did not apply in a particular instance, it might be very difficult to be confident of this; hence * * *

The analysis of the results of a clinical trial centers on estimating the magnitude of treatment effects and assessing the precision of these estimates. The analysis will need to take account of concomitant variables and to adjust for any large discrepancies in base line characteristics arising despite the randomization. Furthermore, there might be interactions between treatments and various characteristics of patients, i.e., a tendency for the differences between the effects of particular treatments to vary with difference categories of patients.

In evaluating the results of trials, one must bear in mind the important role played by sample size in the ability of a trial to detect a difference of a given size. In trials of chronic diseases, where special importance lies in the rate of mortality or in the incidence of particular episodes of morbidity, the accuracy of the results will increase both with the number of patients entered into the treatment groups and also with the length of the follow-up period. When a trial with a relatively small number of patients or a short follow-up,

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References at end of article.

or both, fails to confirm a difference apparently revealed by a larger trial, the discrepancy may well be explained by the relatively large random errors inherent in a small study.

Any clinical trial imposes an administrative burden on the investigator in addition to the effort that he would in any case have to give to the care of his patients. Much of the additional burden is accounted for by the need to produce careful and unambiguous records of all the relevant clinical observations. The random allocation of treatments does not in itself cause much extra work during the trial, although a good deal of effort may go into the preparation of a detailed plan for randomization and blind assessment. Many large-scale trials can only be mounted as collaborative studies, since any one medical center would provide an inadequate number of patients. Multicenter trials give rise to special problems of coordination, and there must be a clear protocol for the study. It is necessary to ensure that principal investigators from different centers meet regularly and to establish a co-ordinating center that monitors the standards of the study, that receives the records as they become available, and that analyzes the data at regular intervals. One of the most difficult problems in multi-institution trials is to have an adequate quality control system for the data. The processing of data from a clinical trial, particularly a multicenter trial, is also a substantial task that must be properly handled to ensure the efficiency, and indeed the success, of the trial.

Randomized clinical trials pose ethical problems. Some of these are common to all medical research involving human subjects, but others are specific to this particular form of study. Three important questions are (1) Is it ethical to assign the proposed treatments to patients according to a study design drawn up by the investigator, even if the patients have given informed consent? (2) What are the criteria that should allow an investigator to depart from an assigned treatment? () When and how should a trial be stopped, or its design be modified, if one of the treatments seems to differ markedly from the others in either adverse or beneficial response?

These and similar questions have received much attention (*13*, *14*) and we cannot discuss them fully here. A few points, however, are particularly relevant to the studies under consideration. The investigator's belief is well-founded. Investigators will differ both in their readiness to undertake a randomized trial and in their reluctance to continue in the face of accumulating data suggesting that a difference may exist in the response to the treatments. In regard to this latter decision, statistical evidence about the possible size of the difference is relevant, as is also a consideration of the sequential nature of the analysis, which may well place exaggerated importance on transitory random fluctuations. Different people will make different assessments of the evidence that may be available from other studies, many of them perhaps nonrandomized, and of the risks and benefits of continuing or stopping the trial. No criteria will satisfy everyone. No matter how long a trial of this sequential type continues, some will criticize it for going on too long and others for stopping before sufficiently conclusive evidence has been obtained. In any attempt to review the propriety of particular decision to stop using all or some treatments in a trial, one must bear in mind the range of decisions that might reasonably and properly be reached.

3. THE UGDP TRIAL

3.1 *Methods*

Patients began to be recruited for the UGDP trial in 1961, and current plans are to continue follow-up through August 1975. The objectives and methods of the trial are described in the published reports (*1*, *2*) and the following account is confined to a review of a few salient features.

3.1.1 *Selection of patients*

The method of recruitment of patients varied somewhat among the 12 centers involved. Some patients were obtained from diabetes clinics or through referral by physicians, and others through special screening procedures. Patients were considered as suitable candidates for the trial if diabetes had been recognized within the preceding year. From these candidates, all those who met one of the following conditions were excluded: (1) those who did not show a positive diagnosis by a standardized glucose tolerance test; (2) patients with a history of ketoacidosis; (3) those who did not remain free of ketosis during

References at end of article.

a one-month period of treatment by diet alone or who, during this one-month period of observation, were judged unable or unwilling to follow the study protocol; and (4) those who had any serious condition that in the judgment of the clinic physician, implied a life expectancy of less than five years.

As a result, the UGDP subjects may be though of as a group of patients with adult-onset, nonketotic diabetes. There was a preponderance of women, who made up 71% of the total. Diabetes ranged in severity from asymptomatic, with no glycosuria, to symptomatic, with permanent glycosuria and marked hyperglycemit. A description of the patients is given by the UGDP (4, pp. 777–783) in the form of several tables that present distributions of base-line characteristics of those in the study.

In the UGDP, many of the criteria for excluding subjects were well defined. There were also situations, however, in which the clinic physician had to use his judgment—for example, in screening to obtain patients with a minimum life expectancy of five years. In view of this and of the fact that patients were drawn from various sources, it would be expected that clinics might differ systematically in the characteristics of the subjects selected.

3.1.2 *Randomization and allocation of treatments*

The UGDP study was arranged as a balanced design, stratified by blocks of 16 and 14 successive patients within clinics but without other restrictions on the pattern of assignment of treatment to subjects. Initially, during 1961 in each of seven clinics, the four treaments—variable-dose insular (IVAR), standard-dose insulin (ISTD), tolbutamide, and placebo—were allocated randomly to patients in blocks of 16—four subjects in each of the four treatments in random order. In 1962–1963, phenformin was added to the treatments at five new clinics as well as at one of the original esven and, in order to achieve overall parity in the total number of patients assigned to each treatment, the block size was fixed at 14, with each block containing six subjects receiving phenformin, and two receiving each of the four other treatments.

For purposes of administrative efficiency, individual patients receiving tolbutamide or placebo were not assigned uniquely identified medication, but were supplied as follows: For the tolbutamide assignments, numbers 1 to 24 were split at random into two groups of 12, one group om numbers being assigned to placebo and the remainder to bottles that would be used for tolbutamide. Each of the first 24 subjects receiving placebo or tolbutamide in a given clinic was allotted a separate bottle number, the sequence then being repeated. Bottles 25 through 48 were used for patients assigned to tolbutamide in the clinics that also used phenformin.

As a consequence of this arrangement for the distribution of medication, sometimes two and as most three subjects in a given clinic were supplied with identical bottle numbers. The administrative advantage of this scheme is that each clinic could be given an initial supply of 48 uniquely labeled medications and could order additional supplies, as need arose, without burdening the central pharmacy with responsibility for more than 800 separately labeled medications.

The orally given medications in the tolbutamide study were in tablet form. The introduction of phenformin in the second part of the study required a change in the method of administration, since phenformin is supplied as granule-filled capsules. In this part of the study all control medication for new patients was given as capsules. Tolbutamide was still supplied as tablets but, unknown to the participating clinics, placebo in the form of tablets was not given in the phenformin clinics. New bottle numbers (49 to 72) were used for the capsules, but the same method of resupply was employed.

In executing this plan, lists of ordered treatment assignments were prepared in advance for each clinic by the Coordinating Center. Random permutations of 16 from the tables given by Cochran and Cox (*15*) were used for the treatment allocations in the first six clinics, and the Rand tables (*16*) were employed for those clinics in which phenformin was administered. The assignments were entered in a log book, and space was left on each list for entry of the name and identifying number of the patient and the date of assignment. To facilitate initiation of treatment, assignment requests could be made by the clinic to the Coordinating Center and filled by telephone, in which case a limited number of individuals had authority to record the name of the patient on the

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appropriate line of the log book, and report back the preselected therapy as shown on the list, that is, either ISRD or IVAR or a bottle number. Confirmatory letters were exchanged subsequently. Alternatively, the assignment requests might come by mail, and the response be reported in like manner. All treatment assignments were made in the sequence laid out in the randomization list.

Once treatments were assigned, therapy was initiated by the clinic. Insulin therapies not being "blind," required no further consideration. In the case of orally given medication, however, the treatment was identified only by a bottle number.

3.1.3 *Data collection*

Cliincal and laboratory data were obtained initially and at subsequent quarterly follow-up visits. Provision was made for getting death reports from the clinic physician who prepared a summary of the medical record and of the attending physician's description of the circumstances surrounding the death. A copy of the death certificate and also a copy of the autopsy report, if one existed, were furnished to a central panel consisting of an internist and a pathologist. This panel made the final decision as to the cause of death and they did so without knowledge of the treatment group to which the patient had been assigned.

3.1.4 *Methods of data analysis*

As the UGDP study progressed, it appeared, unexpectedly, that the patients treated with tolbutamide had an excess mortality from cardiovascular causes. This called for statistical techniques to provide ways of evaluating the magnitude of treatment differences in mortality.

X^2 *Test.*—The first method was to perform a X^2 test to compare the proportion who died in the placebo-treated group with that in each of the other groups.

Life table analysis.—In a study such as the UGDP trial, subjects are enrolled over a period of time, so that when the study ends, the length of follow-up has varied from individual to individual. In order to adjust for these differences, the investigators used a life table method. This involves estimating, for each treatment group, the survival curve, that is, the proportion of subjects surviving a given number of years.

Multiple logistic model.—Since the death rates were affected by many factors, the distribution of which differed somewhat from one treatment group to another, it was desirable to find a method of adjusting for these differences in base-line variables. A multiple logistic model was employed for this purpose. The use of such a model can be regarded as an attempt to take into account simultaneously the covariables that affect the outcome. The probability of death is expressed as a function of the base-line variables, and the data are used to estimate the parameters that appear in this function. The statistical methods that were applied were those appropriate for large samples.

Monte Carlo monitoring procedure.—To provide a statistical basis for comparing drug-placebo differences in mortality as the study proceeded, boundaries for this difference were constructed by simulation. The investigators attempted to simulate the mortality differences that would be observed had the mortality rates from the 1959–1961 US life table been in effect for groups with the same age, race, and sex as the individuals in the study groups. Upper and lower bounds were set to the difference in death rates over time in such a way that there was a probability of only .05 that a greater difference would be observed if the 1959–1961 death rates had prevailed.

Likelihood calculations.—A further method used by the UGDP to monitor the nmber of deaths was the calculation of relative betting odds (RBO). This is a Bayesian statistical procedure by which an attempt was made to incorporate a prior belief in a hypothesis about the difference between the cumulative mortality, as calculated from the life table, of the drug-treated group and the corresponding rate for the placebo-treated group.

3.2 *Findings*

By October 7, 1969, a total of 89 deaths had occurred in the four initial treatment groups.(2) Of these, 61 were due to cardiovascular causes. The number of patients initially assigned to the various treatment groups and the percent of deaths are shown in the top portion of Table 1.

References at end of article.

A X^2 analysis of these data indicated that there were differences, not statistically significant, in the proportion dead from all causes, but the tolbutamide-treated group had a significantly greater proportion of deaths from cardiovascular causes than did the placebo-treated group. Analysis by the life table method confirmed these results. Since there were differences in the base-line characteristics of the patients in the various treatment groups, however, the question arose as to whether the differences in cardiovascular mortality rates might be adequately explained by differences in the incidence of risk factors. The conclusions from the use of the logistic model (*17*) indicated that the expected number of deaths due to cardiovascular causes in the tolbutamide group if it indeed had the same cardiovascular mortality as the placebo group, was only 10.7, whereas 26 cardiovascular deaths had been observed. Further confirmation of these analyses was obtained from the Monte Carlo monitoring procedure and the likelihood calculations. ence, the investigators concluded that there was an excess of cardiovascular deaths in the tolbutamide group—an excess group that could not be explained by differences in the base-line variables.

A closing date of Jan. 6, 1971, was used for the analysis of mortality data in the group receiving phenformin and those receiving other treatments at the phenformin clinics. A total of 47 deaths occurred, of which 37 were due to cardiovascular causes. The treatment groups in this case are the groups in the clinics where phenformin was used. The number of patients and the percent dead in the various treatment groups (*3*) are given in the bottom portion of Table 1.

The investigators concluded that there was an excess of cardiovascular deaths in the phenformin group, and further analysis showed that the excess could not be explained by baseline differences in the groups at risk.

The relatively few published finding on nonfatal untoward events in the UGDP trial show only minor differences among the treatment groups, (*3*) and these data will not be considered further in this report.

In 1969, a decision was made to discontinue treatment with tolbutamide. In contrast to the controversy that this action of the UGDP investigators provoked, there has been relatively little discussion of the decision, taken in 1971, to discontinue treatment with phenformin, and this latter step is not considered in detail in the present report.

4. OTHER STUDIES OF HYPOGLYCEMIC AGENTS

In this section, four other controlled studies of hypoglycemic agents will be reviewed. Uncontrolled studies will not be discussed because it is extremely difficult to tell which of the effects observed in such cases are due to the treatment and which are due to the selection of patients and their assignment to the treatment groups. The studies under discussion are identified by their authors.

4.1 *Keen et al (5, 6) (The Bedford Study)*

The subjects for this trial were people in whom the capillary blood glucose level, measured two hours after a 50-gm glucose load, was between 120 and 200 mg/100 ml. Of the 248 persons identified in this way, 228 were recruited through a screening program and 20 from a glaucoma study. The subjects are described as being borderline between norman and diabetic, and presumably had milder disease, on the average, than those included in the UGDP study. The latter had an average two-hour blood glucose level of 229 mg/100 ml, but this was not necessarily strictly comparable to that obtained in the Bedford study since the glucose load and conditions of the test were not identical in the two studies.

The subjects studied by Dr. Keen and his colleagues included 129 males and 119 females, so that the percentage of females was 48, considerably lower than the 71% in the UGDP study. The average age of the males was 55.4 and of the females 58.9 years. These ages were higher by 1.3 and 6.8 years, respectively than those of the corresponding groups in the UGDP. All subjects entered the trial, effectively, on one of two dates, June 1, 1962 or Jan. 1, 1964, and all were studied at one center.

Half of the subjects were treated with tolbutamide, 0.5 gm twice daily, and the other half with placebo tablets. In addition, one half of each of these groups was recommended to limit carbohydrate intake to 120 gm daily and the other

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half simply to reduce their intake of table sugar. The dose of tolbutamide was two thirds of that used by the UGDP. The subjects were allocated to the treatment groups by a method of randomization that was based on the use of numbers read from a telephone book. here was no stratification according to risk factors prior to the randomization.

At the time of entry to the trial, information was obtained on age, sex, weight, clinical history of arterial disease, blood pressure, and blood glucose level. Follow-up examinations were conducted at intervals of every six months except on three occasions when the interval was one year. The cardiovascular component of the follow-up examination included the administration of the Rose questionnaire and the taking of an electrocardiogram.

Two types of outcome have been considered in the anlyses: (1) death, either from cardiivascular causes, as identified on the death certificate, or from all causes; or (2) cardiovascular events, which, in addition to death from cardiovascular causes, include cardiac infarction, angina, worsening of the ECG, onset of claudication, and stroke. The trial was planned as a double-blind study. A list of treatment assignments was available to the principal investigator and was occasiinally consulted by him when it was thought that the welfare of the patient required it. The principal investigator is confident that the decoded information was promptly forgotten by him and did not influence his assessment of the patient's outcome.

The findings reported by Keen and Jarrett (*6*) on cardiovascular events at the end of the seven years of study are given in Table 2.

The authors noted that in each treatment group, the frequency of cardiovascular events was, as expected, higher in the subjects who were thought a priori to be at higher risk. They found no evidence of a treatment difference in the high risk group but "in the low risk individuals, the rate of events in the tolbutamide-treated group is about half that in the placebo group, a difference significant at the 2% level." (*6*) They further conclude, "a significant degree of primary protection against cardiovascular events can be conferred by tolbutamide in mildly and moderately hyperglycemic people."

Mortality data from the same study are presented in a report by Keen. (*5*) At the end of eight years from the beginning of the trial, 25 deaths had been observed in the placebo group and 24 in the tolbutamide group, 14 of the former and 12 of the latter being due to cardiovascular causes. Both total death rate and that from cardiovascular causes were at approximately the same level in the two treatment groups. The total death rate of 19.8% was approximately double that observed in the UGDP study. One important factor in this difference is the relatively high proportion of subjects over 70 years of age in the Bedford study, as shown in Table 3. Another might be that in the Bedford study there was no selection based on the likelihood of a five-year survival, as was employed by the UGDP.

The data of Table 3 show the higher mean age of the Bedford subjects as compared with those in the UGDP. The percent over 70 years of age is as high as 23.8 in the former and only 5.9 in the latter.

Table 3 also provides an instance of a difference in the distribution of base-line variables between the two treatment groups of the Bedford study. Of the placebo group, 29.6% are over 70 years of age as compared with 17.9% of the tolbutamide group. The difference is statistically significant at the 5% level. In section 6 of this report, an analysis will be given to take such differences in base-line variables into account.

4.2 *Paasikivi (18)*

This is a study of hypoglycemic treatment in 178 survivors from a first myocardial infarction. A further 92 patients who had been treated for an infarction during the same period were excluded for various reasons. The antihypoglycemic agent was tolbutamide, which was tested against a placebo.

Even or odd birth date determined whether the patient received placebo or tolbutamide. The maximal dose of tolbutamide given was 1 gm; this was also the usual dose since it was given to all but 28% of the patients, who mostly received 0.75 gm/day. The period of follow-up ranged from 1 to 5.5 years, the average being 2.9 years for the tolbutamide group and 3.0 years for the placebo group.

Sixteen patients of 83 (19%) died in the control group, and 13 of 95 (14%) died in the tolbutamide group. All deaths were considered to have been due to

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cardiac events. During the first 12 months, 15 controls and six tolbutamide-treated patients died, so that in the early stages a significant difference in favor of tolbutamide became apparent. Thus, there appeared to be a beneficial effect of tolbutamide treatment on short-term survival after the acute episode of a first myocardial infarction. After five years, however, there was no significant difference in survival between the two groups. This study neither confirms nor contradicts the UGDP findings, as the population under consideration was not one of maturity-onset diabetics, and the patients taking tolbutamide had been exposed to a relatively small dose for a shorter time than that applied in the UGDP study.

4.3 *Feldman et al.(19)*

Research subjects in this study were 350 ambulatory patients with newly discovered asymptomatic diabetes, who were between the ages of 15 and 59 years, free of other diseases, and not taking drugs known to influence carbohydrate metabolism adversely. They were randomly assigned to tolbutamide (1 gm daily), phenformin (100 mg daily), or placebo treatment to test whether the orally given drugs were effective in preventing or postponing overt diabetes in these subjects. The study began in December 1964, and the published data cover the first 5.5 years of observation. The average age at admission was 44.4 years and there have been only two deaths. Consequently, the data are insufficient as yet to throw light on the relative mortality rates associated with the different treatments.

4.4 *Tzagournis and Reynertson (20)*

A prospective study of 137 patients with premature coronary artery disease was begun in 1965 to evaluate the influence of phenformin (50 to 100 mg daily) on mortality from cardiovascular disease. In a subgroup of 104 patients, randomized with respect to phenformin treatment, or to diet alone, nine deaths occurred among 50 control patients and six deaths * * *

Persons known to have diabetes were excluded in this study, as were obese individuals, so that the generalization of these results to maturity-onset diabetics is dubious. It is also important to note that there were only about 50 patients in each group in this study. The small differences in the mortality rates for different treatments observed by the UGDP when there were about 200 individuals in each treatment group could not be detected with high probability when groups of 50 individuals are studied.

4.5 *Summary*

In reviewing as a whole the scope of the controlled clinical trials of oral hypoglycemic agents, we conclude that the only mortality data that are extensive enough for our purpose are those from the UGDP study and those from the Bedford trial.

5. CRITICISMS OF THE TRIALS OF ORAL HYPOGLYCEMIC AGENTS

These criticisms are essentially those that have been directed at the UGDP trial. The principal ones appear in papers by Feinstein, (*21*) Schor, (*22*) Seltzer, (*23*) and O'Sullivan et al. (*24*) In addition, there have been several editorials and commentaries about the UGDP trial, and they have relied mainly on these reports for source material. The criticisms have prompted the publication of two rejoinders. The first was by Cornfield, (*17*) who addressed himself to refuting the criticisms of Schor and also some criticisms that had appeared in the report by Feinstein. The scond rejoinder article by Prout et al (*25*) was specifically written to consider the many points raised in Seltzer's communication.

Many of the criticisms that are made in these articles would apply, sometimes even more strongly, to the Bedford study, but it was the UGDP trial that was challenged by the critics. The findings of this latter trial ran counter to prevailing ideas about the usefulness and safety of tolbutamide, and it is appropriate that these conclusions and the methods that led to them, should be carefully scrutinized.

In this section we restrict ourselves to the evaluation of published criticisms; a review of both trials by members of the committee will be included in subsequent sections.

References at end of article.

5.1 *Main issue in criticisms of the UGDP trial*

The primary issue of concern in the published criticism of the UGDP is whether or not the evidence pointing to toxicity of the oral agents is valid. Thus, in Seltzer's discussion of the design of the trial, (*23*) all of the nine points he raised bear on this question to an important degree. In the following account, most attention is therefore given to the UGDP mortality findings, but in addition, reference is made to the selection of patients, the dosage schedule adopted, and the decision to discontinue the use of tolbutamide and phenformin in the UGDP study.

5.2 *Selection of patients*

The first point raised by Seltzer, and also discussed by others, concerns the selection of patients. Criticism of the criteria used embraces the recruitment of subjects known to have concurrent disease (including cardiac disease), the inclusion of some who did not have diabetes, the exclusion of those judged (on somewhat vague criteria) to have a life expectancy of less than five years, and the inevitable arbitrary exclusion of those who proved uncooperative.

The determination of criteria for admission to the study depended on ethical as well as many practical considerations, and was inevitably, to some extent, arbitrary. It is almost never practicable, and rarely desirable, to make treatment comparisons in a strictly random sample from some defined population of subjects. To be useful for clinical purposes, however, the study patients should be so well described as to be identifiable by the clinician and should also be among those for whom the competing therapies are used or considered.

The choice of specific selection criteria adopted by the UGDP was a responsibility that was shared with medical experts and is not a topic on which this committee as a whole claims primary competence. It is important to recognize, however, that criticism of the choices made is largely irrelevant to the primary issue raised by the critics. For example, the concern about possible tolbutamide toxicity would not really be lessened if it could be shown that the study group contained some nondiabetics. A drug found toxic in such subjects would not likely be counted safe for persons with well-documented mild diabetes either. The criteria for inclusion or exclusion do influence the efficiency of the study, and the extent to which its findings can be generalized, but have little bearing on the issue of toxicity. We turn to criticisms that are more important in this regard.

5.3 *The UGDP mortality findings*

The implication of the UGDP mortality results is that the oral hypoglycemics are responsible for an increase in cardiovascular mortality, but that they do not affect mortality from other causes. Several kinds of criticisms have been raised about this interpretation, of which we consider the following to be the most important.

a. Although the total death rate was higher in the tolbutamide group than in those receiving placebo, the difference was not significant. Correspondingly, the death rate from noncardiovascular causes was higher in the placebo group than in the tolbutamide group. As O'Sullivan et al (*24*) have commented, "Interpretation of a study showing no increased risk of * * *

If there were subtle cues that could lead to somewhat different recording of signs and symptoms for different groups, it is conceivable that deaths of uncertain cause might be more likely to be assigned to a cardiovascular cause in the tolbutamide and phenformin groups than in the others. It will be appreciated that the review panel used in the UGDP study had no independent access to primary "objective" data, but depended on data already structured and to some extent interpreted by the clinic physician. Under these circumstances it is not too surprising that in only 2 of 89 cases was there a major disagreement between the panel and the clinic physician. The use of a review panel was an indispensable choice, especially for monitoring possible differences in procedure among clinics. However, its independent contribution to the actual assignment of cause of death should not be thought of as large. The UGDP took unusually strong measures to minimize the possibility of biased evaluation and took care to use well-defined end points in arriving at a diagnosis of cause of death. Nonetheless, the possibility of this sort of biased recording cannot be ruled out completely.

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Our view of this criticism of the UGDP findings is that it has some weight (although we do not interpret it as a criticism of the action of the UGDP) and that the toxic effect of the oral hypoglycemics cannot be affirmed with the certainty that would be present if total mortality were significantly different.

b. The excess mortality appears clearly in only a few of the clinics. This might suggest a peculiarity or defect connected with the study methods employed there, and this would have to be understood before any reasonable interpretation of drug effects could be made. We have considered the question of whether the differences in results between clinics are such as to cast doubt on the meaning of the UGDP findings. We recognize that a clinic in a middle class suburban area is likely to have patients different in many ways from those of an inner city environment, so the fact that clinics differ is in itself not at all surprising. It would at least call for an explanation, nonetheless, if a toxic effect were clearly discernible in one set of clinics and a contrary effect in others. We present data in section 6 (Table A.3) that bears on this point. Looking at the failure rates for females and comparing placebo with tolbutamide groups, we note that there were seven clinics in which there was at least one cardiovascular least in one group or the other. The patients receiving tolbutamide had the higher rate in six of these. In the case of males, the tolbutamide rate was the higher in five of seven instances. We conclude that the excess mortality is not in fact confined to a few clinics and that this * * *

As mentioned previously, the study of Paasikivi gave findings that cannot be appropriately transferred to the UGDP population in view of the differences in dosage of tolbutamide, duration of study, and population at risk.

The study of Keen and his colleagues, however, deals with a population of borderline diabetics somewhat comparable to the UGDP group except that they were mostly ascertained by screening. Since the investigation is still under way, we can consider only the findings currently available. Keen (*5*) found that the death rates for all causes and for cardiovascular causes were essentially the same in the tolbutamide and placebo groups, but that the various pathological outcomes that he designated collectively as cardiovascular events were significantly less common among low risk subjects receiving tolbutamide than among comparable subjects receiving placebo.

The resources available in the Bedford study did not permit as thorough an investigation as was possible in the UGDP. The randomization of patients was carried out without the detailed attention to documentation that a major trial demands. There was restricted coverage of background variables, and all the usual safeguards for the maintenance of "blindness" could not be ensured. Finally, as the work is unfinished, a definitive analysis has still to be produced. The provisional data that Dr. Keen has kindly sent us are reviewed in section 6 and do not throw doubt on the UGDP findings in regard to deaths from cardiovascular causes. We have regarded the data on deaths as more relevant for comparison with the UGDP and also more clearly defined than the data on cardiovascular events.

d. A fourth criticism that has figured prominently in the literature is that the randomization did not succeed in allocating to the treatment groups patients who were comparable with respect to base-line risk factors. Since we have had access to the original data, we have been able to carry out an anlysis that was designed to test whether in fact the differences in mortality in the tolbutamide and placebo groups could be explained by the base-line differences. Our findings, which are given in section 6, take into account the differences between centers and the differences in length of treatment, as well as the base-line variables. They support the view of Cornfield (*17*) that there is no evidence that the base-line differences arising from the randomization contributed in any important way to the finding of adverse effects from tolbutamide.

5.4 *Failure to adapt dosage of drugs to individual need*

Feinstein (*21*) has noted that the oral drugs "were given in unsatisfactory dosage to many people who did not need them," and others have made a similar criticism. It is true that the use of a fixed dose of drug, which was also the approach adopted by Feldman et al (*19*) and Keen et al, (*6*) limits the generalization that can be made about therapeutic effects, but since the dose of tolbutamide is about equal to the average recommended for therapeutic use, an evaluation

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of its possible toxic effect is highly relevant. Moreover, the problem of whether a subject with mild diabetes who would not normally take any hypoglycemic drugs can avoid some vascular complications of the disease by doing so is one that the trial was designed to illuminate or solve. We do not already have the answer to this; what is understood well is that certain patients require hypoglycemic drugs for current needs. It is another question as to whether these patients, and those with milder disease, can produce a prophylactic effect against vascular abnormalities by taking hypoglycemics in an attempt to maintain strict control of their disease. This is a matter for research and not for the simple implementation of current therapeutic practice.

5.5 *Discontinuation of tolbutamide and phenformin in the UGDP study*

The action of the UGDP in discontinuing the use of tolbutamide and phenformin has been criticized by those who believe that the trial of these treatments should have been continued in order to obtain more definitive results. It would have been easier to interpret the findings if there were more data on mortality. We recognize that the precise point at which suspicion of toxicity outweighs the need for scientific information is uncertain and that the choice might have been made differently by another equally qualified group of observers. Although we are not in a position to defend the timing of the UGDP decision in this matter, it is clear that ethics would dictate that a decision about withdrawal had to be made before all important questions concerning the effect of the drug were resolved. We do not criticize the UGDP investigators for having made the decision when they did. Nevertheless, the result of that decision is to leave us with some residual uncertainty about the meaning of the findings, a point that is well understood by the UGDP investigators themselves.

6. DATA FROM THE UGDP AND BEDFORD TRIALS

The directors of the UGDP and Bedford trials have kindly made available certain data that we requested from them in order to review evidence concerning the death rate of subjects taking part in controlled trials of oral hypoglycemic agents. In the case of the UGDP, the data of interest extended to the time at which the drug was discontinued. Events subsequent to that would cast light on the effects, if any, of previous use of the drugs—a question to which we do not propose to address ourselves. In the case of the Bedford trial, data are still being accumulated, and we have examined those available up to June 1972. These must, of course, be regarded as provisional. In both trials the data bear on many questions of great interest that we did not consider since they had limited relevance, if any, to our charge.

A simple method of studying data from a long-term clinical trial is to estimate failure rates for various population groups. Failure may be taken to be any adverse event; commonly, as in the present context, it is interpreted as death. The failure rate for a group after a certain length of follow-up is the rate at which the survivors are then dying. If the failure rate for a group is constant throughout follow-up (so-called exponential survival), its value, Y, may be estimated by $Y=k/t$, where k is the number of deaths in the group and t, the number of persons-periods at risk, each subject contributing a survival period or, if death has not occurred, a period of observation.

Approximately, log Y may be regarded as normally distributed with a mean of $\ln Y$ and a variance of $1/k$.

The failure rate takes into account the length of time for which each subject has been exposed to risk and can be made specific both for demographic characteristics of the subjects and for risk factors of interest. In the present context we have chosen a three-month period as an appropriate unit of time in calculating exposure to risk.

Simple and informative as the failure rates are in many cases, they become unwieldy and increasingly variable as subjects are cross-classified in more and more ways. We have therefore made use of the logistic model in order to carry out a more detailed analysis of the UGDP and the Bedford data.

6.1 *UGDP data*

In this section, we consider a problem relating to randomization and we present our analyses based on failure rates and on the multiple logistic model. We also report analyses designed to take into account the extent of adherence to treatment.

6.1.1 *Randomization by sex within clinics*

In comparing mortality in the treatment groups in relation to background variables, the UGDP investigators presented data that showed that the excess of cardiovascular deaths in the tolbutamide group was particularly marked among the females. The mortality was 10.6% in the tolbutamide group as against 2.1% in the placebo group; the corresponding rates for males were 17.5% and 11.1% respectively. In the course of reviewing this finding in the individual clinics we discovered a puzzling anomaly concerning the distribution of the two sexes to the four treatment groups within clinics.

Table A.1 shows the numbers of patients of each sex allocated to each treatment group within each clinic. The proportion of males allocated to placebo was surprisingly high in Boston and in Seattle. The discrepancy in Seattle alone would represent an unusual event in random allocation (X^2=11.31 on 1 df; P —.001) and the results taken as a whole are also anomalous (X^2=33.33 on 12 df; P—.001).

These unexpected findings do not in themselves explain the cardiovascular mortality differences. In an analysis discussed later in this section, adjustments are made for sex and clinic as well as other covariables, and there is no substantial change in the apparent effect of tolbutamide treatment on cardiovascular mortality. A more important point is whether these findings provide evidence of a breakdown of the randomization procedure—a contingency that might have grave implications for the credibility of the whole study.

The randomization procedure used by the UGDP has already been described briefly in section 3.1.2. In an attempt to find an explanation for the peculiar allocation by sex within clinics, the committee reviewed the randomization in detail. We were given access to the log books in which the Coordinating Center maintained records of the allocation of each patient to a treatment group and were impressed by the quality of the documentation that the investigators provided. We were not able to find an assignable cause for the surprising allocation of the sexes to treatments but have no reason to think that the study has been compromised by a breakdown in the randomization of patients to the treatment groups. Because of the imbalance of sexes in the * * * however, allowance for this has been made in our analysis. In institutions such as Seattle, in which no cardiovascular deaths occurred in either the placebo or tolbutamide groups, there would, of course, be no effect due to the imbalance. In general, however, all analyses of the data should be adjusted simultaneously for sex and clinic.

6.1.2 *Cardiovascular failure rates*

Cardiovascular failure rates in the UGDP study are presented in Tables A.2 through A.4. The rate for the tolbutamide group is 5.4/1,000 quarter-years (Table A.2, top) and this is significantly higher than the rate for the placebo group. In the next two parts of Table A.2 the rates for the treatment groups are presented separately for the two sexes, and the differential between the placebo and tolbutamide groups is substantial and significant for females (4.4 vs 0.8) but less marked and nonsignificant for males (7.5 vs 5.0). The number of subjects at risk is smaller for the males than for the females, and the chance of detecting treatment differences is therefore greater for the latter group. The results are consistent with the view that the tolbutamide rate is higher for both sexes, but if the males were considered in isolation, the evidence in their case would not be strong. Further, it is the older women who in particular show substantially different rates for the two treatment groups. Among women over 53 years of age receiving tolbutamide, the rate is 8.6% and for those receiving placebo, 1.4% For younger women the corresponding rates are 0.6% and 0.5%.

In Table A.3 the failure rates are presented by sex and treatment group at each clinic. These are the data that have already been referred to in section 5.3 to make the point that excess mortality in the tolbutamide group was not confiende to a few clinics. In the case of the females it was observed at the clinics in Boston, Minneapolis, Williamson, Cincinnati, Cleveland, and Birmingham. Of the remaining six clincs, four had less than 200 quarter-years of patent exposure and showed no deaths from cardiovascular causes in either treatment group. In the part of the table showing data for both sexes combined it is seen that in seven clinics the failure rate in the tolbutamide group was higher and in two it was lower than in the placebo group and that in three there was no information.

6.1.3 *Multiple logistic model*

We have used the same model as was employed by the UGDP investigators, in which the probability of death was expressed as a function of the treatment and of the base-line variables. We have, however, added additional variables, 1 to take account of the time between enrollment of the subject and completion of the study, and 11 to account for the influence of the clinics. The lengthy list of variables that was assembled in this way is shown in Table A.5. A brief account of the method of analysis based on the multiple logistic model is given in appendix A.(*26*). The analysis leads to the findings reported in Table A.6.1.

As shown in the upper portion of Table A.6.1, the potential length of follow-up, that is, the length of time from admission to the study to the time of analysis, proved, as one would expect, to be a highly significant predictor of cardiovascular death, the value of X^2 on 1 df being 23.56. This variable was not included in the analyses done by UGDP. Many of the demographic variables and risk factors studied by the UGDP were also highly significant predictors of cardiovascular death. After adjusting for the UGDP variables, treatments, and potential length of follow-up in the analysis, no additional significant improvement was made by adding the clinic effects; however, the UGDP base-line variables as a group still remained highly significant. It is worthy of note that the clinic effects remained significant after adjustment had been made for demographic variables and treatment. It was the additional adjustment by means of the variable length of follow-up that reduced the clinic effects to a nonsignificant level. Although the finding of clinic differences would not be surprising, since they might be due to differences in the patient populations or clinical practice, this indicates that most of the differences are explained by adjustng for the different length of follow-up.

The most important point in this analysis is whether or not the adjustments for covariables could be responsible for the treatment differences observed. Our analysis indicates that the treatment effects have been changed very little by this adjustment. Tolbutamide treatment vs an average of other treatments, adjusted for a subset of the demographic variables and time of potentia' follow-up, showed a X^2 of 12.14 on 1 df. In comparing the tolbutamide treatment with the other treatments, it is apparent that this contrast accounts for almost the entire treatment effect, and thus there is no significant difference between the insulin treatments and placebo.

When the data are presented separately for males and females in the next two parts of Table A.6.1, the comparison of tolbutamide with the remaining treatments results in a X^2 of 2.56 on 1 df in the case of males and 9.06 in 1 df in the case of females. The effect of tolbutamide may further be compared with the placebo treatment alone in such a way that the insulin groups also supply information on the demographic variables. Under these circumstances, the X^2 that tests for the adjusted effect of the tolbutamide treatment is 0.35 for males and 11.70 for females. These results indicate that the effect of tolbutamide treatment is significant in females but not in males.

Table A.6.3 shows that the coefficient for the tolbutamide treatment effect is 2.1158 in females and 0.3528 in males, and that the standard errors are 0.7094 and 0.4983, respectively. This implies, as noted before, that the effect is significant only in females. The effect in females, however, is not significantly different from that in males.

The analysis by means of the multiple logistic model confirms the principal finding from the simpler study of failure rates, namely, that the cardiovascular death rate was higher in certain patients receiving tolbutamide than in those receiving placebo. This result was definite in the case of females; it may well be true also of males, but the evidence in that group is not statistically significant. The multiple logistic analysis indicates that the difference in death rates remains after adjustment has been made for the effect of various base-line variables and cardiovascular risk factors.

6.1.4 *Analysis with respect to adherence to assigned treatment*

The UGDP protocol specified fixed doses for the pacebt, tolbutamide, and insulin standard treatments. Alterations were permitted only if the patient "could not be safely maintained on the assigned medication schedule." Modification of the dosage on the basis of elevated lbood glucose levels alone was not permitted. Adjustments of the dose for the patients taking variable-dose insulin, however,

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could be made on the basis of the observed blood glucose levels from the short times of the glucose tolerance test. Since some patients did not adhere completely to the assigned treatment, they may have gone for periods of time without any medication or with a modified dose, or they may have switched to another therapy.

It is clear that the interpretation of the UGDP data could be influenced by such variation in the assigned treatment. The UGDP analysis and the analysis discussed in the preceding part of this report are based on the assigned treatments. In this section * * *

Caution must be taken, however, in the interpretation of these results. It is quite possible that adherence is related to importnt base-line or other unknown variables for some treatment groups and not for others. If such were the case, subgroups having a particular pattern of adherence might not yield fair comparisons of treatment. The analyses presented in this section are designed to account for the known base-line influences. owever, without the use of randomization to form treatment groups, there is no assurance that an unknown prognostic variable is present that affects adherence patterns selectively for different treatment groups and thus invalidates the treatment comparisons.

6.1.4.1 *The extent of the problem*

Table 4 summarizes the number of patients who continued taking their assigned treatment for the entire follow-up period, and the number who, for at least one quarter, changed to other treatments or none. Thus, for the 205 patients initially assigned to the placebo group, 76 (37%) continued receiving placebo for the entire period of follow-up, and the remainder had at least one quarter of nonassigned treatment as follows: 1 (0.5%) received tolbutamide; 7 (3%), insulin at a variable dose; 92 (45%), no treatment; 4 (2%), tolbutamide and no treatment; and 24 (12%), insulin and no treatment. (One patient did not fit any of these categories.) An interesting point is that 168 (82%) of the patients initially assigned placebo were receiving either the placebo or no medication for the entire study. Since the initial treatment groups were assigned to their treatment by chance, these patients could be regarded as representative of the UGDP patient population. Thus, over the average follow-up time of 6.15 years, a very large proportion of the patients could be maintained without medication.

Another consideration in evaluating the extent of the problem of adherence is the proportion of follow-up time individuals continued receiving their initial therapy exactly as prescribed in the protocol. Table 5 classifies the patients by the proportion of their total follow-up time spent receiving treatment initially assigned. In order to compare the extent of adherence of receiving standard-dose insulin with the adherence of other patients treated with insulin, a dose modification of variable-dose insulin after the initial titration dose was regarded as a "modification." Note that 26% (218/823) of the entire population were 100% adherers for the total follow-up period and some 23% of the patients were receiving the initial treatment less than 50% of the total follow-up time.

Table 6 summarizes the total follow-up time (patient-years) with treatment exactly as assigned, with the assigned treatment at a modified dose, and with other treatments. Note that for each of the treatmetn groups, 14% to 16% of the follow-up time was spent receiving no medication at all. Further, the proportion of follow-up time that patients spent receiving the fixed dose of tolbutamide was 58% and receiving the fixed dose of insulin, 55%. It is interesting that for 25% of the follow-up period, the tolbutamide patients were taking a dose other than that specified by the protocol; similarly, for 30% of the follow-up period, the standard-dose insulin group was taking an altered dose of insulin.

6.1.4.2 *Statistical analysis*

The statistical analysis of the UGDP data in relation to adherence to treatment is divided into two portions. The first part uses a nonstandard method that was developed for the problem at hand and will be called the *relative allocation* method. It takes into consideration (1) time spent receiving no medication, (2) time spent receiving modified doses of the initially assigned therapy, and (3) time receiving other than the initially assigned medication. The second method of analyss is called the *survival modeling* method and is based on techniques recently developed by Cox (*27*) for modeling survival data when base-line

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(concomitant) variables that affect the outcome are present. Both analyses led to the conclusion that women receiving tolbutamide have higher total mortality and higher cardiovascular mortality than women receiving placebo. This holds especially for the older women (over 53 years of age).

Relative allocation method.—The basic idea of this method is explained in appendix B. The problem is to allocate the number of patients, and the deaths, to the treatments when individuals have not been receiving the initially assigned treatment for the full follow-up time. The method of relative allocation assigns numbers of both patients and deaths to the treatments in such a way that they are proportional to the length of time the patients have been taking each treatment. Suppose a subject has been in the study for ten years, half of them with the initially assigned treatment and half with no treatment. This subject would contribute half an observation to each of these categories. If the subject had died, half a death would be allocated to each of the two categories. The sum of these allocations defines an effective sample size, n′, and an effective number of deaths, d′. We then define as follows:

$$\text{death rate} = 0' = \text{d}'/\text{n}'$$

If time of follow-up is allocated in a similar way to the various treatments, and T is the total follow-up time for a subgroup, then

$$\text{failure rate} = \text{Y}' = \text{d}'/\text{T}$$

Appendix Table A.7.1 presents data on total deaths (d′), cardiovascular deaths (d′′) and effective sample size (n′) by initially assigned treatment and by treatment received; and in Table A.7.2, the calculation of $0'$ and of Y′ is illustrated.

Table A.7.2 summarizes the death rates and failure rates corresponding to assigned treatment without modification, treatment modified by change of dose, and no treatment. The cardiovascular mortality associated with tolbutamide is highest among the four assigned treatments, regardless of whether the treatments are pursued with modification or without. A comparison of the cardiovascular mortality in the tolbutamide vs the placebo groups results in statistical significance at $P=.015$ (no treatment modification), $P=.06$ (doses changed), and $P=.50$ (no drug); using the Fisher test for combining tests of significance, one finds that the overall result is significant at the $P=.007$ level.

Since there appeared to be a randomization anomaly with regard to the allocation of treatments with respect to sex, it is of interest to examine the effects of dose modification for each sex. Table A.7.3 summarizes the cardiovascular mortality by sex and dose modification. It is clear that the largest difference in cardiovascular mortality between the placebo and the tolbutamide groups occurs in the female group not having any dose modification ($P=.004$). A simple, overall statistical analysis can be carried out on the mortality rates given in Table A.7.3 by ranking then for each of the six dose-modification groups (rows) and assigning to treatments within a group the ranks 1 through 4. Since those receiving tolbutamide have the highest mortality in five groups and the next highest in one group, this group has a rank sum of $5(4)+3=23$; the rank sums for the other treatments are as follows: placebo, 12; standard-dose insulin, 12; and variable-dose insulin, 13. The probability of obtaining a rank sum equal to or higher than 23 if there were no difference between the treatments is $P=.007$. (This probability is the ratio of the number of ways of obtaining a rank sum equal to or greater than 23 to the total number of possibilities, ie, $28(6(6))/(24)(6)$). If one were to make a two-tailed statistical test, the P value would be multiplied by 2; ie, $P=.014$.

Another way to analyze the effect of adherence is to partition the data according to both (*a*) dose modification and (*b*) whether the patients adhered to the initially assigned drug for the complete follow-up period. Table A.7.4 summarizes the cardiovascular death rates according to these two variables. The highest death rate is found in the tolbutamide group who were 100% adherers, and had no dose modification. The comparison of placebo vs tolbutamide for this subgroup is significant at the $P=.003$ level. The comparison of placebo vs tolbutamide in the case of the other three subgroups is not significant. The cardiovascular death rate for the three tolbutamide subgroups who either did not adhere completely to the medication or had a dose modification is 7.6/93.9=.08. A comparison of this proportion with that for the subgroup that adhered completely and had no dose modification (21) gave significance at the $P=.002$

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level. This is in line with the view that if tolbutamide does indeed increase the risk of cardiovascular death, taking less of it should lower the death rate.

It thus appears that a significant number of the cardiovascular deaths in the tolbutamide group are associated with patients who took the drug for every quarter of the follow-up period without any dose alteration. An attempt has been made to examine this further by subdividing the groups involved. Table A.7.5 presents data separately for males and females. Note that the relative allocation of cardiovascular deaths to the female placebo group totals 2.5. (The total number of cardiovascular deaths among females was 3, of which the relative allocation method assigned 1.2 to no drug treatment and 0.4 to insulin.) A comparison of placebo vs tolbutamide in the group of females who had 100% adherence and no modification of dose results in significance at the P—.01 level. None of the other comparisons of placebo vs tolbutamide are significant at P—.05. The data cannot be meaningfully partitioned if all four treatment groups are kept separate. One way to make a finer subdivision of the covariables is to compare tolbutamide with a composite of the other three treatments. Table A.7.6 summarizes the cardiovascular death rates with respect to both sex and age at entry, using the cut-off age of 53 years (53 years represents the median age at entry). From this table, it is clear that there are too few cardiovascular deaths in the younger women to justify any comparison of tolbutamide with the control treatments. However, this comparison in the older women who adhered 100% and did not modify the dose is significant at the P=.03 level. There are too few patients in the male subgroups to be able to detect real differences by making simple comparisons, although in five of the six instances the talbutamide group has the higher rate.

Survival modeling method.—The analysis in the preceding section was carried out by simple partitions and comparisons of the treatment groups. To take account of the effect of institutions, demographic variables, and base-line variables, however, more sophisticated statistical methods are required. In this section the UGDP data are analyzed by means of a statistical technique recently developed by Cox (*27*) and modified.(*28*) The method relates failure rates to both the treatments under study and concomitant variables (institutions, base-line variables, and demographic variables).

The method, as used in this analysis, took into account the proportion of time each patient was receiving the assigned medication, the time of treatment with other protocol medications, and the time during which no medication was used. (See appendix C for details.) A preliminary analysis was carried out for both total and cardiovascular deaths by means of the following concomitant variables to determine which were important: 4 treatments, 1 variable representing no treatment, the 14 UGDP base-line variables, sum of the initial glucose tolerance tests, 4 variables associated with interaction between treatments (including no treatment), and 12 institutions. The results of the analysis showed that a model could be used that included, in addition to the treatments, 7 base-line variables (sex, race, age, digitalis history, electrocardiographic abnormality, presence of arterial calcification, sum of the glucose tolerance tests), and the 12 institutions. A final analysis was then done with the use of a model incorporating these variables. It was done independently for males and females to allow for differential treatment responses, and was carried out separately for total deaths and cardiovascular deaths.

The final results of the analysis can be expressed as a ratio of adjusted failure rates of different treatments. The term *adjusted* refers to the failure rates after allowing for the effects of the concomitant variables. The data can be summarized by presenting the natural logarithm of the ratio of failure rates and its associated standard deviation. Table A.7.7 exhibits these quantities, comparing each treatment with the placebo. Also given is a comparison of placebo vs no medication.

The conclusion is that for women in the tolbutamide group, as compared with placebo, there is an excessive mortality, both cardiovascular and total deaths. The difference is more dramatic (P=.008 for the cardiovascular deaths, although it is also significant for total deaths among women (P=.04). Thus, this analysis supports the conclusions reached in the previous section that tolbutamide, as used in this study, produces an excess mortality of cardiovascular causes in women, when compared against placebo. The data do not support the same conclusions for men, but one possible reason is that the smaller number of patients in the male group results in lack of sensitivity to detect differences of moderate magnitude.

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6.2 *The Bedford trial*

The data supplied information on both cardiovascular events and mortality.

6.2.1 *Cardiovascular events*

In the analysis of the data from the Bedford study the authors devote major attention to "cardiovascular events." These have been described by Keen and Jarrett (*6*) as "a mixed bag" and indeed do raise problems of classification in that the events are not mutually exclusive and are ascertained partly by questionnaire, partly by electrocardiographic evidence, and partly from mortality data. They include reported episodes of angina and intermittent claudication, and this could cause ambiguity, since reports of pain may be greatly influenced by variations in the mood of the subject and in the style of inquiry. In view of the lack of a formal procedure to ensure blind evaluation, the results of such analyses do not lead to firm conclusions.

6.2.2 *Mortality data*

These will be examined by two methods: the estimation of failure rates and death rates, and the use of the multiple logistic model.

6.2.2.1 *Failure rates and death rates*

These two rates differ only in their denominator, which is person-periods in the first case and persons in the second. The numerator in each instance is the number of deaths. The two rates are highly correlated for this set of data, since there was little variation in the length of exposure to risk.

In Table A.8.1 the influence of binary background variables on the death rate is shown. The rate is increased by hypertension, hyperglycemia, and arterial disease. It is higher for females than for males and higher for those over 45 years of age than for younger patients.

In Table A.8.2, placebo and tolbutamide treatments are compared, taking into account the background variables one or two at a time. In no case is there adequate evidence of a difference between the two treatments.

In Table A.8.3, the death rates (by treatment group and sex) are given for more finely divided age groups. The reason for this is that as shown in Table 3, the proportion of older subjects is higher in the placebo groups, and age is therefore a potentially confounding variable in the comparison of treatment effects. Owing to the relatively small numbers of subjects in the individual age groups, the rates are somewhat irregular. The effect of age is marked, but there is no evidence of a difference between the treatment groups.

6.2.2.2 *Multiple logistic model*

In this trial, all the patients were entered into the study at essentially two different points in time and not over a period of time, as in the UGDP. This feature enables some simplification of the analysis of the data. To adjust for the differences in the length of follow-up, and possibly for other differences as well, between those who entered at the two different times, an indicator variable was included in the logistic analysis to distinguish the two groups of subjects. The variables included in the logistic analysis of these data are given in Table A.9.1.

The results of the analyss of the Bedford study deaths due to cardiovascular causes and deaths due to all causes are shown in Table A.9.2. The variances introduced in this analysis were significant in predicting death either from all causes (X^2=81.02 on 5 df) or from cardiovascular causes (X^2=55.16 on 5 df). Adjusting for these variables, however, did not change the basic conclusion reached from the unadjusted analysis that the death rates did not differ significantly according to treatment.

7. CONCLUSIONS

In this section we summarize our overall findings of the UGDP study with respect to the protocol, the conduct of the study, the methods of analysis, and the findings.

7.1 *Protocol*

Question. Was the target population for this study an appropriate one?

Answer. Critics have pointed out that certain patients were required to accept treatment that would not normally conform to clinical practice, and they

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argue, therefore, that the target population was unsuitable. Such a claim, however, overlooks the important but ill-understood prophylactic aspect of the trial, in which certain treatments were given to patients who, initially at least, could safely go without drugs, in order to test whether the common vascular complications of diabetes could be prevented. The issue was the testing of certain possibly preventive treatments rather than the implementation of certain standard therapeutic regimens.

Question. Was the decision to include phenformin in the study justified?

Answer. In the event it proved to be, since valuable information was obtained about the limitations of that drug. Its use, however, greatly complicated an already difficult study. It is clear that one of the problems of a long-term clinical trial is that potentially interesting therapies may develop while the trial is in progress, and the natural desire to include them may divert resources.

The omission of a history of smoking was a blunder.

7.2 *Conduct of the study*

This was necessarily a lengthy and complex trial, and a substantial pioneering effort was needed to mount it successfully. We have raised a question of whether the randomization was properly carried out. The only evidence that it might not have been is the data on the allocation of treatments according to the sex of the patient. Against this possibility are two * * *

7.3 *Methods of analysis*

The UGDP investigators sought to examine their data from a number of different points of view, and in so doing they made use of some relatively unfamiliar and exploratory statistical techniques. In some cases these methods would not necessarily have been chosen by other groups of statisticians faced with the same situation, but since the results of all the analyses tended to point in the same direction, there would be little advantage in discussing at length the weight to be attached to the different analyses.

The likelihood calculations seem to us to add very little to the other analyses. The results are rather difficult to grasp and require rather arbitrary weighting to be given to the likelihood of different hypotheses. The method does not take concomitant variables into account.

The Monte Carlo monitoring procedure was a major attempt to overcome the selective effect of a sequential analysis of the mortality data. The investigators were concerned lest they had paid undue attention to contrasts between treatments at a particular moment when extreme fluctuations might have occurred. Their method was ingenious, and although minor points of criticism may be raised, we do not think that these materially affect the issue. (Some of these points might be (1) the use of national mortality data, with death rates higher than those in the study population; (2) the use of an "average" survival curve for all patients in the simulation; (3) the adding of life table death rates at different ages to obtain the death rates during intervals; and (4) the arbitrariness of the linear boundaries. For an alternative approach to the sequential analysis of survival data, using internal comparisons only, see Breslow and Haug.(*29*)) The detailed outcome of such a monitoring procedure is of no great importance. The decision to stop the use of tolbutamide must have depended on considerations of various sorts, among which the monitoring procedure provided a contribution—no more than that.

The UGDP did not try to determine whether interactions were present in their data. This criticism was raised by Feinstein and is valid.

7.4 *Findings*

Although we have concerned ourselves almost entirely with issues related to the possible toxicity of tolbutamide, we wish to point out that one of the valuable aspects of the completed UGDP trial will be the provision of data on the long-term treatment of adult-onset diabetes with insulin. It is already clear that the benefits from this treatment are not dramatic, and the only worthwhile information about them will have to come from the relatively precise methods of a controlled clinical trial. In this sphere, the UGDP trial has no competitor. Indeed, we would generalize from this and point out the * * *

On the question of cardiovascular mortality due to tolbutamide and phenformin, we consider that the UGDP trial has raised suspicions that cannot be dismissed on the basis of other evidence presently available.

We find most of the criticisms levelled against the UGDP findings on this point unpersuasive. The possibility that deaths may have been allocated to car-

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diovascular causes preferentially in the groups receiving oral therapy exists, and, in view of the "nonsignificance" of differences in total mortality, some reservation about the conclusion that the oral hyperglycemics are toxic must remain. Nonetheless, we consider the evidence of harmfulness moderately strong. The risk is clearly seen in the group of older women as shown in Table A.2. Whether it acects all subgroups of patients cannot be decided on the basis of the available data. owing to the small number of deaths involved in these subgroups.

There remains the question of generalization of these findings. As has been frequently pointed out, the conditions of drug use in this study were, to some extent, abnormal. Tolbutamide dosage is varied in practice, and the patient unable to maintain adequate control with tolbutamide could be shifted to insulin. A good deal rests, then, on the matter of whether tolbutamide is actually toxic. If this should be admitted, it is hard to see how it could be regarded as a reasonable therapy, even when given in variable rather than fixed dosage.

If, however, this finding is rejected, there remains the question of whether tolbutamide, although ineffective in this fixed-dose regimen, might be an effective therapy as ordinarily used. The UGDP gives no direct answer to this question, but the dose of tolbutamide ordinarily employed varies only moderately.

There is also the question of the extent to which the UGDP subjects reasonably represent the population of maturity-onset diabetics who are candidates for oral therapy. Little of the commentary available to us raises questions on this point, and we assume that the UGDP population is representative of a large fraction of the maturity-onset, non-insulin-dependent diabetic population.

In conclusion, we consider that in the light of the UGDP findings, it remains with the proponents of the oral hyperglycemics to conduct scientifically adequate studies to justify the continued use of such agents.

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APPENDIX A

Use of the logistic model

The logistic model has been recognized as being very useful for studies in which there are only two outcomes, for example, death or survival (–6) In this use of the model it is assumed that the probability of death, P, depends on m independent variables, X_1, X_2, * * *, Xp, according to the relation

$$P=\frac{1}{1+c^{-A}}$$

where

$$A=b_0+b_1X_1+b_2X_2 \ldots +b_mX_m$$

On each subject in the UGDP trial, the data available were the m independent variables and an outcome variable that was given the value 0 or 1 according to whether the patient survived or died The multiple regression equation was fitted to relate the probability of death to the independent variables A maximum likelihood procedure was used to find estimates of the regression coefficients b_0, b_1, . . . bp

Groups of people such as those receiving a treatment or those from a particular clinic were incorporated into the model by the inclusion of an indicator variable that, for a given individual, took the value 1 if the indivudual was in that group, and 0 otherwise In order to avoid redundancy, there must be one fewer variable for clinics than there were clinics, and so for other sets of categories To allow for the varying lengths of follow-up, potential length of follow-up (ie, the length of time between entry into the study and the end of the study) was entered as a covariable in the regression.

As a test of the various covariables in the logit regression, the likelihood ratio χ^2 was computed. The likelihood ratio χ^2 can be computed for a set of parameters, β, by comparison with a set of parameters β^* to which, under the null hypothesis,

p constraints have been applied If the maximum likelihood estimates of the set of parameters are β and β^* respectively, then $-2 \ln [L(\beta^*)/L(\beta)]$ is asymptotically distributed as χ^2 on p degrees of freedom, where L(.) denoted the likelihood function When investigating the regression coefficients themselves, one can use the fact that they asymptotically have a multivariate normal distribution with a variance-covariance $[I(\beta)]^{-1}$ where

$$I(\beta) = \left[\frac{d^2 L(\beta)}{d\beta_i d\beta_j}\right] m \times m$$

This enables one to obtain estimates of the standard deviation of the estimates of the regression parameters.

Table A.5 gives a list of the variables that were considered in the analysis of the UGDP data and Table A.6.1 summarizes the findings on them. The estimates of the regression coefficients when all of these variables have been included are given in Table A.6.2. As often happens when one does multiple regression with many parameters, there are redundancies, so that a relatively small subset of the variables gives nearly as good a prediction as the entire set. In looking for an appropriate subset of variables, one still includes the variables that are of greatest interest, in this case, the treatment effects. Sex was also included because of an interest in the treatment effects for each sex. It has already been noted that after adjusting for treatment variables, demographic variables, and time of follow-up, the clinic differences were not significant, and so the variables for clinics were dropped. Other demographic variables were added to the regression until the maximum of the likelihood did not differ significantly from the maximum of the likelihood when all the variables were included. The order in which the variables were entered into the regression depended on the absolute value of T (see Table A.6.2), the large values being entered first. The subset of variables thus identified (age, sex, systolic blood pressure, electrocardiographic abnormality, cholesterol level, and arterial calcification) is indicated in Table A.5 and these were used in the further analysis. A regression analysis with this subset of variables other than sex was also done separately for each sex. The results of the analysis using the subset of variables are summarized in Table 9.6.1, as well as in Table A.6.3. This analysis indicated that the treatment effects may be different from the two sexes. The harmful effect of tolbutamide treatment is most apparent for women, although the effect for men is not significantly different from that for women. It is not clear whether the results for tolbutamide apply only to women or whether the effect on women is more obvious because of the larger numbers involved.

Table A.6.4 gives the number of deaths observed in each treatment group, broken down by age and sex, along with the number expected on the basis of the model using the subset of variables just mentioned. It appears that the model does reasonably well in predicting the number of deaths in each group.

The variables used in the analysis of the Bedford study data are shown in Table A.9.1. The analysis was done for all causes and cardiovascular causes of death, and the results are summarized in Table A.9.2. The regression coefficients obtained when all the variables are included are shown in Table A.9.3.

APPENDIX B

Relative allocation method

In this section we outline the rudiments of the relative allocation (RA) method of analysis. Define

S_α = Total follow-up time for the α^{th} individual ($\alpha = 1,2,\ldots, n$);

$S_{i\alpha}$ = Total follow-up time for the α^{th} individual on the i^{th} treatment ($i = 0,1,2,3,4$);

$w_{i\alpha} = S_{i\alpha}/S_\alpha$ = Relative time on i^{th} treatment for α^{th} individual;

$\delta_\alpha = \begin{cases} 1 \text{ if } \alpha^{\text{th}} \text{ individual is dead (or if cardiovascular death)} \\ 0 \text{ otherwise.} \end{cases}$

We shall denote the treatments placebo, tolbutamide, standard-dose insulin, and variable-dose insulin by the subscripts $i = 1,2,3,4$, and $i = 0$ will refer to no treatment. Therefore, the α^{th} patient in the study supplies the vector of information $(S_\alpha, w_{i\alpha}, \delta_\alpha)$ i $= 0,1,2,3,4$.

The relative allocation number of deaths for the i^{th} treatment is defined by

$$d_i' = \sum_{\alpha=1}^{n} w_{i\alpha}\delta_\alpha.$$

Similarly the effective number of observations for the i^{th} treatment is

$$n_i' = \sum_{\alpha=1}^{n} w_{i\alpha}.$$

The proportion of deaths for the i^{th} treatment is then estimated by

$$\theta_i' = \frac{d_i'}{n_i'}.$$

The $\{\delta_\alpha\}$ can be defined to take on the value unity depending on whether one is calculating mortality for total deaths or cardiovascular deaths.

The estimate of the proportion of deaths associated with a treatment is usually done for a subset of patients according to whether the patients belong to the subset or not. If C defines such a class, then the RA deaths and sample sizes are

$$d_i'(C) = \sum_{\alpha \epsilon C} w_{i\alpha}\delta_\alpha$$

$$n_i'(C) = \sum_{\alpha \epsilon C} w_{i\alpha}$$

$$\theta_i'(C) = d_i'(C)/n_i'(C).$$

If there is no difference between the treatments for patients belonging to a particular class, the probability of dying while in the study does not depend on the treatment, ie,

$$P\{\delta_\alpha(C) = 1\} = \theta(C),$$

where $_{\alpha\epsilon}C$. Consequently (conditional on the $\{w_{i\alpha}\}$ being fixed), we have

$$E\{\theta_i(C)\} = \theta(C)$$

and

$$\text{var}\{\theta_i'(C) - \theta_j'(C)\} = \sigma_c^2\{A_{ii}(C) + A_{jj}(C) - 2A_{ij}(C)\}$$

where

$$\sigma_c^2 = \theta(C)\ (1 - \theta(C))$$

$$A_{ij}(C) = \sum_{\alpha \epsilon C} w_{i\alpha}w_{j\alpha}/[n_i'(C)\, n_j'(C)].$$

Approximate tests of significance can be made by taking

$$[\theta_i'(C) - \theta_j'(C)]/\sqrt{\text{var}\,[\theta_i'(C) - \theta_j'(C)]}$$

to have a standard normal distribution.

In an analogous way the failure rate for the i^{th} treatment and patients belonging to class C is defined by

$$\lambda_i'(C) = \theta_i'(C)/t_i(C),$$

where

$$t_i(C) = \sum_{\alpha \epsilon C} S_{i\alpha}/n_i'(C)$$

is the associated average follow-up time. Thus, conditional on the average follow-up time, the variance of a difference between two failure rates is

$$\text{var}\{\lambda_i'(C) - \lambda_j'(C)\} = \sigma_c^2\{B_{ii}(C) + B_{jj}(C) - 2B_{ij}(C)\},$$

where

$$B_{ij}(C) = A_{ij}(C)/[t_i(C)t_j(C)].$$

APPENDIX C

Survival Modeling Method

The model used for the survival modeling method expresses the logarithm of the failure rate for the α patient as

$$\log \lambda_\alpha = \log \lambda(t) + \sum_{s=1}^{p} \beta_s x_{s\alpha}\, \alpha = 1, 2, \ldots n,$$

where λ (t) and $\{\beta_s\}$ are unknown parameters to be estimated and $\{x_{s\alpha}\}s=1,2,...,$ p and p covariables associated with the α^{th} patient. The x-variables for the four protocol treatments were taken to be equal to the proportion of time the α^{th} individual was on the particular protocol treatment. That is, if the first four β coefficients refer to the treatments in the standard order, then $x_{s\alpha}=w_{s\alpha}$ for $s=1,2,3,4$. If a patient receiving standard-dose insulin had an altered dose of insulin, this was regarded as contributing information to the variable-dose insulin group.

The estimates of β_s $(s=1,2,3,4)$ correspond to the logarithm of the ratio of the failure rate of the s^{th} treatment to that of the period for which no medication is taken. The differences $\beta_s-\beta_1$ estimate the logarithm of the ratio of the s^{th} treatment to placebo. These ratios are "adjusted" ratios that have been adjusted for base-line and demographic variables as well as institutions. The model is based on the work of Cox, (*27*) utilizing a modification suggested by Kalbfleisch and Prentice. (*28*)

References

TABLE 1.—UGDP STUDY: TREATMENT GROUPS AND CAUSES OF DEATH

Treatment group	Number of subjects	Percent dead: All causes	Percent dead: Cardiovascular causes
Clinics using tolbutamide:			
Placebo	205	10.2	4.9
Tolbutamide	204	14.7	12.7
Standard dose insulin	210	9.5	6.2
Variable dose insulin	204	8.8	5.9
Clinics using phenformin:			
Placebo	64	9.4	3.1
Phenformin	204	15.2	12.7
Standard dose insulin	68	8.8	8.8
Variable dose insulin	65	6.2	4.6

TABLE 2.—BEDFORD STUDY (6): CARDIOVASCULAR EVENTS AND TOLBUTAMIDE

	Placebo			Tolbutamide		
	Number of subjects	With event: Number	With event: Percent	Number of Subjects	With event: Number	With event: Percent
Both risk groups:						
Both sexes	123	46	37.4	125	34	27.2
Male	69	25	36.2	62	19	30.6
Female	54	21	38.9	63	15	23.8
High risk group:[1]						
Both sexes	34	19	55.9	41	21	51.2
Male	14	10	71.4	14	11	78.6
Female	20	9	45.0	27	10	37.0
Low risk group:						
Both sexes	89	27	30.3	84	13	15.5
Male	55	15	27.3	48	8	16.7
Female	34	12	35.3	36	5	13.9

[1] The high risk group consisted of those who, on coming into the trial, had clear clinical evidence of cardiovascular disease or clinically significant hypertension.

TABLE 3.—BEDFORD (5) AND UGDP STUDIES: AGE DISTRIBUTIONS

Age	Bedford study: Placebo Number	Bedford study: Placebo Percent	Bedford study: Tolbutamide Number	Bedford study: Tolbutamide Percent	UGDP study: Placebo Number	UGDP study: Placebo Percent	UGDP study: Tolbutamide Number	UGDP study: Tolbutamide Percent
20 to 29	7	5.6	6	4.9	7	3.4	3	1.5
30 to 39	7	5.6	12	9.8	25	12.2	23	11.3
40 to 49	22	17.6	22	17.9	51	24.9	45	22.1
50 to 59	25	20.0	34	27.6	60	29.3	74	36.3
60 to 69	27	21.6	27	22.0	46	22.4	51	25.0
70 to 79	30	24.0	20	16.3	16	7.8	8	3.9
80 and over	7	5.6	2	1.6	0	0	0	0
All ages	125	100.0	123	100.0	205	100.0	204	100.0
Mean age	58.6		55.4		52.2		53.0	

TABLE 4.—NUMBER OF PATIENTS BY ASSIGNED TREATMENT AND BY TREATMENT SUBSEQUENTLY USED FOR AT LEAST ONE QUARTER

Assigned treatment	Subsequent treatment														
	Placebo		Tolbutamide		Standard dose insulin		Variable dose insulin		None		Tolbutamide and none		Variable dose insulin and none		
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	
Placebo	76	37	1	0.5	0		7	3	92	45	4	2	20	12	[1] 204
Tolbutamide	0		106	52.0	0		8	4	75	37	0		15	7	204
Standard dose insulin	0		1	0.5	50	24	51	24	104	50	4	2			210
Variable dose insulin	0		0		0		82	40	119	58	3				204
Total	76	9	108	13	50	6	148	18	390	47	11	3	35	5	822

[1] One patient omitted. Did not fit any of these categories.

TABLE 5.—NUMBER OF PATIENTS BY INITIAL TREATMENT[1] AND PROPORTION OF FOLLOWUP TIME ON THAT TREATMENT

Initial Treatment	Proportion of total followup time on initial treatment												
	0		0.01 to 0.25		0.26 to 0.50		0.51 to 0.75		0.76 to 0.99		1.0		
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Total
Placebo	3	1.5	19	9	19	9	21	10	79	39	64	31	205
Tolbutamide	3	1.5	18	9	17	8	15	7	74	36	77	38	204
Standard dose insulin	6	3.0	21	10	23	11	41	20	69	33	50	24	210
Variable dose insulin[2]	3	1.5	23	11	35	17	47	23	69	34	27	13	204
Total	15	1.8	81	10	94	11	124	15	291	35	218	26	823

[1] Without dose modification.
[2] Figures reflect proportion of time on initial-titration insulin dose.

TABLE 6.—PATIENT FOLLOWUP TIME (PATIENT-YEARS) BY ASSIGNED TREATMENT AND TREATMENT RECEIVED

Treatment Received	Assigned treatment: Placebo Number	Placebo Percent	Tolbutamide Number	Tolbutamide Percent	Standard dose insulin Number	Standard dose insulin Percent	Variable dose insulin Number	Variable dose insulin Percent	Totals Number	Totals Percent
As assigned	693.8	55.0	712.6	58	709.3	55.0	[1] 304.0	24.0	2,419.7	48
Other treatment:[2]										
Placebo	319.3	25.0							319.3	6
Tolbutamide	3.3	.3	304.1	25	4.6	.4	3.3	.3	315.3	6
Variable dose insulim	43.3	3.0	32.9	3	389.0	30.0	[3] 789.8	62.0	1,255.1	25
None	198.6	16.0	180.9	15	198.0	15.0	177.4	14.0	754.8	15
Total	1,258.3		1,230.5		1,300.9		1,274.5		5,064.2	

[1] This figure represents total patient years on initially selected dose of insulin.
[2] This includes assigned treatment but with modification of dose.
[3] This figure represents total patient years on with insulin at a dose different from the initial dose.

TABLE A.1.—UGDP DATA: DISTRIBUTION BY SEX AND TREATMENT IN EACH CLINIC, AND X^2 VALUES FOR ASSOCIATION OF SEX WITH PLBO/NONPLBO, AND SE WITH TREATMENT

Center	Males					Females					Test of sex vs. PLBO/non-PLBO treatments X_1	Test of sex vs. treatment X_3
	Placebo	Tolbutamide	Standard dose insulin	Standard dose insulin	All treatments	Placebo	Tolbutamide	Standard dose insulin	Variable dose insulin	All treatments		
Baltimore	2	7	7	4	20	22	15	14	16	67	4.02	5.25
Boston	10	6	4	6	26	5	11	12	9	37	5.24	6.00
Minneapolis	9	9	6	5	29	13	15	18	19	65	1.36	3.05
New York	4	6	10	2	22	18	14	11	20	63	.92	9.26
Williamson	9	8	6	4	27	14	14	17	20	65	1.42	3.56
Cincinnati	7	6	4	5	22	16	16	20	16	68	.60	1.33
Cleveland	0	3	1	5	9	19	15	19	15	68	3.34	7.25
Birmingham	4	0	2	2	8	9	11	11	10	41	2.70	4.14
Chicago	2	6	2	1	1	9	6	10	10	35	.26	6.36
St. Louis	5	4	5	5	19	5	7	7	6	25	.25	.43
San Juan	3	6	8	5	22	9	8	5	8	30	1.91	3.52
Seattle	8	2	2	2	14	3	9	9	9	30	11.31	11.31
Total	63	63	57	46	229	142	141	153	158	594	$X^2=33.33$	$X^2=61.46$

TABLE A.2.—UGDP DATA: CARDIOVASCULAR FAILURE RATES FOR EACH TREATMENT GROUP

Treatment group	Number of patients	Number of failures	Total time at risk quarter-years	Failure rate (in thousands)
Both sexes:				
Placebo	205	10	5,033.6	2.0
Tolbutamide	204	26	4,922.2	5.3
Standard dose insulin	210	13	5,203.9	2.5
Variable dose insulin	204	12	5,098.1	2.4
Males:				
Placebo	63	7	1,389.2	5.2
Tolbutamide	63	11	1,491.5	7.4
Standard dose insulin	57	5	1,340.0	3.7
Variable dose insulin	46	2	1,137.5	1.8
Women:				
Placebo	142	3	3,644.4	.8
Tolbutamide	141	15	3,430.7	4.4
Standard insulin dose	153	8	3,863.8	2.1
Variable dose insulin	158	10	3,960.6	2.5

TABLE A.4.—UGDP DATA: CARDIOVASCULAR FAILURE RATES FOR EACH TREATMENT GROUP BY AGE, AND SEX

Treatment Group	Number of patients	Number of failures	Total time at risk, quarter-years	Failure rate (in thousands)
Males:				
≤53 yr old:				
Placebo	28	1	664.6	1.5
Tolbutamide	26	5	656.6	7.6
Standard dose insulin	28	0	722.5	0
Variable dose insulin	21	1	521.7	1.9
≤53 yr old:				
Placebo	35	6	724.5	8.3
Tolbutamide	37	6	834.9	7.2
Standard dose insulin	29	5	617.6	8.1
Variable dose insulin	25	1	615.8	1.6
≤53 yr old:				
Placebo	85	1	2,187.8	.5
Tolbutamide	71	1	1,793.8	.6
Standard dose insulin	79	1	2,048.6	.5
Variable dose insulin	82	1	2,118.9	.5
≤53 yr old:				
Placebo	58	2	1,456.6	1.4
Tolbutamide	70	14	1,636.9	8.6
Standard dose insulin	74	7	1,815.2	3.9
Variable dose insulin	76	9	1,841.7	4.9

TABLE A.5—VARIABLES USED IN THE LOGISTIC ANALYSIS OF THE UGDP DATA

Time: Length of time from admission to study to time of analysis.
Treatments: [1] (Coded 1 if the patient was assigned to the treatment and 0 otherwise).
- Tolbutamide.
- Insulin (standard-dose).
- Insulin (variable-dose).

Demographic variables and risk factors: ("demographic variables").
- Age.[2]
- Sex (1=male, 2=female).
- Race (1=white, 2=nonwhite).
- Relative body weight.
- Systolic blood pressure.[2]
- Diastolic blood pressure.
- History of use of digitalis (1=yes, 2=no.).
- History of angina pectoris (1=yes, 2=no).
- Significant electrocardiographic abnormality [2 3] (1=yes, 2=no.).
- Serum cholesterol.[2]
- X-ray evidence of arterial calcification [2 4] (0=no, 2=yes).
- Fasting value from baseline glucose tolerance test.
- Serum creatinine value, mg 100 ml.
- Visual acuity for both eyes (0=>20/200 for both eyes; 1=≤20/200 for either eye).

Clinics: [1] (Coded 1 if the patient was in the clinic and 0 otherwise).
- Boston.
- Minneapolis.
- New York.
- Williamson.
- Cincinnati.
- Cleveland.
- Baltimore.
- Birmingham.
- Chicago.
- St. Louis.
- San Juan.

[1] There is 1 fewer treatment variable than there are treatments, and 1 fewer clinic variable than clinics. This avoids redundancy; in effect, the treatments are compared to the missing treatment (placebo) and the clinics to the missing clinic (Seattle).

[2] These variables constitute the subset referred to in tables A. 6.1 and 6.3. Sex was not included as a variable in the analyses done separately for each sex.

[3] Major or minor Q-waves, S-T depression, T-wave inversion, complete heart block, left bundle-branch block, or ventricular tachycardia.

[4] Evidence of arterial calcification noted in both of 2 independent readings of the same set of soft tissue X-rays of the right lower limb.

TABLE A.6.—ANALYSIS OF CARDIOVASCULAR DEATHS IN THE UGDP TRIALS USING THE LOGISTIC MODEL

	df	Likelihood ratio X^2	P
Both sexes:			
Constant	1	706.03	.001
Time	1	23.56	.001
Treatments	3	10.46	.02
Treatments adjusted for time	3	10.68	.02
Demographic variables and risk factors	14	95.87	.001
Treatments adjusted for demographic variables	3	11.55	.01
Treatments adjusted for demographic variables and time	3	12.30	.01
Clinics adjusted for treatments and time	11	27.68	.01
Treatments adjusted for clinics and time	3	10.91	.02
Treatments adjusted for demographic variables, clinics, and time	3	11.98	.02
Clinics adjusted for demographic variables, time, and treatments	11	14.33	------
Clinics adjusted for demographic variables and treatments	11	30.53	.01
Demographic variables adjusted for clinics, time, and treatments	14	82.56	.001
Tolbutamide treatments adjusted for demographic variables, clinics, and time	1	11.66	.001
Other treatments adjusted for demographic variables, clinic, time, and tolbutamide treatment	2	0.32	------
Subset of demographic variables adjusted for treatment and time [1]	6	83.05	.001
Other demographic variables and clinics	19	27.19	------
Treatments adjusted for subset of demographic variables and time	3	12.31	.01
Tolbutamide treatment adjusted for subset of demographic variables, time, and insulin treatments (tolbutamide vs. placebo)	1	8.49	.01
Insulin treatments adjusted for subset of demographic variables, time, and tolbutamide treatment (insulin vs. placebo)	2	0.17	------
Tolbutamide treatment adjusted for subset of demographic variables and time (tolbutamide vs. other treatments)	1	12.14	------
Insulin treatments adjusted for subset of demographic variables and time (insulin vs. other treatments)	2	3.82	------
Men:			
Constant	1	159.53	.001
Demographic variables and time	6	35.45	.001
Treatments adjusted for variables and time	3	5.07	------
Tolbutamide treatment adjusted for insulin treatments, demographic variables, and time (tolbutamide vs. placebo)	1	0.35	------
Insulin treatments adjusted for demographic varibles time and tolbutamide treatment (insulin vs. placebo)	2	2.52	------
Tolbutamide treatment adjusted for demographic variables and time (tolbutamide vs. other treatments)	1	2.56	------
Insulin treatments adjusted for demographic variables and time (insulin vs. other treatments)	2	4.72	------
Women:			
Constant	1	551.79	.001
Demographic variables and time	6	67.66	------
Treatments adjusted for variables and time	3	12.23	------
Tolbutamide treatment adjusted for insulin treatments, demographic variables, and time (tolbutamide vs. placebo)	1	11.70	.01
Insulin treatments adjusted for demographic variables, time, and tolubuamide treatment (insulin vs. placebo)	2	2.52	------
Tolbutamide treatment adjusted for demographic variables and time (tolbutamide vs. other treatments)	1	9.06	.01
Insulin treatments adjusted for variables and time (insulin vs. other treatments)	2	0.53	------

[1] See table A.5.

TABLE A.6.3.—UGDP DATA: ESTIMATES OF THE COEFFICIENTS, THEIR STANDARD DEVIATIONS AND T FOR THE LOGISTIC REGRESSIONS USING A SUBSET OF THE VARIABLES

	All patients			Males only			Females only		
	Coefficient	Standard deviation	T	Coefficient	Standard deviation	T	Coefficient	Standard deviation	T
Age	0.0866	0.0183	4.72	0.0698	0.0285	2.45	0.1024	0.0253	4.04
Sex	.5210	.3338	−1.56						
Systolic blood pressure	.0097	.0060	1.61	.0126	.0108	1.12	.006	.0077	.79
Abnormal ECG	1.6746	.4835	3.46	1.8856	.7112	2.65	1.3762	.7078	1.94
Cholesterol	.0047	.0024	2.00	.0047	.0049	.95	.0045	.0028	1.64
Arterial calcification	.3733	.1708	2.19	.2572	.2758	.93	.5591	.2257	2.48
Time	.6068	.1398	4.34	.6595	.2281	2.89	.5818	.1825	3.19
Tolbutamide	1.1917	.4283	2.78	.3528	.5983	.59	2.1158	.7094	2.98
Insulin:									
Standard dose	.1872	.4742	0.39	−.5389	.6912	−.78	1.1222	.7489	1.50
Variable dose	.0575	.4960	0.12	−1.3661	.9358	−1.46	1.1144	.7388	1.51
Constant	−14.2446	−.7910	−7.95	−13.6974	2.8336	−4.83	−16.3790	2.4914	−6.57

[1] Estimates divided by the standard deviation.

TABLE A.3.—UGDP DATA: CARDIOVASCULAR FAILURE RATES BY SEX AND CLINIC FOR EACH TREATMENT

Clinic and treatment group	Both sexes				Males				Females			
	Total number of patients	Total number of failures	Total time at risk, quarter-years	Failure rate (in thousands)	Total number of patients	Total number of failures	Total time at risk, quarter-years	Failure rate (in thousands)	Total number of patients	Total number of failures	Total time at risk, quarter-years	Failure rate (in thousands)
Boston:												
Placebo	15	1	391.0	2.6	10	1	260.3	3.8	5	0	130.7	0
Tolbutamide	17	4	385.7	10.4	6	1	133.9	7.5	11	3	251.8	11.9
Standard dose insulin	16	1	412.9	2.4	4	0	96.4	0	12	1	316.4	3.2
Variable dose insulin	15	1	397.9	2.5	6	0	158.2	0	9	1	239.7	4.2
Minneapolis:												
Placebo	22	2	522.7	3.8	9	2	200.3	10.0	13	0	322.3	0
Tolbutamide	24	6	461.6	13.0	9	2	166.2	12.0	15	4	295.5	13.5
Standard dose insulin	24	2	566.1	3.5	6	1	126.9	7.9	18	1	439.2	2.3
Variable dose insulin	24	2	582.4	3.4	5	0	124.3	0	19	2	458.1	4.4
New York:												
Placebo	22	3	553.7	5.4	4	2	86.4	23.2	18	1	467.3	2.1
Tolbutamide	20	2	516.2	3.9	6	2	150.7	13.3	14	0	365.5	0
Standard dose insulin	21	0	512.6	0	10	0	237.5	0	11	0	275.1	0
Variable dose insulin	22	0	565.2	0	2	0	46.1	0	20	0	519.1	0
Williamson:												
Placebo	23	1	629.1	1.6	9	1	209.4	4.8	14	0	419.8	0
Tolbutamide	22	3	601.8	5.0	8	2	210.9	9.5	14	1	390.9	2.6
Standard dose insulin	23	2	601.6	3.3	6	1	138.5	7.2	17	1	463.1	2.2
Variable dose insulin	24	3	610.4	4.9	4	2	70.3	28.4	20	1	540.1	1.9
Cincinnati:												
Placebo	23	2	550.4	3.6	7	0	166.6	0	16	2	383.8	5.2
Tolbutamide	22	7	572.9	12.2	6	3	163.3	18.4	16	4	409.6	9.8
Standard dose insulin	24	4	646.9	6.2	4	1	98.5	10.2	20	3	548.4	5.5
Variable dose insulin	21	4	581.6	6.9	5	0	166.5	0	16	4	415.1	9.6
Cleveland:												
Placebo	19	0	521.5	0	0	0	0	----------	19	0	521.5	0
Tolbutamide	18	1	461.8	2.2	3	0	77.3	0	15	1	384.5	2.6
Standard dose insulin	20	0	548.2	0	1	0	25.1	0	19	0	523.0	0
Variable dose insulin	20	1	528.7	1.9	5	0	126.9	0	15	1	401.7	2.5

Baltimore												
Placebo	24	0	658.9	0	2	0	51.3	0	22	0	607.6	0
Tolbutamide	22	1	624.1	1.6	7	1	201.9	5.0	15	0	422.2	0
Standard dose insulin	21	0	609.0	0	7	0	218.9	0	14	0	390.0	0
Variable dose insulin	20	0	579.5	0	4	0	116.9	0	16	0	462.6	0
Birmingham:												
Placebo	13	0	292.2	0	4	0	65.4	0	9	0	226.7	0
Tolbutamide	11	2	252.9	7.9	0	0	0	----------	11	2	252.9	7.9
Standard dose insulin	13	0	327.6	0	2	0	52.4	0	11	0	275.3	0
Variable dose insulin	12	0	295.3	0	2	0	45.2	0	10	0	250.1	0
Chicago:												
Placebo	11	1	221.9	4.5	2	1	26.6	37.6	9	0	195.3	0
Tolbutamide	12	0	271.4	0	6	0	129.3	0	6	0	142.1	0
Standard dose insulin	12	1	255.7	3.9	2	0	39.4	0	10	1	216.4	4.6
Variable dose insulin	11	1	228.2	4.4	1	0	25.3	0	10	1	202.9	4.9
St. Louis:												
Placebo	10	0	229.8	0	5	0	109.5	0	5	0	120.2	0
Tolbutamide	11	0	255.1	0	4	0	97.3	0	7	0	157.7	0
Standard dose insulin	12	1	268.8	3.7	5	1	110.2	9.1	7	0	158.6	0
Variable dose insulin	11	0	253.2	0	5	0	119.9	0	6	0	133.3	0
San Juan:												
Placebo	12	0	259.5	0	3	0	61.4	0	9	0	198.1	0
Tolbutamide	14	0	305.2	0	6	0	123.8	0	8	0	181.3	0
Standard dose insulin	13	1	255.7	3.9	8	1	150.7	6.6	5	0	105.0	0
Variable dose insulin	13	0	265.6	0	5	0	102.3	0	8	0	163.3	0
Seattle:												
Placebo	11	0	203.0	0	8	0	152.0	0	3	0	51.0	0
Tolbutamide	11	0	213.4	0	2	0	36.8	0	9	0	176.6	0
Standard dose insulin	11	1	198.8	5.0	2	0	45.5	0	9	1	153.2	6.5
Variable dose insulin	11	0	210.1	0	2	0	35.6	0	9	0	174.5	0

TABLE A.6.2.—UGDP DATA: ESTIMATES OF THE COEFFICIENTS, THEIR STANDARD DEVIATIONS AND T[1] FOR THE LOGISTIC REGRESSIONS USING ALL VARIABLES

Variable	Coefficient	Standard deviation	T
Age	0.0692	0.0213	3.25
Sex	−.3956	.3919	−1.01
Race	−.6432	.4560	−1.41
Relative weight	−1.1122	.7768	−1.43
Blood pressure Systolic	.0143	.0076	1.89
Diastolic	−.0125	.0154	−.81
Digitalis use by history	−.6748	.5117	−1.32
Angina by history	−.6519	.5171	−1.26
Abnormal ECG	1.3907	.5693	2.44
Cholesterol	.0041	.0026	1.58
Arterial calcification	.2750	.1877	1.47
Glucose tolerance test	.0011	.0031	.36
Serum creatinine	.6990	.8727	.80
Visual acuity	−.1592	.6095	−.26
Boston	1.3005	1.2477	1.04
Minneapolis	1.5444	1.1989	1.29
New York	.8680	1.3323	.65
Williamson	1.0567	1.2473	.85
Cincinnati	2.3536	1.3089	1.80
Cleveland	.8507	1.4507	.59
Baltimore	−.1780	1.6263	−.11
Birmingham	.6587	1.3571	.49
Chicago	1.1578	1.3484	.86
St. Louis	.4500	1.5386	.29
San Juan	.3470	1.5304	.23
Time	.4362	1.1805	2.42
Tolbutamide	1.2412	.4470	2.78
Insulin:			
Standard dose	.2424	.4939	.49
Variable dose	−.0005	.5257	−.001
Constant	−8.8522	2.9440	−3.01

[1] Estimate divided by standard deviation.

TABLE A.6.4.—UGDP DATA: NUMBER OF CARDIOVASCULAR DEATHS OBSERVED AND PREDICTED FROM THE LOGISTIC MODEL

	Treatment			
	Placebo	Tolbutamide	Standard dose insulin	Variable dose insulin
Males:				
≤53:				
Observed	1	5	0	1
Expected	0.521	2.600	0.952	0.447
>53:				
Observed	6	6	5	1
Expected	3.640	9.310	4.398	3.130
Total:				
Observed	7	11	5	2
Expected	4.162	11.910	5.350	3.577
Females:				
≤53:				
Observed	1	1	1	1
Expected	0.898	3.260	1.107	1.057
>53:				
Observed	2	14	7	9
Expected	4.940	10.829	6.543	7.365
Total:				
Observed	3	15	8	10
Expected	5.838	14.088	7.649	8.422

TABLE A.7.1.—UGDP DATA: RELATIVE ALLOCATION OF TOTAL AND CARDIOVASCULAR DEATHS AND EFFECTIVE SAMPLE SIZE

Treatment received	Assigned treatment: Placebo	Tolbutamide	Standard dose insulin	Variable dose insulin	Totals
Treatment as assigned: [1]					
d′	12.9	19.9	6.9	[2] 6.9	46.6
d″	6.4	17.9	3.9	5.6	33.8
n′	115.6	119.5	65.7	53.9	354.7
Dose modification or other treatment:					
Placebo:					
d′	2.8				2.8
d″	1.0				1.0
n′	48.6				48.6
Tolbutamide:					
d′	0	7.7	0	0	7.7
d″	0	5.7	0	0	5.7
n′	.5	51.4	.8	.6	53.3
Variable dose insulin:					
d′	1.2	.4	12.5	[3] 8.5	22.6
d″	1.2	.4	8.6	[3] 4.6	14.8
n′	6.9	10.7	111.1	[3] 121.9	250.6
None:					
d′	4.1	2.0	.6	2.6	9.3
d″	1.4	2.0	.5	1.8	5.7
n′	33.4	22.4	32.4	27.6	115.8
Totals:					
d′	21.0	30.0	20.0	18.0	89.0
d″	10.0	26.0	13.0	12.0	61.0
n′	205.0	204.0	210.0	204.0	823.0

[1] d′ indicates total deaths; d″, deaths from cardiovascular causes; and n′, effective sample size.
[2] These figures are associated with the initially selected dose of insulin.
[3] These figures are associated with the subsequently selected dose of insulin.

TABLE A.7.2.—UGDP DATA: DEATH RATES AND FAILURE RATES BY ASSIGNED TREATMENT AND DOSE GIVEN [1]

Dose given	Assigned Treatment: Placebo	Tolbutamide	Standard dose insulin	Variable dose insulin [2]
Cardiovascular deaths:				
As assigned:				
θ'	0.06	0.15	0.06	0.10
λ'	.9	2.5	1.0	1.8
Dose modified:				
θ'	.02	.11	.08	.04
λ'	.3	1.9	1.2	.6
No drug:				
θ'	.04	.09	.02	.07
λ'	.7	1.1	.3	1.0
Total deaths:				
As assigned:				
θ'	.11	.17	.11	.13
λ'	1.9	2.8	1.8	2.3
Dose modified:				
θ'	.06	.15	.11	.07
λ'	.9	2.5	1.8	1.1
No drug:				
θ'	.12	.09	.02	.09
λ'	2.1	1.1	.25	1.5

[1] Death rate (θ') is effective number of deaths/effective sample size; failure rate (λ') is deaths per hundred patient-years of follow-up.
[2] Combining both modification groups results in $\theta'=10.2/175.9=0.06$, $\lambda'=0.9$ for cardiovascular deaths; $\theta'=15.4/175.9=0.09$, $\lambda'=1.4$ for total deaths.

TABLE A.7.3.—UGDP DATA: CARDIOVASCULAR DEATH RATES BY ASSIGNED TREATMENT, SEX, AND DOSE GIVEN [1]

Dose given	Assigned treatment			
	Placebo	Tolbutamide	Standard dose insulin	Variable dose insulin [2]
Females:				
As assigned	1.4/79.8=0.02	10.8/78.0=0.14	3.9/52.8=0.07	4.6/42.4=0.11
Dose modified	0/33.6=0	3/39.7=0.08	3.7/76.4=0.05	3.6/94.3=0.04
No drug	1.2/23.6=0.05	1.2/19.6=0.06	0.4/23.5=0.02	1.8/20.9=0.09
Males:				
As assigned	5/35.9=0.14	7.0/41.5=0.17	1/14.0=0.07	1/11.5=0.09
Dose modified	1/15.0=0.07	2.7/11.7=0.23	3.9/33.7=0.12	1/27.6=0.4
No drug	.2/9.8=0.02	0.8/8.6=0.09	0.1/9.0=0.01	0/6.7=0

[1] Tables give ratio of cardiovascular deaths (relative allocation) to number of patients (relative allocation).
[2] Combining both dose modification groups for IVAR results in the following: females $\theta = 8.2/136.7 = .06$; males $\theta = 2/39.1 = .05$.

TABLE A.7.4.—UGDP DATA: CARDIOVASCULAR DEATH RATES BY ADHERENCE AND DOSE MODIFICATION

Dose Modification	Treatment				Totals
	Placebo	Tolbutamide	Standard dose insulin	Variable dose insulin	
100 percent adherence: [1]					
No	4/64=0.06	16/77=0.21	4/51=0.08	4/27=0.15	28/219=0.13
Yes	1/12=.08	4/29=.14	3/50=.06	2/55=.04	10/146=0.07
<100 percent adherence:					
No	2.4/51.6=.05	1.9/42.5=.04	4.6/60.1=.08	1.6/26.9=.06	10.5/181.1=.06
Yes	1.8/36.6=.05	1.7/22.4=.08	0.9/15.7=.06	2.6/66.9=.04	7/141.6=.05
Totals	912/164.2=.06	23.6/170.9=.14	12.5/176.8=.07	10.2/175.8=.06	55.5/687.7=.08

[1] 100% adherence is defined as taking the initially assigned drug for every quarter of follow-up.

TABLE A.7.5.—UGDP DATA: CARDIOVASCULAR DEATH RATES BY ASSIGNED TREATMENT, SEX AND COMPLIANCE

Compliance [1]	Treatment			
	Placebo	Tolbutamide	Standard dose insulin	Variable dose insulin
Females:				
100 percent adherence—no dose modification	0/41=0	9/51=0.18	1/28=0.04	3/21=0.14
<100 percent adherence or dose modification	1.3/72.3=.02	4.8/66.6=.07	6.6/101.2=.07	5.2/115.8=.04
No drug	1.2/23.6=.05	1.2/19.6=.06	0.4/22.5=.02	1.8/20.9=.09
Males:				
100 percent adherence—no dose modification	4/23=.17	7/26=.27	2/22=.09	1/6=.17
<100 percent adherence or dose modification	2/27.8=.07	2.7/27.2=.10	2.9/25.7=.11	1/32.9=.03
No drug	0.2/9.8=.02	0.8/8.6=.09	0.1/9=.01	0/6.7=0

[1] Compliance is based on both adherence to the assigned treatment group and use of the prescribed dose.

TABLE A.7.6.—UGDP DATA: CARDIOVASCULAR MORTALITY RATES BY SEX, COMPLIANCE, AND MEDIAN AGE AT ENTRY

Compliance	Control [1]	Tolbutamide
Females:		
≤53 yr old:		
100 percent—no DM [2]	0/45=0	0/22=0
<100 percent or DM	2.6/155.9=.02	1/33.4=.03
No drug	0.4/39=.01	0/11.7=0
>53 yr old:		
100 percent—no DM	4/45=.09	9/29=.31
<100 percent or DM	10.5/133.4=.08	3.8/33.2=.11
No drug	3/28=.11	1.2/6.9=.17
Males:		
≤53 yr old:		
100 percent—no DM	1/23=.04	3/10=.30
<100 percent or DM	1/35.6=.03	1.8/10.5=.17
No drug	0/16.7=0	0.2/4.9=.04
>53 yr old:		
100 percent—no DM	6/28=.21	4/16=.25
<100 percent or DM	4.9/51=.10	0.9/16.7=.05
No drug	0.3/8.8=.03	0.6/3.7=.16

[1] Control is made of of placebo and standard- and variable-dose insulin treatment groups.
[2] DM indicates dose modification.

TABLE A.7.7.—UGDP DATA: TREATMENT [1] VS PLACEBO ADJUSTED LOGARITHMS OF RATIOS OF FAILURE RATES BY SEX FOR CARDIOVASCULAR AND TOTAL DEATHS

	Tolb/Plbo	ISTD/Plbo	IVAR/Plbo	None/Plbo
Cardiovascular deaths:				
Female:				
Log ratio	2.64	1.79	1.75	1.69
SD [2]	.99	1.05	1.03	1.21
P [3]	.008	.09	.09	.16
Male:				
Log ratio	.094	−.35	−.29	−4.48
SD	.59	.69	.86	2.08
P	.87	.61	.73	.03
Total deaths:				
Female:				
Log ratio	1.12	.23	.64	−.51
SD	.55	.63	.56	.78
P	.04	.72	.26	.52
Male:				
Log ratio	−.30	.037	−1.49	−1.65
SD	.5	0	.86	1.18
P	.56	.94	.08	.16

[1] Tolb indicates tolbutamide; Plbo, placebo; ISTD, standard-dose insulin; and IVAR. variable-dose insulin.
[2] Refers to estimate of standard deviation of log of ratio of failure rates.
[3] Refers to test of significance (two-tail) using normal theory.

TABLE A.8.1.—BEDFORD DATA: INFLUENCE OF BACKGROUND VARIABLES ON DEATH RATES

Factor	$\hat{p}$*	$\hat{\lambda}(\times 10^2)$†
Hypertension:		
No	27/193=0.14	1.54
Yes	15/53=0.28	3.41
Blood glucose level:		
≤139 mg/100 ml	17/124=0.14	1.55
>139 mg/100 ml	25/123=0.20	2.28
Arterial disease:		
No	30/218=0.14	1.54
Yes	12/30=0.40	5.02
Sex:		
Male	20/129=0.15	1.76
Female	22/119=0.18	2.08
Age:		
≤45 yr	0/54=0	
>45 yr	42/194=0.22	2.52

*$\hat{p}$ is the number of deaths/total.
†$\hat{\lambda}$ is the number of deaths/total time followed up (6-mo periods).

TABLE A.8.2.—BEDFORD DATA: DEATH RATES FOR PLACEBO AND TOLBUTAMIDE GROUPS, BY BACKGROUND VARIABLES

Variable	Placebo	Tolbutamide
$\hat{p}$*	24/125=0.19	18/123=0.14
Hypertension:		
No	17/102= .17	10/93= .11
Yes	7/23= .30	8/30= .27
Blood glucose level:		
≤139 mg/100 ml	10/64= .16	7/60= .12
>139 mg/100 ml	14/61= .23	11/63= .17
Sex:		
Males (>45 yr old)	11/52= .21	9/46= .20
Females (>45 yr old)	13/46= .28	9/50= .18
Arterial disease:		
Yes:		
Females	2/7= .29	1/6= .17
Males	6/8= .75	3/9= .33
No:		
Females	11/50= .2	8/56= .14
Males	5/60= .08	6/52= .12
Hypertension:		
Yes:		
Females	5/15= .33	4/23= .17
Males	2/8= .25	4/7= .57
No:		
Females	8/42= .19	5/39= .13
Males	9/60= .15	5/54= .09
Blood glucose level:		
≤139 mg/100 ml:		
Females	3/28= .11	4/32= .12
Males	7/36= .19	3/28= .11
>139 mg/100 ml:		
Females	10/29= .34	5/30= .17
Males	4/32= .12	6/33= .18

*$\hat{p}$ is the number of deaths/total.

TABLE A.8.3.—BEDFORD DATA: NUMBER AT RISK, NUMBER OF DEATHS, AND DEATH RATE BY AGE, SEX, AND TREATMENT

Age, years	Males		Females	
	Placebo	Tolbutamide	Placebo	Tolbutamide
20 to 29	0/4=0	0/4=0	0/3=0	0/2=0
30 to 39	0/6=0	0/4=0	0/1=0	0/8=0
40 to 49	0/10=0	1/14= .07	1/12= .08	0/8=0
50 to 59	1/19= .05	3/18= .17	3/6= .50	3/16= .19
60 to 69	6/14= .43	3/12= .25	1/13= .08	5/15= .33
70 to 79	6/12= .50	5/8= .62	11/18= .61	7/12= .58
80 and over	3/3=1.00	1/1=1.00	3/4= .75	0/1= .00
All ages	16/68= .24	13/61= .21	19/57= .33	15/62= .24

TABLE A.9.1.—VARIABLES USED IN THE LOGISTIC ANALYSIS OF THE BEDFORD STUDY DATA

Group: A variable indicating whether the individual entered the study in 1962 or 1964.
Tolbutamide: A variable indicating that the patient was receiving tolbutamide.
Diet: A variable indicating that the patient was receiving dietary advice.
Tolbutamide-diet interaction: A variable indicating that the patient was receiving both dietary advice and tolbutamide.
Variables:
Sex.
Age.
Arterial disease history (0=no, 1=yes).
Significant hypertension (0=no, 1=yes)
Blood glucose.

TABLE A.9.2.—ANALYSIS OF CAUSES OF DEATH IN THE BEDFORD TRIAL USING THE LOGISTIC MODEL

Source	df	Likelihood ratio χ^2
Deaths from all causes:		
Constant	1	62.68 ($p<.001$)
Group	1	0.00
Tolbutamide adjusted for group and diet	1	0.90
Diet adjusted for group and tolbutamide	1	0.02
Tolbutamide-diet interaction adjusted for group, diet, and tolbutamide	1	0.57
Variables adjusted for group, diet, tolbutamide, and tolbutamide-diet interaction	5	81.02 ($p<.001$)
Tolbutamide adjusted for group, diet, and variables	1	0.02
Diet adjusted for group, tolbutamide, and variables	1	0.19
Tolbutamide-diet interaction adjusted for group, tolbutamide, diet, and variables	1	0.01
Deaths from cardiovascular causes:		
Constant	1	118.17 ($p<.001$)
Group	1	0.14
Tolbutamide adjusted for group and diet	1	1.02
Diet adjusted for group and tolbutamide	1	0.73
Tolbutamide-diet interaction adjusted for group, diet, and tolbutamide	1	0.66
Variables adjusted for group, diet, tolbutamide, and tolbutamide-diet interaction	5	55.16 ($p<.001$)
Tolbutamide adjusted for group, diet, and variables	1	0.06
Diet adjusted for group, tolbutamide, and variables	1	0.22
Tolbutamide-diet interaction adjusted for group, tolbutamide, diet, and variables	1	0.03

TABLE A.9.3—BEDFORD DATA: ESTIMATES OF THE COEFFICIENTS, THEIR STANDARD DEVIATION, AND T[1] FOR THE LOGISTIC REGRESSION ON CARDIOVASCULAR AND ALL DEATHS

	Cardiovascular deaths			All deaths		
	Coefficient	Standard deviation	T	Coefficient	Standard deviation	T
Sex	−0.1950	0.4231	−0.46	−0.0856	0.3776	−0.23
Age	.1069	.0207	5.16	.1259	.0194	6.48
Arterial disease history	1.1197	.4908	2.28	.7148	.4798	1.49
Significant hypertension	.7126	.4386	1.62	.4399	.4119	1.07
Blood glucose	−.0009	.0091	−.10	−.0109	.0084	−1.30
Group	.8525	.7124	1.20	.7279	.6668	1.09
Diet	.1842	.3922	.47	−.1557	.3541	−.44
Tolbutamide	−.0967	.4039	−.24	.0448	.3634	.12
Constant	−8.4326	1.8741	−4.50	−7.4192	1.6450	−4.51

[1] T is the estimate divided by the standard deviation

The Effects of Long Term Therapy with Oral Hypoglycemic Agents on the Oral Glucose Tolerance Test Dynamics in Chemical Diabetics

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ABSTRACT

The effect of fixed doses of oral hypoglycemic agents and placebo upon the blood glucose, serum insulin, triglyceride and cholesterol responses during oral glucose tolerance tests done annually for up to 4 years follow-up was studied, in a double blind manner, in 5 groups of mild chemical diabetics. The drugs used were chlorpropamide (100 mg O.D.), tolbutamide (500 mg b.i.d.), phenformin (50 mg C.D.), acetohexamide (250 mg O.D.) and placebo. Each subject wag given an individualized diet aimed at attaining and maintaining ideal weight, Comparison by Chi square analysis between the placebo group and each of the drug groups showed: (a) no significant differences with regards to the number of subjects with normal glucose tolerance test in each of the tests and (b) no change in the insulin secretion dynamics. Comparison between the initial test and each of the subsequent tests within each group showed: (a) a greater number of subjects had normal glucose toelance in test 2 in the placebo group, test 2 and 3 in the tolbutamide group and tests 2–4 in the chlorpropamide group; (b) no change in the insulin secretion dynamics except in the chlorpropamide group where there was an increase insulin/glucose ratio in test 2 and (c) no change in the fasting serum triglyceride and cholesterol levels.

INTRODUCTION

A goal in the detection of the early stages of diabetes mellitus is the hope that prompt therapeutic intervention may retard the clincal manifestations of the later stages of the disease. Both remisson of the disease (*1,2*) and improvement of the carbohydrate tolerance (*3–16*) following the use of oral hypoglyceagents have been reported. Some groups reported the improvement of the carbohydrate tolerance to be associated with incrased insulin secretion (*4–7*) whilst others indicated otherwise (*8–16*). A lowering of fasting serum lipid levels in diabetics treated with oral hypoglycemic agents has also been reported (*5, 10, 17–20*). Most of the above studies were performed after relatively short term (weeks to months) therapy with the oral hypoglycemic agents. The present study reports on the effects of long term (up to four years) therapy with fixed doses of oral hypoglycemic agents and diet upon (a) the glucose tolerance, (b) the insulin secretion dynamics, and (c) the lipid dynamics during oral glucose tolerance tests of chemical diabetics.

METHODS AND SUBJECTS

Over a six year period, 365 mild chemical diabetics participated, with informed consent, in a double blind prospective study to evaluate the influence

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of fixed doses of oral hypoglycemic agents and proper diet on the natural history of the disease. Each of them was asymptomatic, had normal fasting blood glucose levels, but had two abnormal oral glucose tolerance tests prior to entering the study. They were randomly assigned to four groups, each group taking a different drug. In each group one out of every four subjects was placed on a placebo (fig 1). The drugs used were: Chlorpropamide 100 mg daily, Tolbutamide 500 mg twice daily, Phenformin 50 mg daly and Acetohexamide 250 mg daily, Drug adherence was assessed by history during the follow up visits every three months. Each subject was given an individualized diet aimed at attaining and maintaining ideal weight as defined by the Metropolitan Life Insurance Company—1959.

In this prelminary report, only male subjects who had at least two tests and complete data (namely, glucose, insulin, cholesterole and triglyceride values) in the initial (test 1) and subsequent tests (test 2–5) were included. As shown in table 1, there were 37 in the placebo group, 18 in the chlorpropamide, 28 in the tolbutamide group, 23 in the phenformin group and 14 in the acetohexamide group. As the follow up years increased, the number of subjects in each group decreased.

Each subject had an oral glucose tolerance test (100 mg dextrose) at the beginning of the study (test 1) and then annually during the follow up years. Each subject followed his usual diet which contained 100–200 grams carbohydrate and took no medication on the day of the test. Each test was done after an overnight fast and begun between 0800 and 0900 hours. Blood samples were obtained by venipuncture prior to and at 30, 60, 120 and 180 minutes after ingesting the glucose. Blood glucose was measured by Hoffman's method as modified for the AutoAnalyzer (*21*). Serum insulin was assayed by the double antbody method of Soeldner and Slone (*22*). Serum cholesterole and triglycerides were measured by the Technicon AutoAnalyzer method (*23*).

The criteria for an abnormal oral glucose tolerance test are those used in the Joslin Clinic. A test was judged abnormal if any one blood glucose value at a given time interval exceeded that listed below: Fasting = 100 mg/dl, 30 min. = 160 mg/dl, 60 min = 160 mg/dl, 120 min = 120 mg/dl and 180 min–110 mg/dl.

The criteria for normal fasting serum cholesterol and triglycerides are those of Goldstein et al (*24*).

Statistical analyses were done by Chi Square, paired and unpaired Students' t–tests as indicated.

COMPARISON OF THE GROUPS AT THE BEGINNING OF THE STUDY

The placebo group did not differ significantly from each of the treated groups in mean age and percent ideal weight at the beginning of the study and in subsequent years (table 2). The percentage of obese subjects n each group was also comparable. A comparison of the percent ideal weight of the subjects in each between the initial test and each of the subsequent tests was made by paired 't' analysis. No significant difference was noted except in the phenformin group. In this group there was a significant decrease in percent ideal weight in test 2 (100.2 ± 2.9 $p < 0.01$) and test 5 (98.2 ± 3.7 $p < 0.01$).

The glucose tolerance and insulin secretion dynamcs during the initial test showed no significant differences between the placebo and each of the drug treated groups (fig 2).

COMPARISON BETWEEN AND WITHIN GROUPS

In tables 3 to 5, two types of comparisons are made by Chi Square analysis. The between group comparison (shown vertically) compares the placebo group with each of the drug group in each test. The within group comparison (shown horizontally) compares test 1 with each of the subsequent four test in each group. As shown n the tables, each comparison consists of two numerators and one denominator. The two numerators represent the number of subjects wth normal values in each test being compared. The denominator of each comparison represents the total number of subjects who had the two tests under consideration.

References at end of article.

COMPARISON OF SUBJECTS WITH NORMAL GLUCOSE TOLERANCE

In the between group comparison no significant difference was seen in the number of subjects with normal glucose tolerance tests between the placebo and each of the drug groups (table 3). Unpaired t–tests showed the glucose values at the various time intervals to be comparable between the placebo and each of the drug groups. The within group comparison showed that compared with the appropriate initial test: (a) a greater number of subjecs thad normal glucose tolerance in test 2 but not in subsequent tests in the placebo group; (b) a significantly greater number of subjects had normal glucose tolerance tests in test 2, 3 and 4 in the chlorpropamide group; (c) a significantly greater number of subjects had normal glucose tolerance in test 2 and 3 in the tolbutamide group; (d) no significant change in the number of subjects with normal glucose tolerance tests in the follow up years despite the decrease in percent ideal weight in tst 2 and 5 in the phenformin group and (e) a significantly greater number of subjects had normal glucose tolerance in test 3 in the acetohexamide group. A comparison of glucose levels was done by paired 't' analysis where each individual's initial test served as the control. The following results were obtained: (a) in the placebo group the blood glucose levels were lower at 30 min and 60 min in test 2 and higher at 0 min and 120 min in test 4; (b) in the chlorpropamide group the blood glucose levels were lower at fasting, 30 min, 60 min and 120 min in test 2 and at 30 min and 60 min in test 3; (d) in the phenformin group the blood glucose levels were higher at 0 min and 30 min in test 5 and (e) no significant change was observed in the acetohexamide group.

COMPARISON OF INSULIN SECRETION

In fig. 3 the insulin response to oral glucose was calculated as the total incremental area above fasting for the stated time interval (μU/ml/min). Similarly the insulin response reative to gucose stimulus was calculated as the total incremental area for insulin divided by the total incremental area for glucose for the stated time interval. In the between group comparison by th unpaired 't' test, no significant difference was noted between the placebo and each of the drug groups in each of the five tests n all the four variables shown. The mean ($\pm$ S.E.M.) time peak insulin during the initial test for the five groups were: placebo = 93.2 ($\pm$ 5.7) min, chlorpropamide = 96.6 ($\pm$ 11.8) min, tolbutamide = 85.4 ($\pm$ 7.9) min, phenformin = 99.1 ($\pm$ 9.5) min and acetohexamide 87.9 ($\pm$ 9.1) min. The placebo group did not differ signficantly from each of the drug groups in all five tests the mean time of peak insulin. In the within group comparisons by pared 't' analysis, the only significant differences between test one and each of the subsequent tests in the above five variables was seen in the chlorpropamide and acetohexamide group. In the former group the 0–60 min and 0–180 min insulin/glucose area ratios were significantly higher in test 2 compared with those in test 1. In the latter group, the 0–180 min insulin/glucose area ratio o ftest 3 was higher than test 1. These differences were due not to an increase in insulin secretion but to a decrease in glucose area.

COMPARISON OF FASTING LIPID LEVELS

Table 4 shows the number of subjects with normal fasting serum triglyceride levels in each test and group. As a group, 76 of the 120 chemical diabetics had normal fasting triglyceride levels in the initial test. In the between group comparison by chi square analysis, the following results were obtained: compared with the placebo group (a) the tolbutamide group had a significantly greater number of subjects with normal fasting triglycerides in test 3, 4 and 5; (b) the phenformin group had a greater number of subjects with normal fasting triglycerides in test 3 and (c) the acetohexamide group had a greater number of subjects with normal fasting triglycerides in test 2 and 3. Unpaired 't' analysis indicated that, compared with the placebo group, the tolbutamide group showed lower fasting trigycerides in test 4 and 5 whilst the other groups showed no differences. In the within group comparison both by chi square analysis and the paired 't' test, no significant differences were seen between the fasting triglycerid levels in test 1 and each of the follow up tests in all five groups.

Table 5 shows the number of subjects with normal fasting serum cholesterol levels. In the initial test 85 out of the 120 chemical diabetics in the whole group

had normal fasting cholesterol levels. In the between group comparison by chi square analysis, the following results were obtained: compared with the placebo group (a) the chlorpropamide group had a significantly greater number of subjects with normal values in test 2 and (b) the acetohexamide group had greater number of subjects with normal values in all tests. Comparison made by unpaired 't' test indicated that only the acetohexamide group differed from the placebo group and ony in test 1, 2 and 3. The within group comparison by chi square analysis showed no significant difference between test 1 and each of the follow up tests in all five groups. However, by paired 't' analysis, the phenformin group showed higher fastng cholesterol levels in test 3 and 5 when compared with test 1. None of the other groups showed any significant differences.

LIPID DYNAMICS DURING ORAL GLUCOSE TOLERANCE TEST

Fig 4 shows the serum cholesterol and triglyceride changes during the initial test for the entire group. By paired 't' analysis, there was a significant increase over baseline (7–12%) in the serum triglyceride at half and one hour followed by a significant decrease (6%) at three hours after the ingestion of glucose. On the other hand, the serum cholesterol showed a significant decrease at one, two and three hours after the ingestion of glucose. This pattern of change in serum triglyceride and cholesterol was seen in all five groups and in all five tests.

MORTALITY

During the study period, the following deaths occurred in the entire group of 365 patients. In the placebo group, two males died with myocardial infarction, one male by automobile accident. In the chlorpropamide group, one female died of uremia. In the tobutamide group, one male died by automobile accident and one female by reticulum cell sarcoma. In the phenformin group, one male died with a pulmonary embolus and in the acetohexamide group, one male died with carcinoma of the lung and one female with myocardial infarction. In the group reported here, the only deaths were two males in the placebo group who died of myocardial infarction.

DISCUSSION

In this study the number of subjects with normal glucose tolerance signifi cantly greater in the placebo (diet treated), tolbutamide and chlorpropamide groups after one year of treatment. In the tolbutamide and chlorpropamide groups this improvement was still present after two and three years of therapy respectively. This improvement was not related to weight loss in these subjects.

Improvement of glucose tolerance in chemical diabetics on placebo therapy has been reported by Wilansky and Shochat (*2*). This was also reported in diabetics by Turtle (*8*) but not by Arky and Abramson (*5*). This current study shows that this improvement is transient, being present only in the first follow up test. Whether this is due to spontaneous remission secondary to rigid adherence to diet or other factors remains ot be elucidated.

Improvement in glucose tolerance during chlorpropamide (*5, 7, 9, 14–16*), tolbutamide (*1, 3, 4, 14*), acetohexamide (*6*), tolazamide (*8*) and glybenclamide (*10–13*) therapy has been reported previously and this study corroborates these findings. In contrast, this study did not confirm the finding that chemical diabetics or diabetics, when treated with phenformin, improved their glucose tolerance (*2, 5, 25*). This apparently is not because the subjects in this study are on fixed doses of phenformin (50 mg daily) as Wilansky and Shochat's subjects were on a similar dose.

A possible explanation for the improved glucose tolerance in chemical diabetics treated with sulfonylureas is increased insulin secretion in response to glucose. Indeed, several groups have demonstraetd an increase in insulin secretion during glucose tolerance tests in diabetics after short term therapy with sulfonylureas, i.e., one week (*14*), three weeks of therapy (*5*), four weeks of therapy (*16, 26*), seven weeks of therapy (*7*) and eight weeks of therapy (*4, 6*). Two other groups (*15, 27*) reported higher insulin secretion in diabetics when they were on sulfonylurea therapy than when they were off therapy.

References at end of article.

In the present study, improvement in glucose tolerance was seen in the placebo, chlorpropamide and tolbutamide groups. This improvement was not associated with an increase in insulin secretion luring the glucose tolerance test. Improvement in glucose tolerance unassociated with increased insulin secretion has been reported by many groups (*8–13, 28*). The discrepancy is most likely due to timing of the test after initiation of drug therapy. An increase in insulin secretion during oral or intravenous glucose tolerance tests is observed when the tests are performed after 1–8 weeks of therapy. Despite this improvement in glucose tolrance, tests done after three months of therapy in diabetics almost invariably show no increase in insulin output when compared with the initial test. Indeed four of the studies (*6, 14, 16, 26*) which demonstrated increased insulin output during glucose tolerance test after short term therapy with sulfonylureas could not demonstrate the same finding when the tests were repeated after three months of therapy. In this present study, the first follow up test was performed after one year of therapy.

The absence of an increased insulin output to account for the improved glucose tolerance would suggest that the sulfonyureas have some extrapancreatic effects which facilitate the disposal of a glucose load. Several mechanisms have been postulated: (a) an acquired loss of insulin antagonism (*6*); (b) an increased biological activity of the endogenous insulin (*29*); (c) an enhancement of the sensitivity of the beta cell wthout affecting its total response (*30*) and/or (d) an increased secretion of insulin coupled with an increased degradation by the liver of the secreted insulin (*9*).

Before attributing the improvement of glucose tolerance in diabetics on long term sulfonylurea therapy to extrapancreatic effects of the drugs, two "pancreatic factors" must be considered. These are the influence of sulfonylureas on glucagon secretion and on early phase of insulin secretion after a glucose load. Experience is too limited to speculate on the role of glucagon in the mechanism of action of the sulfonylureas. In normal humans, oral administration of chlorpropamide (*31*) and gliburide (*32*) did not suppress plasma glucagon levels whereas, in the only reported study in dabetics, therapy with chlorapropamide for 12 days in six maturity onset diabetics reduced levels of circulating glucagon levels (*33*).

Recent observations of the regulation of diabetes in dogs and man using an artificial pancreas suggested the importance of the early phase on insulin secretion (*34, 35*). An absent or reduced early phase would decrease the effectiveness of insulin whilst a restored first phase could lower the subsequent hyperglycemia after a glucose load without increasing the late phase of insulin secretion. In the present study the time of peak insulin was not corrected by diet with or without drug therapy. Three other groups reported similar findings (*10, 26, 28*) whilst another three groups reported a correction of the delay in the peak insulin (*8, 16, 30*). In one of the latter groups (*16*), a highly significant rise in the early phase of insulin release was shown at five minutes after rapid intravenous glucose administration to diabetics on drug therapy.

Previous studies on the effect of phenformin on glucose tolerance tests in diabetics showed improvement of glucose tolerance associated with a decrease in insulin secretion (*5, 25*). Recently, the suggestion was put forth that phenformin's primary action is to enhance peripheral glucose assimilation, and that the changes in insulin secretion are secondary to this (*36*). The present study demonstrated neither an improvement in glucose tolerance nor a decrease in insulin secretion. The discrepancy may be due to the subjects used and the dose of phenformin given. In the two studies quoted, all subjects were obese and a higher dose of phenformin was used. In addition, the subjects were studied after a very short period of therapy.

The need to re-evaluate periodically the necessity of long term therapy with oral hypoglycemic agents in diabetics was recently raised (*37, 38*). The present study also raises the same question because a group of chemical diabetics on placebo therapy did not differ significantly from another group on drug therapy as far as glucose tolerance was concerned. Two points need to be emphasized. First, the chemical diabetics treated wth drugs were on a fixed dose of drug, no attempt being made to regulate the hyperglycemic closely. Second, on an

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individual basis, more chemical diabetics seem to respond better to a combination of diet and chlorpropamide therapy than to diet alone.

Both sulfonylureas and biguanides have been known to lower serum cholesterol and triglycerides (*5, 10, 17–20*). In the present study the number of subjects with normal fasting cholesterol or triglycerides was not significantly changed when the number in the initial test was compared with each of the subsequent test by chi square analysis. A comparison of the mean fasting values in the initial test with each of the subsequent test by paired 't' analysis also did not show any difference. The reason for the discordance is not apparent.

The patterns of change in serum triglycerides and cholesterol during the oral glucose tolerance test are similar to those of normal subjects (Unpublished data). The early increase in serum triglycerides may be due to two possible causes: (a) increased endogenous triglyceride synthesis from fatty acids which are not utilized as fuel when glucose is available and insulin is present and (b) conversion of glucose to triglycerides. A later decrease in serum triglycerides has been reported previously (*39*). This is most likely due to decreased substrate (fatty acids) availability due to decreased lipolysis in adipose tissue and to increased triglyceride removal secondary to an increase in lipoprotein lipase (*40*). A decrease in serum cholesterol following prolonged glucose feeding has also bee recently reported (*41*). This study demonstrates the acuteness of the effect. The mechanism responsible for the change remains to be elucidated.

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TABLE 1.—NUMBER OF SUBJECTS IN EACH TEST AND GROUP

Group	Initial test 1	Followup tests (years) 1=test 2	2=test 3	3=test 4	4=test 5
Placebo	37	37	29	21	19
Chlorpropamide	18	18	17	13	11
Tolbutamide	28	28	25	21	17
Phenformin	23	23	21	18	16
Acetohexamide	14	14	12	10	7

TABLE 2.—DEMOGRAPHIC FEATURES OF THE SUBJECTS IN EACH GROUP AT THE INITIAL TEST

Group	Mean age (years)	Percent ideal weight (mean±sem)	Percent ideal weight median value	Subjects in group Obese	Nonobese
Placebo	46.1±2.1	110.5±2.1	111.0	10	27
Chlorpropamide	42.3±2.7	114.4±3.9	115.5	5	13
Tolbutamide	43.8±2.3	107.7±3.6	103.5	8	20
Phenformin	45.7±2.7	103.9±3.1	102.0	3	20
Acetohexamide	44.4±3.9	108.4±4.3	108.0	4	10

TABLE 3.—COMPARISON BETWEEN PLACEBO AND EACH OF THE DRUG GROUPS FOR EACH TEST AND BETWEEN TEST 1 AND SUBSEQUENT TESTS IN EACH GROUP

Group	Number of subjects with normal OGTT in each group and test indicated Test 1 vs. test 2	Test 1 vs. test 3	Test 1 vs. test 4	Test 1 vs. test 5
Placebo	5 vs. 11* / 37	5 vs. 9 / 29	5 vs. 16 / 21	3 vs. 6 / 19
Chlorpropamide	1 vs. 8** / 18	1 vs. 6* / 17	1 vs. 4* / 13	1 vs. 3 / 11
Tolbutamide	5 vs. 11* / 28	5 vs. 12* / 25	5 vs. 7 / 21	4 vs. 4 / 17
Phenformin	4 vs. 5 / 23	4 vs. 5 / 21	3 vs. 4 / 18	3 vs. 2 / 16
Acetohexamide	1 vs. 3 / 14	1 vs. 5* / 12	1 vs. 3 / 10	1 vs. 2 / 8

Degree of significance between test 1 and other test (within group comparison) is indicated as :* =p<0.05, **=p<0.01

TABLE 4.—COMPARISON BETWEEN PLACEBO AND EACH OF THE DRUG GROUPS FOR EACH TEST AND BETWEEN TEST 1 AND SUBSEQUENT TESTS IN EACH GROUP

Group	Number of subjects with normal fasting triglycerides level indicated			
	Test 1 vs. test 2	Test 1 vs. test 3	Test 1 vs. test 4	Test 1 vs. test 5
Placebo	21 vs. 22 / 33	19 vs. 17 / 26	15 vs. 15 / 19	12 vs. 12 / 17
Chlorpropamide	9 vs. 9 / 16	9 vs. 11 / 15	8 vs. 7 / 12	7 vs. 6 / 10
Tolbutamide	21 vs. 23 / 25	19 vs. 20+ / 22	20++ vs. 20++ / 20	17++ vs. 16++ / 17
Phenformin	16 vs. 18 / 22	15 vs. 18+ / 20	13 vs. 14 / 18	12 vs. 12 / 16
Acetohexamide	9 vs. 11++ / 11	10 vs. 10+ / 11	7 vs. 7 / 8	5 vs. 5 / 7

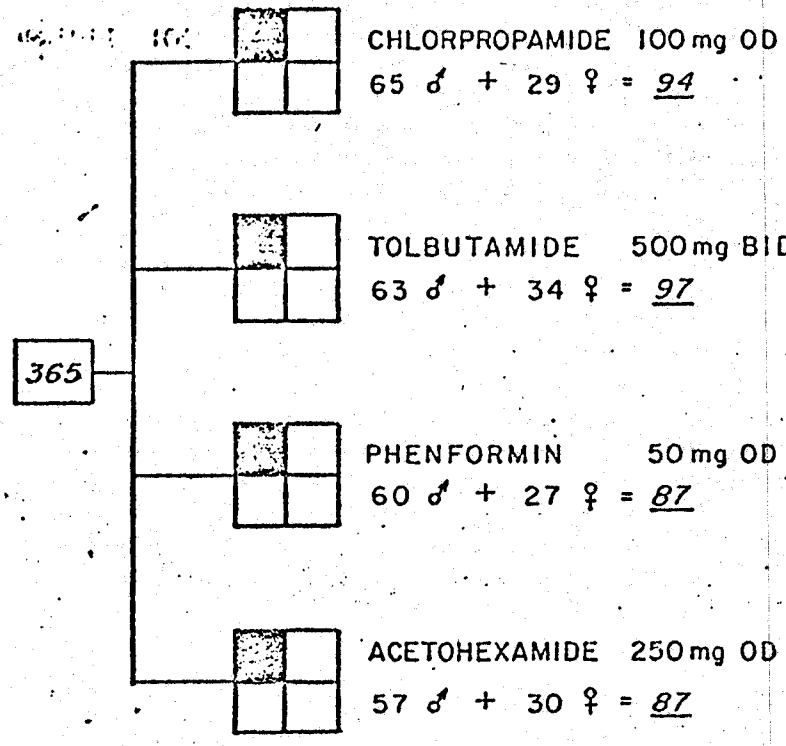
Degree of significance between placebo and drug groups (between group comparison) is indicated as: +=p<0.05, ++=0.01.

TABLE 5.—COMPARISON BETWEEN PLACEBO AND EACH OF THE DRUG GROUPS FOR EACH TEST AND BETWEEN TEST 1 AND SUBSEQUENT TESTS IN EACH GROUP

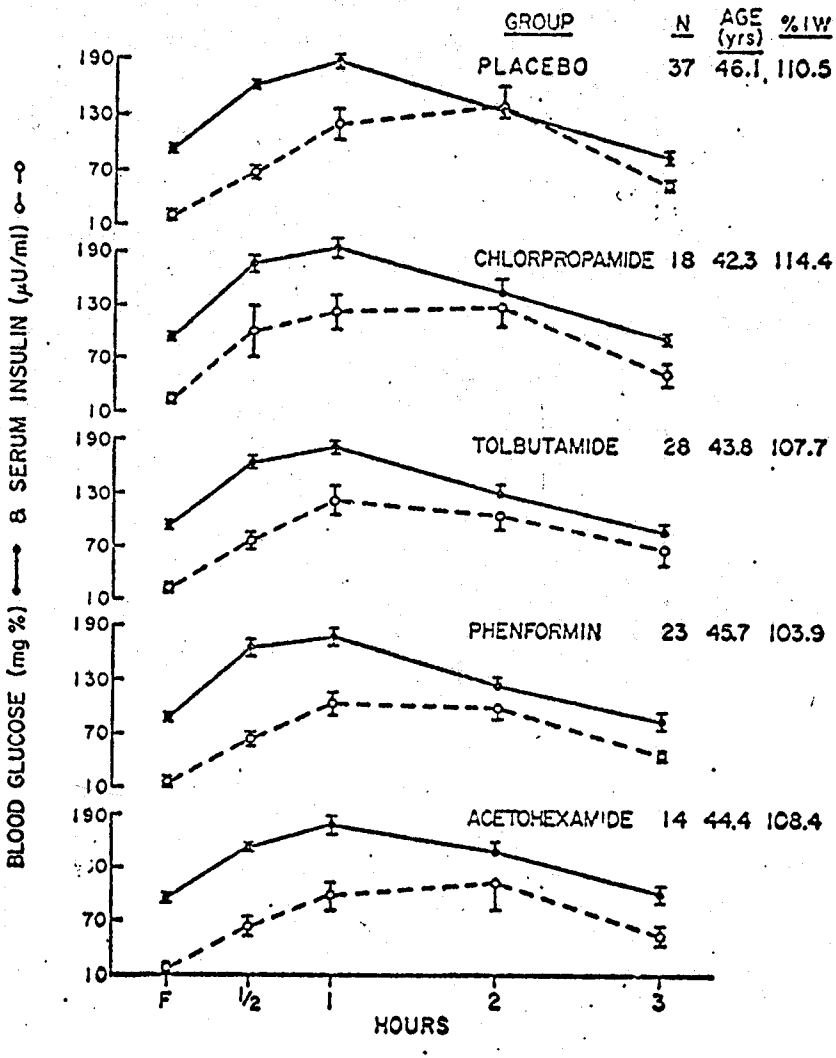
Group	Number of subjects with normal fasting cholesterol level indicated			
	Test 1 vs. test 2	Test 1 vs. test 3	Test 1 vs. test 4	Test 1 vs. test 5
Placebo	22 vs. 22 / 33	18 vs. 19 / 26	12 vs. 13 / 19	10 vs. 12 / 17
Chlorpropamide	12 vs. 15+ / 16	11 vs. 12 / 15	9 vs. 10 / 12	7 vs. 9 / 10
Tolbutamide	21 vs. 21 / 25	18 vs. 19 / 22	16 vs. 16 / 20	14 vs. 14 / 17
Phenformin	19 vs. 19 / 22	17 vs. 16 / 20	15 vs. 18 / 18	13 vs. 11 / 16
Acetohexamide	11++ vs. 11++ / 11	11+ vs. 11+ / 11	8+ vs. 8* / 8	7+ vs. 7+ / 7

Degree of significance between placebo and drug groups (between group comparison) is indicated as: +=p<0.05, ++=p<0.01.

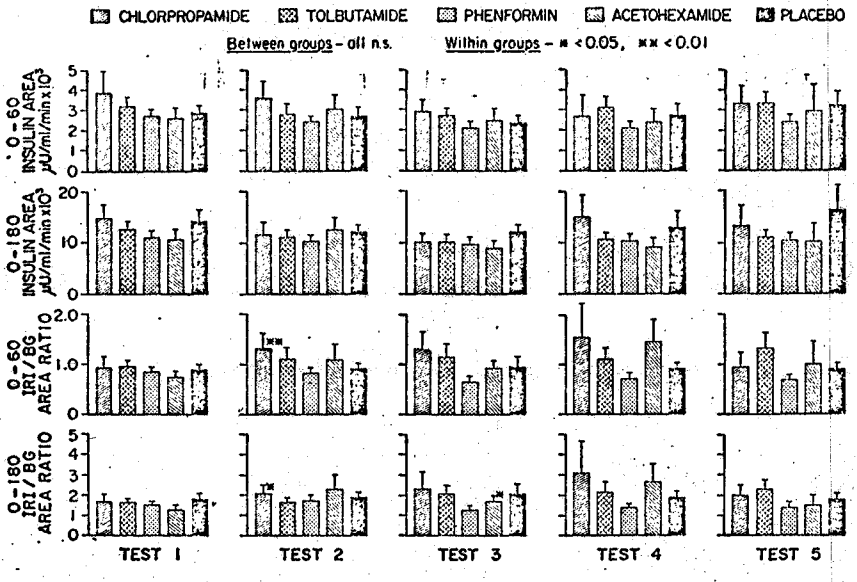
Design of Study



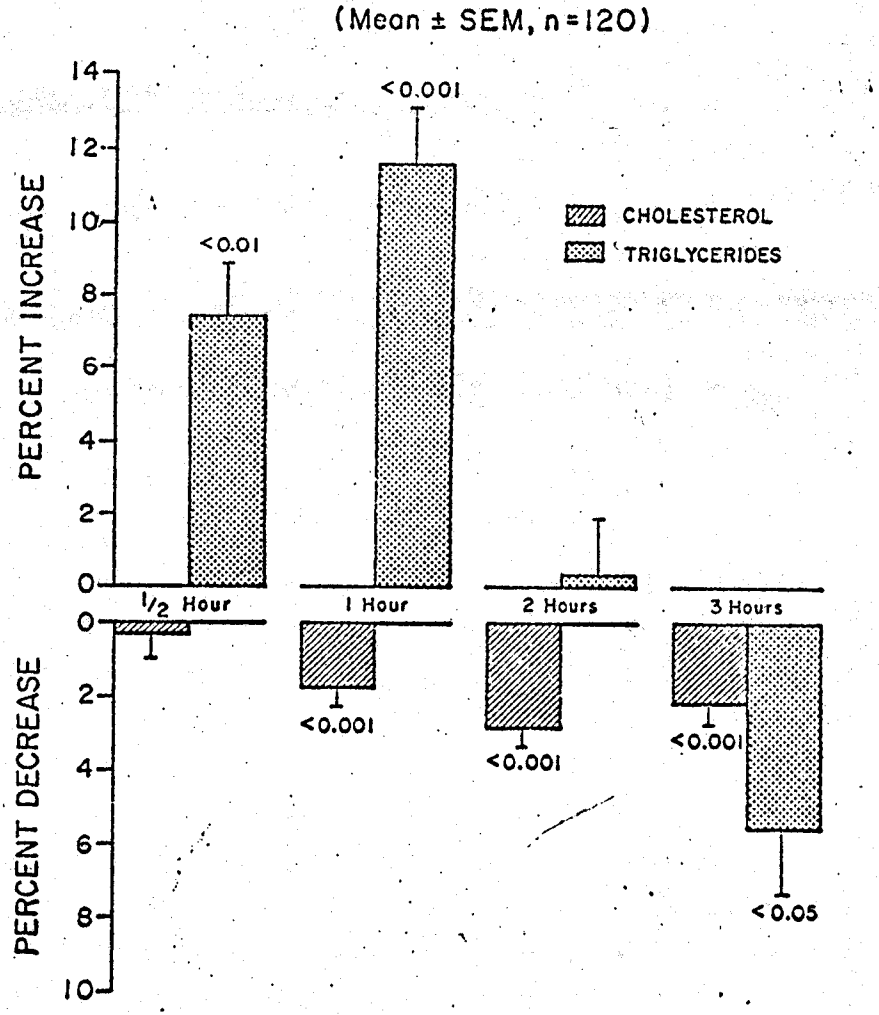
Mean levels of blood glucose, serum insulin, age and percent ideal body weight during initial oral glucose tolerance test. Vertical bars represent SEM about means.

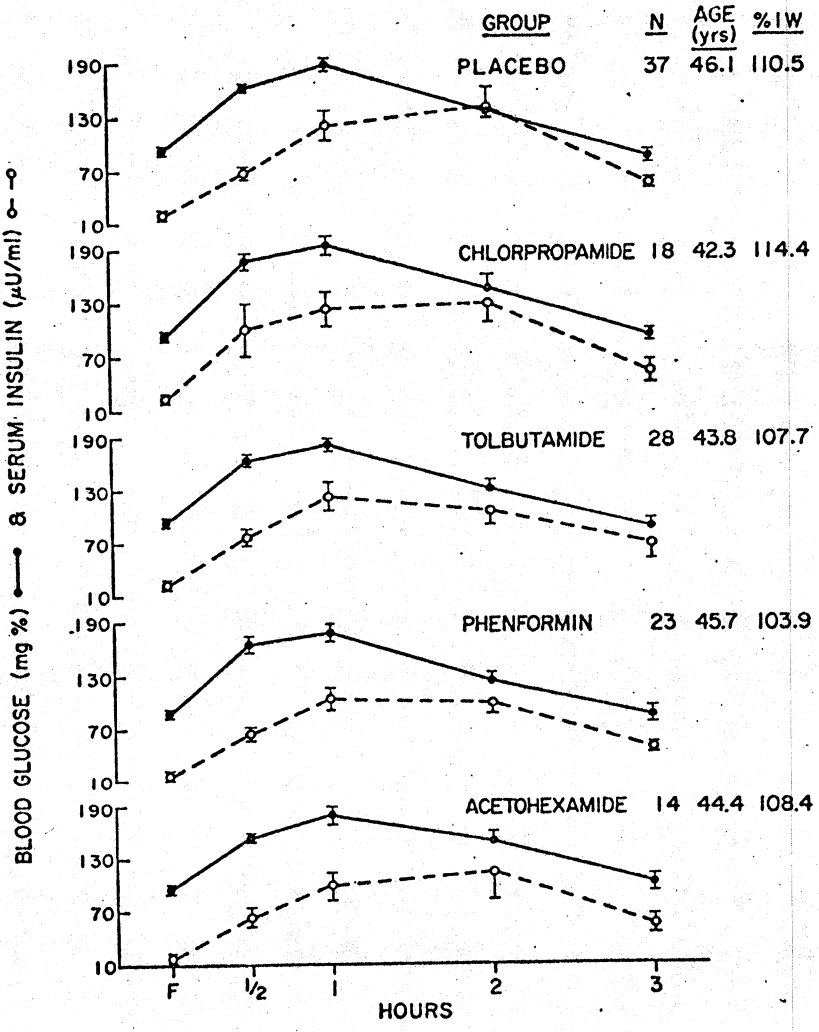


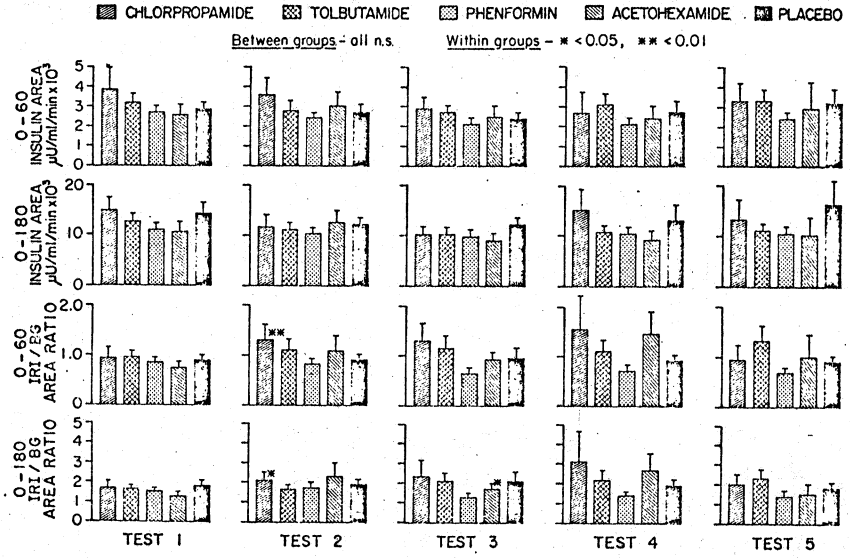
The absolute and relative insulin responses in each group for each of the five sequential oral glucose tolerance tests.



The percent change of serum cholesterol and triglyceride levels during the oral glucose tolerance test.




GROUP
N
AGE (yrs)
%IW
PLACEBO 37 46.1 110.5
CHLORPROPAMIDE 18 42.3 114.4
TOLBUTAMIDE 28 43.8 107.7
PHENFORMIN 23 45.7 103.9
ACETOHEXAMIDE 14 44.4 108.4
BLOOD GLUCOSE (mg %) ● — ● & SERUM INSULIN (μU/ml) ○ — ○
190
130
70
10
F
1/2
1
2
3
HOURS


CHLORPROPAMIDE
TOLBUTAMIDE
PHENFORMIN
ACETOHEXAMIDE
PLACEBO
Between groups - all n.s.
Within groups - * < 0.05, ** < 0.01
0-60 INSULIN AREA μU/ml/min x10³
0-180 INSULIN AREA μU/ml/min x10³
0-60 IRI/BG AREA RATIO
0-180 IRI/BG AREA RATIO
TEST 1
TEST 2
TEST 3
TEST 4
TEST 5

[Excerpts]

Assessing Survival in a Diabetic Population

(By Paula Helene Kanarek)

A thesis submitted to the faculty of the Harvard School of Public Health. In partial fulfillment of the requirements for the degree Doctor of Science in the field of Biostatistics, Boston, Mass., January 1973.

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Paula H. Kanarek.

CHAPTER I. INTRODUCTION

In 1970, the Joslin Clinic in Boston, Massachusetts began a study of nearly 6300 patients in an attempt to evaluate the effects of specific diabetic treatments on survival. The study design does not allow for random allocation of individual to the specific treatment regimens and, therefore, the distribution of covariates such as age, sex, history of cardiovascular problems and the severity of diabetes at the time of entry to the study are not distributed simi-

larly in the groups. Since the primary purpose of this study is to isolate the effects of treatment on survival, a method of analysis which would correct the observed survival experience for the effects of these covariates is necessary.

The thesis presented here is divided into two parts. The first portion deals with the development and testing of a mathematical model [which considers covariables] to predict survival in this diabetic population. The second portion is concerned with analyzing these data to determine the comparative effects of severe antihypoglycemic therapies on survival.

Dissimilarities in the distribution of potentially confounding variables are not unusual in observatonal studes. If the sze of the study population is large then analysis of survival is possible by subclassifying individuals on the basis of risk level and appyling the traditional life table methods described by Chiang (*1*), Elveback (*2*) or Cutler and Ederer (*3*) or by methods of relative survival discussed by Ederer et al. (*4*) within each risk category. Often, however, the size of the study population is not large enough for this to be a feasible approach. In such cases, it is desirable to have an appropriate mathematical model which considers the effect on survival both of the confounding variables and the specific treatments.

Most often, models of the exponential form, i.e. where

$$(1.1)\quad P(T)=Pr(\text{surviving to time } T)=e\alpha^{\lambda T}$$

(λ is known as the force of mortality) are postulated as the appropriate formulation for describing survival over time. Recently the form of the exponent in (1.1) has been modified (*5*, *6*, *7*) to include covariables.

For example,

$$(1.2a)\quad P_i(T)=Pr\ (\text{ith person survives to time } T)=e^{-\lambda_i T}$$

where

$$(1.2b)\quad \lambda_i=1/(a+bx_i)$$

or

$$(1.2c)\quad \lambda_i=e^{(a+bx_i)}$$

and x_i is the value of the covariate for the ith person. Generally such models include only one covariable and even in such simple cases, iteration is necessary to estimate the parameters in the exponent. Mantel and Myers (*8*) have recently extended the model to the case of three covariates and discuss the problems in covergence encountered in the iterative process. Further discussion of these covariate approaches may be found in Chapter II.

In each of the cases discussed above, the model is used to predict the survival experience of persons acutely ill with cancer. In only one case (of 34 total individuals) is there any attempt to test goodness of fit. Work done by Drolette (*9*) suggests that simple exponential models are not sufficient to describe the observed survival experience of a chronically ill population.

In chapter II an exponential model is postulated which considers the effects of four covariates plus three treatments on survival in the Joslin Clinc data. It is the purpose of this paper to generate the maximum liklihood equations necessary to estimate the parameters of this model; to compare the problems in convergence observed here with those encountered by Mantel and Myers and to investigate methods of handling them; and, finally, to evaluate the ability of this exponential model to describe the observed surviva experience of lthe popuation both in terms of the overall fit to the data and as compared to two simpler forms of the exponential.

The results of this investigaton show that estimation o fthe parameters is difficult and requires some unuual (though common sensical) manipulations to ensure convergence; and that although this model does make it possible to delineate individuals on the basis of risk, it does not adequately reproduce the observed survival experience of this population.

In the discussion, several alternatives to the exponential formuation are considered athough the best one (if any) is not readily aparent. It is suggested that the ability of the exponential to describe survival in other chronically ill populations be investigated as well as the alternative models.

The purpose of Chapter III is to present data about the relationship of three anti-diabetic treatments on survival in a population of diabetics. The three treatments considered are: insulin, tolbutamide (both given to control the level of blood glucose) and control by diet alone. It is of particular interest to determine if individuals treated with tolbutamide are more likely to die from cardiovascular causes than persons treated by either of the other two regimens.

As was mentioned previously, patients are not randomly assigned to treatment groups and, therefore, treatment is intimately linked to the severity of the

diabetes. Because the volume of data is relatively large and the methods proposed in Chapter II are found to be inadequate for describing survival methods in this population, results are analyzed by life table and relative survival methods within categories of risk. The results and discussion of these analyses are presented in Chapter III.

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CHAPTER III.—SURVIVAL IN A POPULATION OF DIABETIC PATIENTS

1. Maturity onset diabetes (onset occurred after age 40)
2. Massachusetts resident at the time of the first visit to the clinic
3. Positive diagnosis of diabetes made at the Clinic
4. First seen at the Clinic between January 1, 1957 and December 31, 1963.

Information concerning the history of diabetes, as well as information about selected risk factors present at the time of the first visit was abstracted. In addition, the patients were followed through their course of treatment at the Clinic and data on blood sugar, and type, dose and duration of treatment was collected. Since deaths due to cardiovascular causes were most of interest, information on risk factors related to cardiovascular mortality was also collected. Risk factors considered were the following: age at first visit, sex, blood pressure, duration of diabetes prior to first visit, relative weight, history of heart disease, e.g. MI hypertension, ASHD, or rheumatic heart disease, history of kidney disease, cancer, and diseases of the respiratory and/or GI systems, smoking history, and history of early death in the parents. Data on cholesterol levels were not available on enough patients to warrant collecting it.

All patients were followed until death or December 31, 1971 and status as of that date was recorded. For those who died, the date, place and cause of death and, if present, results of autopsy were recorded. The clinic has maintained an updated patient status file so a majority of deaths to this population was already known. However, an extensive effort was made to locate individuals not known to be dead and who were not seen in the clinic after 1970, (persons seen in the clinic and known to be alive in 1970 to 1971 were assumed to have survived until the end of the study.) Three separate mailings went to the patients. If these all went unanswered, additional mailings went to the patient's doctor, family, neighbors and to the town clerk of the city in which the patient last resided. Further follow up was continued by telephone. At the end of the study, 132 of 6291 (2.2%) were untraced.

In an attempt to determine the underlying cause of death, death certificates were examined by a physician wthout knowledge of which regimen the patient had employed to control his diabetes. Information from the death certificate was obtained either through the town clerk, or, if possible through the state department of vital statistics by mail. Town clerks in cites as large as Boston (where a large proportion of the deaths occurred) were unable to provide the desired data and therefore information for deaths occuring in Boston was ob-

tained by a hand search of the records of the Massachusetts and Boston Departments of Health.

In most cases (95%) the physician's determination of the cause of death agreed with that indicated to be the underlying cause on the death certificate. However, certain causes e.g. congestive heart failure, uremia and pulmonary edema were not accepted as causes but rather considered as "modes of dying". In cases where these were coded as the cause of death, the records of the physician attending the death, hospital discharge summary and if present autopsy information were obtained in order to determine more precisely the cause of death.

One of the objectives of this study was to isolate the specific effects of treatment on survival in general and, specifically, on deaths from cardiovascular causes. It was, therefore, imperative to have well-defined treatment groups. The study design was non-experimental and therefore no control of treatment was possible. Hence a variety of treatment patterns were observed in the population. In order to quantitate the effect of treatment, it was necessary to devise a scheme to summarize these patterns. For purposes of this analysis, an individual's treatment was defined as that which he received 90% or more of the time between entry to the study and 1972 or death. A total of 6291 patients were entered into the study population and from there three basic treatment groups emerge:

1. "pure" insulin group with 2393 or 38.8% of the total population,
2. "pure" tolbutamide group with 1271 or 20.2% of the total population,
3. "pure" diet group with 951 or 15.1% of the total population.

Together these groups comprised 4615 or 73.2% of the entire population. The other 28.6% of the population received a mixed variety of treatments. The "mixed variety" group included people who received other oral agents (sulfonylureas or phenformin) either alone or in conjunction with either tolbutamide or insulin. This group also included people who had uncontrollable diabetes and who were switched from one regimen to another and back again. The majority of persons in this group were of the first type. However, no other drug was given to a sufficient number of persons (90% of the time) to enable a separate analysis comparable with the analyses of the three regimens previously specified. In addition, there were no data available to investigate why individuals were switched from one regimen to another.

These groups were compared with respect to risk factors associated with the severity of their diabetes such as mean blood glucose level and duration of diabetes prior to first visit. In addition they were compared with respect to risk factors influencing mortality such as age, sex, weight and history of cardiovascular problems prior to first visit. (It should be noted that the only endpoint considered in this study was survival status. Non fatal cardiovascular events which occurred after first visit to the clinic were not recorded.)

The seven-year period of entry to the study necessitated the use of life table methods in the analysis of survival. The methods chosen were those suggested by Drolette (*12*). Because it was of interest to investigate cardiovascular deaths, methods (discussed by Chiang (*13*)) which dealt with the case of competing risks were adopted. Standard errors were calculated using the procedure suggested by Greenwood (*14*). In addition, because of the possible effect of age differences in the three groups, survival was assessed in relation to a standard population (in this case the population of Massachusetts).[1] This relative survival approach (*15*) estimates the number of deaths expected in each of the groups over time if the age and sex specific mortality rates for the standard population were operating in the study population. Both the observed and expected probabilities of survival were computed for each one year interval (the expected probabilities were calculated by using the expected survivors rather than the observed survivors in the numerator and adjusting the denominators appropriately). The relative survival rate is the ratio of these observed to expected probabilities of survival. A relative survival of 100 indicates that

[1] Data for the reference population for the calculation of relative survival were taken from the age-sex data on deaths and population structure for the population of Massachusetts 1955–1970. These data were taken from the Vital Statistics Reports for the Commonwealth of Massachusetts 1955–1970. For the overall age-sex specific death rates calculations were done using data on all causes of death; however, for assessment of relative survival for cardiovascular causes, age-sex specific death rates were calculated using data for cardiovascular causes only. In all cases, the age-sex specific rates were calculated in the relative survival computer program written by Dr. Richard Monson, Department of Epidemiology, Harvard School of Public Health.

the observed survival experience of the study population is identical with that of the standard population. A relative survival of less than 100 indicates that factors other than age are causing the study population to live a shorter than expected amount of time. In part the use of measures of relative survival corrects for discrepancies in the age distribution; however, if relative survival is a function of age, the relative survival approach will not totally account for age differences between the groups and adjustment for age will be necessary.

In the analysis which follows relative survival was considered both for all causes as well as for those specifically due to cardiovascular diseases. Because the cause of death used in this study was not always what was specified on the death certificate as the underlying cause of death, the value of relative survival with respect to cardiovascular mortality is only approximate. However, since the determination of the cause of death was made prior to the determination of treatment group, discrepancies between the "true" relative survival and that indicated by the results of this study may be assumed to be present equally in all treatment groups. Further, since in 95% of the cases, the cause of death was identical to that on the death certificate, the problem is of minor importance.

The non-random allocation of individuals to treatment increased the likelihood that the distribution of risk factors, at entry, especially ones associated with disease severity was not similar in each of the groups. In order that the survival results be more comparable between the groups as well as more comparable with those presented by the UGDP, analysis of survival was restricted to individuals with newly diagnosed diabetes. (known duration of diabetes less than or equal to one year prior to entry to the study). This reduced the size of the insulin group to 789, the tolbutamide group to 702 and the diet group to 676.

The major difficulty encountered in analyzing these data was the high degree of confounding between treatment and blood glucose. Because of the non-experimental nature of this study, patients received treatment according to the severity of their diabetes—persons with the mildest diabetes were treated by diet alone while persons with severe diabetes required insulin. The best measure of both the severity of the disease and the degree of control obtained was the mean blood glucose for an individual during the duration of his Joslin Clinic visits. As was expected, the levels were highest for persons treated with insulin and lowest for those controlled by diet alone. Because of the deleterious effect of poor control or high blood glucose values on survival, differentiation of the treatment from those of blood glucose was desirable. However, the large degree of confounding between these two factors made such a distinction difficult.

RESULTS

Description of the study population

The distribution of the "clinical" characteristics of this population by treatment and sex are given in Table 1. Of the total 2167, 1065 or 49.1% were females. The proportion of females varied by treatment: 417 of 789 (52.9%) of people on insulin, 335 of 702 (47.7%) of those on tolbutamide and 313 of 676 (46.3%) treated by diet alone were female. The mean age of the population was 53.4 years and the mean ages in the three groups were similar to the overall mean although the tolbutamide group was slightly older than either of the other two groups. The mean age for females was consistently higher than that for males. Although the mean ages were similar between the groups, the distribution of those ages were different. For patients on tolbutamide 46.5% of those on insulin and 59.6% treated by diet alone were under 60. Both males and females exhibited a similar trend in the distribution of age at entry to the study.

The severity of the diabetes at the time of entry to the study was controlled to some extent by considering only patients with known duration of diabetes= one year at the time of entry. However, this control was not sufficient to assume that the groups be comparable with respect to disease severity at entry. As was stated previously the groups differed in the levels of the mean blood glucose. For persons treated by diet alone it was 101.8 mg/100 ml, for persons on tolbutamide it was 131.9 mg/100 ml, and for those on insulin 169.3 mg/100 ml. In addition, the distribution of blood glucose values was quite different in the three groups; the values in the diet group were concentrated at the lower end of the scale, the tolbutamide values in the middle ranges and the insulin values at the upper end. The distribution of values by sex showed similar trends; and in general males had slightly lower values than females.

Since one of the aims of this study was to assess the effect of treatment on deaths from cardiovascular causes, it was imperative to evaluate the distribution of risk factors associated with cardiovascular mortality. The distribution of those considered here is presented in Table 2. In this population 10.4% of the individuals had a positive history of arteriosclerotic heart disease (ASHD). This proportion did not vary much between the groups; however, large differences by sex were present in both the insulin and diet groups. Hypertension was defined as blood pressure greater than 150/90. The prevalence of hypertension at entry varied between the groups as well as between the sexes. Consistently the proportion of hypertensives was greater among females than among males. The prevalence among males was similar in each of the groups, however it varied a great deal among females from 56.7% amoung women on tolbutamide to 40.3% among women on diet alone.

Previous history of cerebral vascular accidents was negligible and present in only 0.38% of the population. A previous history of all other cardiovascular complications occurred in 21.3% of the population. This percentage did not vary among the treatments, although, in general the prevalence of cardiovascular complications was higher among females than among males.

Differences in smoking histories were evident between the groups although the variation was seen in part to be a reflection of differences in the distribution of sex. The average proportion of non-smokers was 27.2% among males and 64.9% among females. Percentages by sex varied between the groups, but in general persons on tolbutamide smoked less than those on either insulin or diet alone.

Obesity or relative weight was another factor thought to influence cardiovascular mortality. Florey (*16*) had described and investigated several mathematical measures of correcting weight for height. For purposes of this study weight/(height) was chosen as a relevant measure. In general, the males appeared to be less obese than females. Among males there appeared to be relatively little difference between these indices in the groups; however, females on insulin appeared to be relatively heavier than those on either of the other two treatments.

The final factor considered was history of early death in the parents. A positive history was defined as that parent dying before the age of 60. Four hundred ninety-six (496) out of 2167 or 22.9% had fathers who died before age 60 and 451 of 2167 or 2o.8% had mothers who died before age 60. These proportions were very similar between treatments and sexes.

It has been shown that major differences occur between the groups in the distribution of age, sex and level of blood glucose. Differences in factors such as history of ASHD, hypertension and smoking have been shown to be correlated with sex; analysis of survival will therefore have to consider age, sex and level of blood glucose.

Mortality results

Crude mortality results for this population are presented in Table 3. Of the total 2167, 884 (40.8%) had died by the end of the study period. Of these 884 total deaths 444 (50.2%) were attributable to arteriosclerotic heart disease (including myocardial infarction), 63 (7.1%) to other heart disease, 105 (11.9%) to cerebral vascular accidents and 153 (17.3%) to all cancers. Autopsy information was available for 20% of the population and 6% of the deaths were listed as sudden on the death certificate. The distribution of deaths by cause was similar for both sexes although in all cases more males died than females.

Differences in mortality by treatment are striking. In general, mortality among persons on either tolbutamide or insulin was considerably higher than that for individuals on diet alone; mortality among those on insulin was only slightly higher than for those on tolbutamide. Differences in mortality from all causes by sex were not evident in either the insulin or tolbutamide groups; however, a much larger proportion of males on diet died than did females. Although the overall probability of death was higher among those on insulin than tolbutamide, the probability of death from ASHD was higher among persons on tolbutamide; this was especially true among males. Of the 264 total deaths to males on tolbutamide 97 (59.1%) were due to ASHD whereas 72 of the 177 total deaths (40.6%) among males on insulin were due to ASHD. The same pattern is observed for all cardiovascular causes of death.

The results presented in Table 3 are crude since they consider neither differences in observation time nor levels of disease severity. The life table and relative survival methods discussed previously were used to evaluate the survival experience of this population.

Table 4 presents cumulative relative survival information for 0–5 years and for 5–10 years for all causes of death by sex and level of blood glucose. It was seen previously that there were differences between the groups in the prevalence of ASHD and hypertension. To consider the possibility that selectivity in the choice of treatments (i.e. that persons with history of cardiovascular problems might be more likely given one specific treatment) might account for observed differences in survival between the groups, relative survival was also evaluated separately for individuals with and without previous history of ASHD or hypertension. Results for all causes of death are presented in Table 5 for those with negative history and in Table 6 for patients with a positive history.

For both sexes the overall relative survival in the first 5 years is lower for persons on insulin than for those in either of the other two groups, and the experience of both the tolbutamide and diet groups is similar. For individuals who survive at least 5 years, however, the relative survival experience for persons receiving tolbutamide is worse in all cases than that of those on diet and in the middle ranges of blood glucose it is worse than for persons on insulin alone. The results are most striking for persons with positive histories of ASHD or hypertension.

The above results have considered all causes of death. Tables 7, 8 and 9 present similar findings for deaths attributable to all cardiovascular causes (ASHD and all heart related deaths). These results are consistent with and are more striking than those presented above. In most cases, there appears to be a decline in relative survival with increasing level of blood glucose among persons who survive at least 5 years.

During the first 5 years, the relative survival between the groups is not very different and is generally higher in the subgroups with no history of ASHD or hypertension. In the period from 5 to 10 years, however, relative survival from cardiovascular causes is lower among those on tolbutamide than either those on insulin or those controlled by diet alone. The lower relative survival for those on tolbutamide is more pronounced among males.

Because all of the risk factors discussed previously are important and a method of quantitating an individual's overall risk without substantially reducing the numbers available for comparison is desirable.

Kanarek (*17*) has recently investigated a method of using risk factors to predict survival. Basically this method involves calculating a risk for each individual which is a function of his particular set of risk factors (e.g. age, sex, average blood sugar). These individual risks, λ_i, are known in statistical terms as the force of mortality or instantaneous risk of death and are defined by:

$$\lambda_i = a + \sum_{k=1}^{c} b_k x_{ki}$$

where we are concerned with evaluating the effect of c risk factors. For purposes of this analysis four factors were selected: age at first visit, history of previous myocardial infarction, interval between onset of diabetes and first visit and average blood sugar. Therefore an individual's risk is defined as follows:

$\lambda_i = a + b_1$ (age at first visit)
$+ b_2$ (history of previous myocardial infarction)
$+ b_3$ (interval be ween onset and first visit)
$+ b_4$ (average blood glucose).

Estimates of a set of coefficients (a, b_1, b_2, b_3, b_4) were obtained for each of 4 age-sex groups: males 40–59 at first visit, females 40–59, males 60 and over and females 60 and over. Each age-sex group was then stratified into three levels of risk—low, middle and high on the basis of the λ_i and survival by treatment was evaluated using life table methods. The λ_i as described above have been shown to be reasonable delineators of low and high risk individuals. (See ref .16.) The estimated coefficients and risk level stratification are presented elsewhere (*18*). Table 10 presents the 0–5 and 5–10 year cumulative survival rates and their respective standard errors for all causes of death and from cardiovascular causes for males and females 40–60 and Table 11 presents the same information for individuals over 60 at entry to the study.

In all groups the probability of surviving either 5 or 10 years decreased with increasing risk level. For all causes of death, in the first five years, survival was lowest among persons on insulin and best among those on diet. However, for individuals who survive at least 5 years, the probability of surviving the next 5 years did not follow this pattern. In fact, in many cases most notably those over 60 at entry, survival for the second 5 years was poorer for the

tolbutamide group than for either of the other two. Considering deaths from cardiovascular causes, this observation is even more striking: while certainly in all risk categories, the probability of dying from cardiovascular causes in years 5-10 was consistently higher in the tolbutamide group than in the diet group, for those over 60 the probability was also higher in the tolbutamide group than in the insulin group at all risk levels. This observation is not as apparent among those under 60 at entry although in this age group the initial differences in survival between the tolbutamide and insulin groups become negligible.

It has been seen that the delineation of the population by consideration of all risk factors is a sensitive indicator of survival because observed probability of survival decreases as level of risk increases. It has also been seen that within risk factor categories the probability of death from cardiovascular causes is greater for persons on tolbutamide than for those on other treatments. The most comparable group is that of individuals with low risk levels. Even within this sub-group the numbers are small and therefore the standard errors associated with the probabilities are large. The increased risk among those on tolbutamide is nonetheless present.

Discussion

The major purpose of this study was to compare the effects of long term hypoglycemic therapy prescribed in the usual clinical manner with tolbutamide to that of treatment with insulin and to that with diet alone. Specifically, it was desired to assess the effects of the individual therapies on mortality and especially on that portion attributable to cardiovascular causes. Because individuals were not randomly allocated to the specific treatment groups, disease severity within the three groups considered here is not comparable. Evaluation of survival was restricted to individuals with known duration of diabetes = one year prior to entry to the study. However, even in this group disease severity could not be assumed to be comparable. The symptoms of diabetes can be insidious in their appearance and therefore, although symptoms of the disease were noticed in the year previous to the first visit, the true onset of the disease could have been 5 to 10 years earlier. Unmeasured differences between the groups in the true duration of diabetes prior to the first visit could influence the severity of the disease at the time of the first visit and consequently the results observed here. However, in order for any analysis to be performed it must be assumed that the discrepancies between true and observedduration of diabetes were distributed equally among the different groups.

The best available indicator of severity over the course of the study was mean blood glucose level and it has been seen that even in this group of newly diagnosed diabetics the distribution of blood glucose was different. Nonetheless, evaluation of relative survival within 4 blood glucose groups showed (whether or not history of ASHD or hypertension was considered) some positive evidence that for persons with low and moderate mean blood glucose levels treated with tolbutamide, the probability of deaths during the 5-10 year period was greater than in either of the two other treatment groups. This result was most noticeable when considering deaths due to cardiovascular causes. Evaluation of survival within general classes of overall risk supports this hypothesis for cardiovascular causes.

The fact that in the first five years after entry to the study those on insulin appear to exhibit poorer survival than either the tolbutamide or diet groups is most likely related to differences (unmeasured) in disease severity at the time of entry to the study rather than to the treatment itself. This hypothesis is consistent with the way in which treatment is prescribed. Observation made after five years are, therefore, more likely to be related to the effects of long-term treatment of the diabetes.

The results of the UGDP strongly suggested that tolbutamide was not an effective treatment for diabetes. The excess of cardiovascular deaths observed in the tolbutamide group was sufficient to warrant termination of that portion of the clinical trial. The Joslin Clinic data presented here are not directly comparable with the results presented by the UGDP; it cannot be assumed that the underlying populations of diabetics from which each of the study groups was drawn were the same. In addition, the administration of treatment was done randomly in the UGDP project whereas in the Joslin Clinic data treatments were prescribed according to the physician's biases. While from the UGDP data it was possible to quantitate the excess cardiovascular mortality attributable to tolbutamide, the sizes of the groups in the Joslin Clinic data were small and in addition, treatment and blood glucose were highly confounded so that

in this population definitive results quantitating excess mortality attributable to tolbutamide were impossible.

Taken alone, the results from the Joslin Clinic data are marginal; however, the results presented here are consistent with those of the UGDP in that they show no indication that long term tolbutamide therapy substantially reduces the probability of death from cardiovascular complications. Comparisons of low risk individuals (defined either by those with low blood glucose or by a linear combination of all risk factors) indicated that both survival as a whole and relative survival are lower after five years among individuals treated with tolbutamide as compared to those treated with diet alone and in certain subgroups as compared to those on insulin. In all cases, although patients treated with insulin were sicker than those treated with tolbutamide, the lack of difference in survival between the groups after five years suggested that tolbutamide did not better in preventing deaths from cardiovascular causes. While the ultimate question—what would have been the survival experience of the patients treated with tolbutamide had they been treated with insulin or by diet alone?—cannot be directly answered, the results of this observational study suggest that the findings of the UGDP may be generalizable to other diabetic populations.

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TABLE 1.—DISTRIBUTION OF CLINICAL CHARACTERISTICS

	Males						Females						Total					
	Insulin		Tolbutamide		Diet		Insulin		Tolbutamide		Diet		Insulin		Tolbutamide		Diet	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Total	371	100.0	367	100.0	363	100.0	417	100.0	335	100.0	313	100.0	789	100.0	702	100.0	676	100.0
Age of first visit:																		
40 to 49	107	28.8	72	19.6	107	29.6	96	23.1	42	12.5	72	23.0	203	25.7	114	16.1	179	26.5
50 to 59	143	38.4	117	31.9	120	32.9	155	27.0	96	28.7	104	33.2	298	37.8	213	30.3	224	33.1
60 to 69	80	21.5	124	33.8	102	28.2	122	29.3	119	35.5	99	31.6	202	25.7	243	34.4	201	30.0
70 and over	42	11.3	54	14.7	34	9.4	44	10.6	78	23.3	38	12.1	86	10.8	132	19.2	72	10.4
Mean age	51.5		54.4		51.7		52.7		57.0		58.3		52.2		55.6		52.6	
Mean blood glucose:																		
<120mg/100ml	42	11.3	119	32.4	251	69.1	41	9.9	103	30.8	231	73.8	83	10.5	222	31.6	482	71.3
120 to 139	60	16.1	157	42.8	97	26.7	50	12.0	139	41.5	61	19.5	110	13.9	296	42.2	158	23.4
140 to 159	43	11.6	57	15.5	13	3.6	46	11.0	57	17.0	14	4.5	89	11.3	114	16.2	27	4.3
160 and over	227	61.0	34	9.2	2	.5	280	67.1	36	10.7	7	2.2	507	64.3	70	10.0	9	1.3
Mean blood glucose	169.2		128.4		101.1		171.0		132.7		102.3		169.3		131.9		101.8	

Note: Percentages are based on the total number of individuals on the specific regimen.

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TABLE 2.—DISTRIBUTION OF CLINICAL CHARACTERISTICS

	Males						Females						Total					
	Insulin		Tolbutamide		Diet		Insulin		Tolbutamide		Diet		Insulin		Tolbutamide		Diet	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Total	372	100.0	367	100.0	363	100.0	417	100.0	335	100.0	313	100.0	789	100.0	702	100.0	676	100.0
History, first visit of:																		
ASHO*	24	6.5	45	12.3	41	11.3	55	13.2	38	11.3	23	7.3	79	10.0	83	11.8	64	9.5
Hypertension	124	33.3	110	32.2	112	30.9	193	46.3	190	56.7	126	40.3	317	40.2	308	43.9	238	35.2
CVA*	0	0	1	.3	0	0	3	.7	1	.3	1	.3	3	.4	2	.3	1	.1
All other disease	69	18.5	71	19.3	60	16.3	90	23.5	92	27.5	62	23.1	167	21.2	163	23.2	132	19.5
Smoking history:																		
None	86	23.1	119	32.4	95	26.2	268	64.4	245	73.1	178	56.9	354	44.9	364	52.0	273	40.4
<1 pk/day	57	15.3	42	11.4	40	12.7	59	14.2	32	9.6	44	14.1	116	14.7	74	10.5	90	13.3
1+ pks/day	115	00.9	88	24.0	100	27.6	60	14.4	25	7.5	45	14.4	175	22.2	113	16.1	145	21.4
Other	67	18.0	69	18.8	65	17.9							67	8.5	69	9.8	65	9.6
Unknown	47	12.6	49	13.3	57	15.7	30	7.1	33	9.9	46	14.6	77	9.7	82	11.7	103	15.1
Father's age at death:																		
<60	88	23.7	84	22.8	75	20.7	103	24.7	69	20.6	77	24.6	191	24.2	153	21.8	152	22.5
60 to 74 (dead)	70	18.8	65	17.7	60	16.5	73	17.5	70	20.9	64	20.4	143	18.1	135	19.2	124	18.3
60 to 74 (alive†)	62	16.7	52	14.3	55	15.2	65	15.6	51	15.2	51	16.3	127	16.1	103	14.7	106	15.7
75+ (dead and alive)	137	36.8	173	39.8	156	43.0	154	36.9	132	39.4	105	33.5	291	36.8	278	39.6	261	38.6
Unknown	15	4.0	20	5.4	17	4.7	22	6.2	13	3.8	16	5.1	37	4.7	33	4.7	33	4.9
Mother's age at death:																		
<60	78	21.0	73	19.9	71	19.6	89	41.3	79	23.6	61	19.5	167	21.2	152	21.7	132	19.5
60 to 74 (dead)	68	18.2	73	19.9	61	16.8	78	18.7	63	18.8	64	20.4	146	18.5	136	19.4	125	18.5
60 to 74 (alive†)	64	17.2	58	15.8	52	14.3	62	14.9	42	12.5	55	17.6	126	16.0	100	14.2	107	15.8
75+ (dead and alive)	131	35.2	142	38.7	160	44.1	169	40.5	142	42.3	116	37.1	300	38.0	284	40.5	276	40.8
Unknown	31	8.3	21	5.7	19	5.2	19	4.5	9	2.7	17	5.4	50	6.3	30	4.2	36	5.3
Mean weight	163.6±0.1		171.2±1.2		173.8±1.3		150.2±0.9		155.1±1.4		149.7±1.7		155.9±0.7		163.3±0.9		163.0±1.1	
Mean height	67.0±0.1		66.8±0.1		67.2±0.1		62.4±0.1		62.1±0.1		62.7±0.1		64.5±0.1		64.5±0.1		65.2±0.1	
Weight/Height²	.036±.001		.038±.001		.039±.001		.045±.007		.040±.001		.038±.001		.041±.004		.039±.001		.039±.001	

*ASHO=Arteriosclerotic heart disease.
*CVA =Cerebral vascular accident.
†"Alive" indicates that the parent was alive at the time of the patient's first visit to the clinic.
Note: Percentages are based on the total number of individuals on the specific regimen.

TABLE 3.—OVERALL MORTALITY RESULTS

	Males						Females						Total					
	Insulin		Tolbutamide		Diet		Insulin		Tolbutamide		Diet		Insulin		Tolbutamide		Diet	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Total	372	100.0	367	100.0	363	100.0	417	100.0	335	100.0	313	100.0	789	100.0	702	100.0	676	100.0
Alive	188	50.5	198	54.9	220	60.6	231	55.4	191	57.0	217	69.3	419	53.1	389	55.4	437	64.5
Untraced	7	1.9	5	1.4	9	2.5	4	1.0	6	1.8	7	2.2	11	1.4	11	1.6	16	2.4
Dead	177	47.6	164	44.7	134	36.9	182	43.6	138	41.2	89	28.4	359	45.5	302	43.0	223	33.0
Causes of death:																		
ASHD	72	19.4	93	28.3	65	18.0	91	21.8	71	21.2	38	12.1	163	20.7	164	23.4	103	16.2
Other heart disease	11	3.0	6	1.8	10	2.7	16	3.7	11	3.3	9	2.9	27	3.4	17	2.4	19	2.8
CVA	25	6.7	11	3.0	11	3.0	25	6.0	18	5.4	15	4.8	50	6.4	29	4.0	26	3.8
Renal diseases	5	1.3	6	1.6	2	.6	8	1.9	1	.3	2	.6	13	1.6	7	1.0	4	.6
Cancer	38	10.2	26	7.1	26	7.2	26	6.3	21	6.3	16	5.1	64	8.1	47	6.7	42	6.2
GI	14	3.8	6	1.8	5	1.4	2	.5	4	1.2	4	1.2	16	2.0	10	1.4	9	1.3
Respiratory	4	1.1	7	1.9	10	2.7	5	1.2	6	1.8	1	.3	9	1.1	13	1.9	11	1.6
All other	8	2.1	9	2.4	5	1.4	9	2.3	6	1.8	4	1.2	17	2.2	15	2.0	9	1.3

Note: Percentages are based on the total number of individuals on the specific regimen.

TABLE 4.—RELATIVE SURVIVAL BY SEX AND BLOOD GLUCOSE. ALL CAUSES OF DEATH

Relative survival	Males									Females								
	Insulin			Tolbutamide			Diet			Insulin			Tolbutamide			Diet		
	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE
0 to 5 yrs, blood glucose:																		
Less than 120	42	0.93	0.06	119	0.98	0.04	251	0.97	0.03	41	0.77	0.08	103	1.02	0.04	231	0.99	0.02
120 to 139	60	.94	.06	157	.99	.04	97	.94	.04	50	.82	.06	139	1.00	.03	61	.92	.06
140 to 159	43	.84	.07	57	1.02	.06	13	.86	.13	46	.89	.06	57	.91	.06	14	1.02	.08
160 and over	227	.93	.03	34	.75	.09	2	1.00	0	280	.91	.02	36	.91	.08	7	.91	.14
5 to 10 yrs, blood glucose:																		
Less than 120	34	.80	.09	99	.78	.07	205	.96	0.04	28	0.78	.10	90	.81	.07	201	.98	.03
120 to 139	47	.93	.08	129	.89	.05	78	.90	.06	37	0.95	.07	118	.91	.05	50	.86	.07
140 to 159	32	.84	.11	45	.76	.10	10	1.06	.12	37	0.95	.07	45	.77	.10	13	1.12	0
160 and over	177	.78	.04	22	.86	.10	2	1.06	0	231	0.83	.03	29	.79	.10	6	1.11	0

TABLE 5.—RELATIVE SURVIVAL BY SEX AND BLOOD GLUCOSE, ALL CAUSES OF DEATH

[Persons with no history of ASHD or hypertension]

Relative survival	Males									Females								
	Insulin			Tolbutamide			Diet			Insulin			Tolbutamide			Diet		
	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE
0 to 5 yrs, blood glucose:																		
Less than 120	27	1.02	0.07	68	1.01	0.04	163	1.09	0.03	15	0.94	0.10	47	1.07	0.04	142	1.01	0.02
120 to 139	37	.97	.06	105	1.03	.04	52	1.12	.02	25	.95	.07	53	1.11	.03	25	.93	.08
140 to 159	31	.97	.07	34	1.08	.07	12	.85	.14	22	.96	.08	19	.98	.07	7	1.07	0
160 and over	137	1.0	0	16	.86	.11	2	1.10	0	142	.95	.03	15	1.01	.07	4	.79	.23
5 to 10 yrs, blood glucose:																		
Less than 120	24	.91	.10	61	.93	.07	140	1.02	.04	13	.92	.14	34	.99	.08	129	1.02	.03
120 to 139	31	.92	.10	90	.90	.06	50	.91	.09	21	.96	.10	49	.87	.08	21	.95	.10
140 to 159	27	.83	.11	30	.78	.12	9	.52	.25	19	.87	.13	17	.81	.14	7	1.09	0
160 and over	117	.75	.05	13	.79	.19	2	1.16	0	124	.82	.04	14	.77	.13	3	1.15	0

TABLE 6.—RELATIVE SURVIVAL BY SEX AND BLOOD GLUCOSE, ALL CAUSES OF DEATH

[Persons with history and ASHD or hypertension]

Relative survival	Males									Females								
	Insulin			Tolbutamide			Diet			Insulin			Tolbutamide			Diet		
	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE
0 to 5 yrs, blood glucose:																		
Less than 120	15	0.76	0.09	51	0.94	0.05	88	0.75	0.05	26	0.67	0.08	56	0.98	0.06	89	0.96	0.05
120 to 139	23	.89	.08	52	.94	.06	45	.73	.07	25	.69	.09	86	.93	.05	36	.91	.09
140 to 159	12	.50	.08	23	.93	.11	1	----	----	24	.82	.09	38	.88	.08	7	.97	.20
160 and over	90	.82	.05	18	.65	.09	0	----	----	138	.87	.04	21	.85	.08	3	1.07	0
5 to 10 yrs blood glucose:																		
Less than 120	10	.54	.10	38	.58	09	65	.83	.06	15	.66	.11	56	.72	.07	72	.91	.04
120 to 139	16	.95	.07	39	.87	.08	28	.88	.09	16	.94	.10	69	.94	.06	29	.79	.09
140–159	5	.89	.25	15	.72	.22	1	----	----	18	1.03	.09	28	.75	.10	6	1.15	0
160 and over	60	.84	.07	9	.96	.22	0	----	----	107	.84	.04	15	.81	.11	3	1.05	0

TABLE 7.—RELATIVE SURVIVAL BY SEX AND BLOOD GLUCOSE, CARDIOVASCULAR DEATHS

Relative survival	Males									Females								
	Insulin			Tolbutamide			Diet			Insulin			Tolbutamide			Diet		
	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE
0 to 5 yrs, blood glucose:																		
Less than 120	42	0.88	0.06	119	0.91	0.04	251	0.90	0.03	41	0.73	0.08	103	0.95	0.03	231	0.94	0.02
120 to 139	60	.88	.05	157	.91	.03	97	.88	.04	50	.78	.06	139	.93	.93	61	.87	.05
140 to 159	43	.78	.07	57	.91	.06	13	.81	.12	46	.84	.06	57	.85	.06	14	.97	.07
160 and over	227	.85	.03	34	.70	.09	2	1.05	0	280	.87	.02	36	.86	.07	7	.88	.14
5 to 10 yrs, blood glucose:																		
Less than 120	34	.83	.08	99	.71	.06	205	.87	.03	28	.74	.10	90	.75	.06	201	.91	.03
120 to 139	47	.86	.07	129	.80	.05	78	.82	.06	37	.90	.07	118	.83	.05	50	.81	.07
140 to 159	32	.78	.10	45	.68	.06	10	.59	.21	37	.90	.07	45	.71	.09	13	1.02	0
160 and over	177	.72	.04	22	.72	.10	2	1.08	0	231	.78	.03	29	.69	.10	6	1.00	0

TABLE 8.—RELATIVE SURVIVAL BY SEX AND BLOOD GLUCOSE, CARDIOVASCULAR DEATHS

[Persons with no history of ASHD or hypertension]

Relative survival	Males									Females								
	Insulin			Tolbutamide			Diet			Insulin			Tolbutamide			Diet		
	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE
0 to 5 yrs, blood glucose:																		
Less than 120	27	0.95	0.06	68	0.97	0.04	163	0.95	0.03	15	0.90	0.09	47	1.00	0.04	142	0.97	0.02
120 to 139	37	.91	.06	105	.94	.04	52	1.05	.02	25	.91	.07	53	1.03	.03	25	.88	.08
140 to 159	31	.92	.06	34	.98	.06	12	.87	.13	22	.91	.08	19	.93	.07	7	1.03	0
5 to 10 yrs, blood glucose:																		
160 and over	137	.93	.03	16	.86	.10	2	1.05	0	142	.91	.03	15	97	.07	4	.77	.22
Less than 120	24	.84	.10	61	.80	.07	140	.94	.04	13	.88	.14	34	.90	.07	129	.97	.03
120 to 139	31	.82	.09	90	.79	.05	50	.81	.08	21	.89	.09	49	.79	.07	21	.89	.09
140 to 159	27	.77	.11	30	.69	.11	9	.40	.24	19	.81	.12	17	.75	.10	7	1.04	0
160 and over	117	.73	.05	13	.62	.08	2	1.08	0	124	.74	.04	14	.74	.12	3	1.01	0

TABLE 9.—RELATIVE SURVIVAL BY SEX AND BLOOD GLUCOSE, CARDIOVASCULAR DEATHS

[Persons with history of ASHD or hypertension]

Relative survival	Males									Females								
	Insulin			Tolbutamide			Diet			Insulin			Tolbutamide			Diet		
	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE	N	Relative survival	SE
0 to 5 yrs, blood glucose:																		
Less than 120	15	0.75	0.08	51	0.83	0.07	88	0.81	0.08	26	0.63	0.11	56	0.91	0.06	89	0.89	0.06
120 to 139	23	.83	.10	52	.85	.07	45	.68	.07	25	.65	.10	86	.87	.06	36	.86	.00
140 to 159	12	.42	.14	23	.81	.09	1			24	.78	.09	38	.81	.08	7	.91	.10
160 and over	90	.73	.06	18	.56	.11	0			138	.83	.06	21	.78	.10	3	1.03	0
5 to 10 yrs, blood glucose:																		
Less than 120	10	.81	.09	38	.56	.09	65	.72	.06	15	.57	.11	56	.61	.07	72	.80	.06
120 to 139	16	.88	.07	39	.82	.07	28	.69	.10	16	.91	.08	69	.85	.05	29	.75	.10
140 to 159	5	.82	.15	15	.60	.10	1			18	.99	.09	28	.68	.08	6	.98	.03
160 and over	60	.70	.07	9	.86	.12	0			107	.82	.05	15	.64	.10	3	1.00	0

TABLE 10.—CUMULATIVE SURVIVAL PATIENTS 40 TO 59 AT ENTRY

	All causes of death						Cardiovascular deaths					
	Males			Females			Males			Females		
	Insulin	Tolbutamide	Diet	Insulin	Tolbutamide	Diet	Insulin	Tolbutamide	Diet	Insulin	Tolbutamide	Diet
Low risk:												
N	120	86	139	56	38	83	64	80	131	53	33	73
0 to 5 yr survival	0.93	0.96	0.92	0.98	0.93	0.95	0.98	0.97	0.96	0.98	1.00	0.97
SE	.04	.05	.04	.06	.06	.03	.06	.05	.04	.04	.00	.03
5 to 10 yr survival	.83	.88	.90	.89	.95	.95	.92	.93	.93	.94	.97	.99
SE	.06	.06	.06	.08	.06	.06	.06	.06	.06	.08	.04	.03
Middle risk:												
N	97	74	64	163	84	73	147	84	75	168	90	86
0 to 5 yr survival	0.86	0.85	0.85	0.89	0.92	0.95	0.91	0.92	0.94	0.94	0.94	0.97
SE	.07	.08	.08	.03	.04	.05	.03	.04	.05	.05	.03	.03
5 to 10 yr survival	.70	.82	.79	.81	.86	.92	.86	.89	.87	.88	.91	.96
SE	.03	.08	.08	.06	.05	.06	.04	.06	.08	.07	.05	.03
High risk:												
N	43	29	24	33	20	20	39	25	21	29	15	17
0 to 5 yr survival	0.76	0.65	0.63	0.80	0.79	0.90	0.95	0.94	0.95	0.85	0.93	0.87
SE	.09	.10	.12	.08	.09	.08	.07	.06	.08	.09	.08	.09
5 to 10 yr survival	.62	.63	.69	.56	.71	.72	.88	.91	.90	.77	.76	.85
SE	.10	.15	.12	.10	.12	.12	.09	.06	.10	.11	.15	.18

TABLE 11.—CUMULATIVE SURVIVAL PATIENTS 60 AND OVER

	All causes of death						Cardiovascular deaths					
	Males			Females			Males			Females		
	Insulin	Tolbutamide	Diet	Insulin	Tolbutamide	Diet	Insulin	Tolbutamide	Diet	Insulin	Tolbutamide	Diet
Low risk:												
N	57	82	73	70	98	85	30	61	58	67	92	83
0 to 5 yr survival	0.73	0.81	0.82	0.78	0.87	0.87	0.92	0.80	0.90	0.90	0.90	0.94
SE	.08	.05	.04	.02	.02	.04	.06	.04	.04	.06	.04	.05
5 to 10 yr survival	.62	.62	.78	.73	.73	.84	.82	.74	.89	.84	.80	.87
SE	.12	.06	.05	.05	.05	.04	.08	.07	.06	.06	.04	.06
Middle risk:												
N	37	55	42	52	60	34	51	63	42	50	55	27
0 to 5 yr survival	0.63	0.72	0.74	0.61	0.74	0.83	0.85	0.82	0.88	0.82	0.92	0.86
SE	.09	.06	.05	.06	.04	.08	.06	.06	.06	.06	.05	.07
5 to 10 yr survival	.56	.42	.65	.62	.59	.66	.72	.75	.84	.84	.73	.76
SE	.12	.08	.07	.08	.06	.12	.07	.08	.06	.07	.05	.08
High risk:												
N	28	41	24	16	39	18	41	54	36	51	50	27
0 to 5 yr survival	0.42	0.56	0.57	0.57	0.66	0.67	0.62	0.69	0.64	0.70	0.74	0.75
SE	.10	.08	.09	.10	.08	.10	.08	.10	.10	.08	.08	.10
5 to 10 yr survival	.38	.47	.52	.49	.45	.57	.64	.59	.69	.57	.64	.71
SE	.15	.18	.08	.20	.12	.20	.12	.17	.15	.10	.11	.20

[From The New York Times, July 8, 1975]

A.M.A. AIDE LET UPJOHN USE LETTER TO SELL DRUG

(By David Burnham)

WASHINGTON, July 7—The chief executive officer of the American Medical Association wrote a letter early this year to state and county officials of the association minimizing questions that had been raised in the association's own magazine about the safety of a widely used diabetes drug.

The official, according to confidential A.M.A. documents, then permitted the 1,100 salesmen of the largest manufacturer of the controversial drug to use his letter in their sales talks despite a warning that such use violated A.M.A. policy and might prove embarrassing.

Details about the distribution of the letter, written by Dr. James H. Sammons, executive vice president of the A.M.A., became known as the Food and Drug Administration published today a proposed rule requiring a new label for the drug stating that it may lead to death from heart disease.

The drugs are often called oral hypoglycemic drugs. They are taken by mouth by an estimated 1½ million adult diabetics to lower blood sugar level. The pills are believed to represent a $100-million market for the pharmaceutical industry.

Dr. Sammons sent his letter concerning oral hypoglycemics to the executives of state, county and medical speciality societies on Jan. 28.

The letter said that the Feb. 10 issue of The Journal of the American Medical Association would contain both an article and an editorial raising questions about the drugs.

Dr. Sammons said that the article, by a committee of the Biometric Society, supported an earlier critical study of oral hypoglycemics that had been challenged by some other scientists. He reported that the editorial, written by Dr. Thomas Chalmers, formerly with the National Institutes of Health, alleged that the drug might be associated with as many as 10,000 to 15,000 unnecessary deaths a year in the United States alone.

"A considerable body of expert scientific opinion contradicts these published findings," Dr. Sammons wrote. "Diabetic patients should not be influenced by press reports, and should continue on whatever diabetic management program their own physician had prescribed."

Shortly after Dr. Sammons wrote his letter, the Upjohn Company requested permission to reprint it for use by Upjohn salesmen. The company manufactures two oral hypoglycemic drug products under the brand names Orinase and Tolinase. The Upjohn product Orinase has been for years the most widely used of the oral hypoglycemic drugs.

An A.M.A. staff lawyer said in a memorandum dated March 18 that the "policy of the A.M.A. is that the association's name may not be used for trade purposes."

"Permission to reprint A.M.A. materials has not been granted if there is any indication that the name of the association or its materials will be used in any manner that might directly or indirectly be construed as an endorsement by the A.M.A. of a particular product or manufacturer," the memo said.

The staff lawyer, Betty Jane Anderson, said that if this policy was waived, "Dr. Sammons should be cautioned that the use made of the letter by Upjohn salesmen may cause embarrassment to him personally or to the A.M.A.

COMMENT BY COMPANY

The lawyer added that "Upjohn's purpose could be better accomplished by having an article presenting the other side of the controversy published in The Journal of the American Medical Association." A notation at the bottom of the memorandum indicated that a copy of it had been sent to Dr. Sammons.

A spokesman for Upjohn, reached at the company's headquarters in Michigan, said that the A.M.A. had granted the request for use of the letter, and that copies of Dr. Sammon's letter had been given to each of the company's 1,100 salesmen. The spokesman was unable to say how frequently the letter had been used.

The warning that the Food and Drug Administration proposed requiring on the

label of the drugs would be set in boldface type and would say: "Oral hypoglycemic drugs may be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin."

Cardiovascular mortality means death from disorders of the heart and circulatory system.

ADVANTAGE AND RISK

The warning would indicate that the drugs should be used only for adult patients not totally dependent on insulin, whose blood sugar cannot be controlled by diet alone and who can not or will not take insulin.

The warning would also say that the doctor should inform the patient of the advantages and potential risks of the drugs, and that the patient should participate in the decision whether to use them.

The F.D.A.'s warning would apply to a number of oral drug products in addition to the two manufactured by Upjohn. These include: Diabinese, Pfizer, Inc.; Dynelor, Eli Lilly & Co.; two forms of a drug called DBI, Geigy Pharmaceuticals; two forms of the drug Meltrol, USV Pharmaceutical Laboratories, Inc., and the drug Tolbutamide from Premo Pharmaceutics Laboratorities, Inc.

[Excerpt from The Pharmocological Basis of Therapeutics, Fifth Edition, Goodman and Gilman]

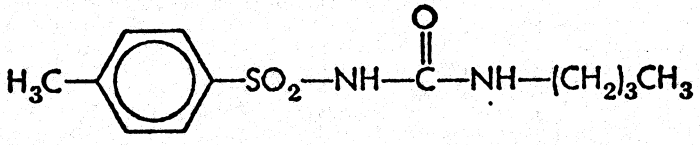
ORAL HYPOGLYCEMIC AGENTS

History. An important event in the history of the treatment of diabetes mellitus was the introduction of orally effective hypoglycemic agents. Janbon and coworkers (1942), in the course of clinical studies on the treatment of typhoid fever, discovered that a sulfonamide(*p*-amino-benzene-sulfonamido-isopropylthiadiazole) induced hypoglycemia. Janbon's colleague Loubatières (1957), made the fundamental discovery that the compound exerted no hypoglycemic effect in the completely pancreatectomized animal and suggested that the action was the result of stimulation of the pancreas to secrete insulin. There was no practical application of these findings until Franke and Fuchs capitalized on the discovery that the antibacterial agent *carbutamide* lowered the blood sugar in patients treated for infectious diseases. These workers demonstrated the apparent usefulness of carbutamide in the treatment of diabetes mellitus. Soon thereafter, the compound *tolbutamide* was introduced. This substance is not antibacterial, is less toxic than carbutamide, and soon became popular for the management of certain diabetic patients. Tolbutamide is a member of the class of oral hypoglycemic agents designated as *sulfonylureas.*

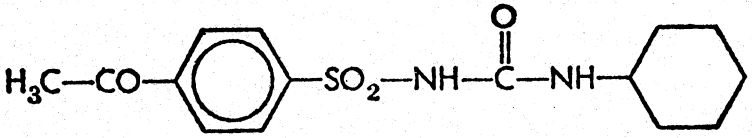
Another group of compounds, the *biguanides,* was developed independently of the sulfonylureas. Historically, the development began with the discovery in 1918 by Watanabe that guanidine is hypoglycemic in rats. Guanidine and its substituted derivatives were found to be too toxic to be therapeutically useful. *Diguanides,* two guanidine molecules joined by a chain of methylene groups, were more effective and less toxic than the substituted guanidines. SYNTHALIN A, a potent diguanide, was given clinical trial in diabetes, but it also was found to be too toxic for therapeutic use. Finally, *phenformin* (Ungar *et al.,* 1957), a member of the biguanide series (derived from two molecules of guanidine with elimination of ammonia), was found to have an apparently acceptable toxicity, and this compound has since had widespread use.

SULFONYLUREAS

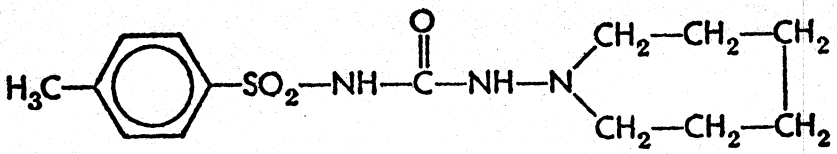
Chemistry. A number of sulfonylurea compounds exert hypoglycemic activity. The commercially available preparations are *tolbutamide, acetohexamide, tolazamide,* and *chlorpropamide,* which have the following structural formulas:



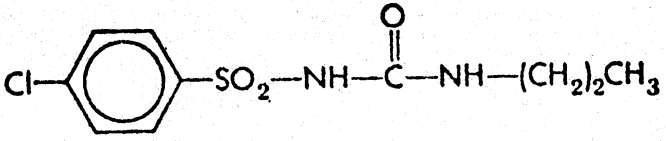
Tolbutamide



Acetohexamide



Tolazamide



Chlorpropamide

All of the effective compounds are arylsulfonylureas with substitutions on the benzene and the urea groups. In the case of tolbutamide, the aryl group is tolyl and the urea substitution is butyl. Tolbutamide differs from the antibacterial compound carbutamide in having methyl instead of amino on the benzene ring. This substitution accounts for the loss of antibacterial properties and for the reduction of toxicity.

Mechanism of Action. The sulfonylureas stimulate the islet tissue to secrete insulin. The evidence, coming as it does from a variety of experimental and clinical studies, unequivocally supports such a conclusion. Administration of sulfonylureas increases the concentration of insulin in the pancreatic vein in cross-circulation experiments. Recipient animals, diabetic or nondiabetic, exhibit hypoglycemia in response to the infusion of pancreatic vein blood from donor animals treated with sulfonylureas but not to the infusion of mesenteric or femoral vein blood from the same animals. Sulfonylureas cause degranulation of the β cells, a phenomenon associated with increased rate of secretion of insulin. Clinical studies demonstrate that the sulfonylureas are ineffective in completely pancreatectomized patients and in juvenile-onset diabetic subjects. On the other hand, they are effective in maturity-onset diabetic patients in whom the pancreas retains the capacity to secrete insulin.

Although the molecular mechanism of action of these agents is not understood, several pertinent observations have been made, Hellman and associates (1971) concluded that labeled tolbutamide is restricted in its action to the extracellular space and does not need to enter the β cell. The invoked release of insulin is immediate and is intimately related to the action of glucose; the drug may sensitize the cell to the normal secretagogue (Widstrom and Cerasi, 1973). Sulfonylureas do not increase the secretion of glucagon.

Extrapancreatic effects of the sulfonylureas have been noted in various organs, and certain of these may potentiate the effects of insulin. A reduction in the hepatic uptake of endogenous insulin has been described (Marshall *et al.*, 1970). Tolbutamide enhances the antilipolytic action of insulin in adipose tissue. This appears to be related to an altered effectiveness of cyclic AMP rather than to any change in metabolism of the cyclic nucleotide (Brown *et al.*, 1972; Fain *et al.*, 1972), and an inhibitory effect of the drug on cyclic AMP-dependent protein kinase has been observed (Wray and Harris, 1973). Other reports indicate a variety of influences on cyclic AMP metabolism in different tissues (Brooker and Fichman, 1971; Kuo *et al.*, 1972; Lasseter *et al.*, 1972); their significance is difficult to assess.

Duration of action, fate, and excretion. The sulfonylureas are absorbed from the gastrointestinal tract and hence are effective when given by mouth. The most important difference among the sulfonylureas, for clinical purposes, is in their duration of action; in increasing order they are tolbutamide, acetohexamide, tolazamide, and chlorpropamide.

Tolbutamide can be detected in the blood within 30 minutes after oral administration; peak concentrations are reached within 3 to 5 hours. The drug is bound to plasma proteins. Tolbutamide is oxidized in the body to butyl-*p*-carboxyphenylsulfonylurea, which is a major excretory product. The half-life of tolbutamide is about 5 hours. Two or occasionally three doses are required daily.

Acetohexamide is rapidly absorbed, and maximal hypoglycemic activity is observed about 3 hours after ingestion. The total duration of action is 12 to 24 hours. Much of the activity is ascribable to a metabolite, *hydroxyhexamide*, which has a plasma half-life of about 6 hours; the parent compound, acetohexamide, has a plasma half-life of 1⅓ hours. In persons with normal renal and hepatic function, more than 80% is excreted, largely as metabolites, in 24 hours. Two doses are usually required daily.

Tolazamide is slowly absorbed; the onset of hypoglycemic action occurs at 4 to 6 hours and persists at a significant level up to 15 hours after a single dose. Tolazamide is metabolized to a number of hypoglycemic substances that are largely excreted by the kidney. For most patients controlled by tolazamide, a single daily dose is sufficient; a few patients require administration of the drug twice daily.

Chlorpropamide is also rapidly absorbed from the gastrointestinal tract and is bound to plasma proteins. In contrast to tolbutamide, chlorpropamide is not metabolically altered to any significant degree and is excreted very slowly in unchanged form. The half-life of a single dose is about 36 hours, or seven times as long as that of tolbutamide. With daily doses of 250 to 500 mg, blood concentrations may not be expected to reach a plateau before 3 or more days. Chlorpropamide is administered in a single daily dose.

Toxicity. O'Donovan (1959) analyzed the incidence of side effects to *tolbutamide* in 9168 cases. The total incidence of side effects was 3.2%; the drug was withdrawn in 1.5% of the patients. The reactions have been classified as hematological (0.24%), cutaneous (1.1%), and gastrointestinal (1.4%). Of the 22 subjects exhibiting hematological abnormalities, 19 had a transient leukopenia; in 9 instances, the leukocyte count returned to normal despite continuation of the drug. Paresthesia, tinnitus, and headache may also occur.

The total incidence of untoward reactions is about 6% for *chlorpropamide* (hematological, 0.6; cutaneous, 3; gastrointestinal, 2; and jaundice, 0.4%). The jaundice is of the cholestatic type and is usually transient. Hyponatremia has been reported in a small number of patients treated with tolbutamide and chlorpropamide.

Experience with *acetohexamide* and *tolazamide* suggests that the frequency and the kinds of toxic reactions are similar to those encountered with tolbutamide and chlorpropamide. Hematological (leukopenia, agranulocytosis, thrombocytopenia, pancytopenia, and hemolytic anemia), cutaneous (rashes, photosensitivity), gastrointestinal (nausea, vomiting, rarely hemorrhage), and hepatic

(increased serum alkaline phosphatase, cholestatic jaundice) reactions have been reported.

Hypoglycemic reactions, including coma, may occur (Seltzer, 1972a). While they are usually not severe, several fatalities have been reported. Hypoglycemic episodes may last for several days so that prolonged or repeated glucose administration is required. Reactions have occurred after one dose, after several days of treatment, or after months of drug administration. Most reactions are observed in patients over 50 years of age, and they are more likely to occur in patients with impaired hepatic or renal function. Overdosage or inadequate or irregular food intake may initiate hypoglycemia. Drugs that may increase the risk of hypoglycemia from sulfonylureas include other hypoglycemic agents, sulfonamides, propranolol, salicylates, phenylbutazone, probenecide, dicumarol, chloramphenicol, monoamine oxidase inhibitors, and alcohol.

Sulfonylureas should not be used in a patient with hepatic or renal insufficiency because of the important role of the liver in their metabolism and of the kidney in the excretion of the drugs and their metabolites. Intolerance to alcohol reminiscent of the disulfiram reaction has occurred occasionally in patients taking sulfonylureas.

These agents are also not recommended for use in pregnancy, but only sparse data have been reported on this point. Teratogenesis in animals has been observed to follow the administration of large doses.

A cooperative clinical trial in 12 university-based clinics (University Group Diabetes Program; UGDP) was established in 1961 to determine if the control of blood glucose concentration helps to prevent or delay vascular disease in non-insulin-requiring diabetic patients. About 200 subjects in each of five therapeutic regimens were treated with diet and either placebo, a standard dose of tolbutamide, a standard dose of insulin, a variable dose of insulin, or a standard dose of phenformin.

During a period of over 8 years of observation, there were 120 deaths, including 87 from cardiovascular causes; while 10 to 12 cardiovascular deaths occurred in each of the placebo or insulin groups, 26 such deaths (a significantly higher number) were recorded among the patients in each group taking oral hypoglycemic agents. The overall mortality rate was correspondingly higher in these two groups of diabetic patients. The conclusions of this study were that the combination of diet and either tolbutamide or phenformin was no more effective in prolonging life than diet alone; furthermore, it was felt that diet and either tolbutamide or phenformin may be less effective than diet alone or diet together with insulin in preventing cardiovascular mortality. (*See* University Group Diabetes Program, 1970; Knatterud *et al.*, 1971.)

Since the UGDP report, a flood of comments and reports have appeared, both critical (*see* Seltzer, 1972b) and supportive of this massive study. However, no warning has yet been included in the package inserts for these drugs, and there have now appeared a "second generation" of even more potent sulfonylureas (*glimidine* and *glibenclamide*), which are in clinical use in Europe and elsewhere.

Additional studies have continued to indicate an increased incidence of serious difficulties in patients taking oral hypoglycemic drugs. More episodes of ventricular tachycardia and ventricular fibrillation were noted in such diabetic subjects, usually during the early stages of acute myocardial infarction, although there was no difference in the number of deaths (Clayman, 1974; Soler *et al.*, 1974). Patients taking oral hypoglycemic agents in England have been reported to have twice the incidence of myocardial infarctions observed in subjects being treated with diet alone (Boyle *et al.*, 1972; Hadden *et al.*, 1972). Furthermore, at the instigation of the Director of the National Institutes of Health, the Biometric Society appointed a committee to review the UGDP report. The committee concluded that the shortcomings of the study do not invalidate the observations and conclusions, the most pertinent of which are described above, and that other studies do not contradict that of the UGDP. (*See* Chalmers, 1975; Report of the Committee, 1975.)

Preparations and Dosage. *Tolbutamide*, U.S.P. (ORINASE), is marketed in the form of 500-mg tablets. The sodium salt (1 g) is also available for administration intravenously for diagnostic use. *Acetohexamide*, U.S.P. (DYMELOR), is available in 250- and 500-mg tablets. *Tolazamide*, U.S.P. (TOLINASE), is supplied in 100-, 250-, and 500-mg tablets. *Chlorpropamide*, U.S.P. (DIABINESE), is marketed as 100- and 250-mg tablets.

The usual daily dose of tolbutamide is 1000 mg, while 2000 mg is the maximally effective total dose; corresponding dosages are 500 and 1500 mg for acetohexamide. Tolazamide and chlorpropamide are usually administered in a daily dosage of 250 mg, while 750 to 1000 mg is maximal.

Therapeutic Uses. *The sulfonylureas should be used only in subjects with diabetes of the maturity-onset type who cannot be treated with diet alone or who are unwilling or unable to take insulin if weight reduction and dietary control fail.* The physician must realize that he is using these agents only to control symptoms associated with hypoglycemia, and that dietary control with or without insulin is more effective for this purpose. There is no evidence that the oral hypoglycemic agents prevent cardiovascular complications from diabetes, and the best data available suggest that the incidence of such complications is increased in patients taking these drugs. This is obviously too high a price for the convenience of an oral agent, unless *all* other measures have been exhausted.

In general, the likelihood of adequate control with an oral hypoglycemic agent is inversely proportional to the dose of insulin required to maintain the patient. When the insulin requirement is in excess of 40 units per day, the chances of success are relatively low. The sulfonylureas are of no value in the juvenile-onset type of diabetes, in which the pancreas has lost all or nearly all of its capacity to secrete insulin. However, whatever the age of onset, in unstable, ketoacidotic diabetes, sulfonylureas will not provide adequate control. *Such patients require insulin, and attempts to control them with oral therapy are dangerous and doomed to failure.* Deaths from acidosis and dehydration have occurred in patients with unstable ketotic diabetes in whom regulation was attempted with sulfonylureas.

There is no fixed dosage of sulfonylurea to be used in diabetes mellitus. Treatment is guided by the individual patient's response, which must be frequently monitored with chemical determinations, because the requirements change from time to time.

The mildly diabetic patient, whose insulin requirement is fewer than 20 units daily, can be started on the usual dose of the agent chosen, and at the same time all insulin is discontinued. The dose is then adjusted up or down, depending on the patient's response. In the instance of chlorpropamide, about 3 days is required to attain steady-state concentrations in blood. Consequently, upward adjustments of dose should be made at 3-day intervals. Patients of advanced age should begin with about half the usual daily dose, for some are very responsive to sulfonylureas and may develop severe hypoglycemia after usual doses. During the period of initiating treatment, all patients should test their urine four times daily and communicate the results to the physician daily.

The patient who requires more than 20 and fewer than 40 units of insulin daily should be started on the usual dose of the chosen agent and his insulin dosage should simultaneously be reduced by 50%. Thereafter, guided by the patient's response, insulin dosage is progressively reduced and eventually discontinued. Sulfonylurea dosage may need adjustment.

The patient requiring more than 40 units of insulin daily should be given the usual dose of the agent chosen and his insulin dosage should be reduced by 25%. Insulin is then cautiously withdrawn and eventually discontinued, and sulfonylurea is adjusted according to the observed response. It is to be emphasized that the chance of success is relatively poor. In the patient who requires more than 40 units of insulin daily, it may be desirable to carry out the attempted transfer to the sulfonylurea therapy in the hospital to provide assurance against development of dehydration and acidosis.

Stimulation of the pancreas of the maturity-onset diabetic can often maintain these subjects under ordinary circumstances. However, when insulin requirements are increased, as fever, surgical interventions, or trauma, the sulfonylureas are inadequate and the patient must be given insulin to carry him through such critical situations.

Weight reduction is of the greatest importance in the treatment of diabetes. A vigorous effort must be made by the patient and the physician to reduce the patient's weight as an integral part of diabetic treatment, irrespective of the drug chosen.

Patients whose diabetes is not controlled by sulfonylureas from the initiation of treatment are said to experience "primary failure." Patients whose diabetes is regulated for a month or more after beginning sulfonylurea treatment, fol-

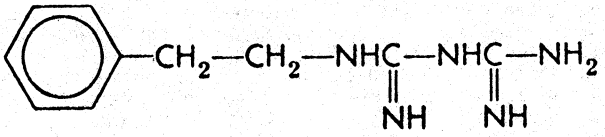
lowing which inability to maintain control developes, are said to experience "secondary failure." The incidence of this type of failure may be very high, regardless of the agent chosen.

In patients with pancreatic islet-cell tumors, the blood glucose concentration drops rapidly after intravenous injection of tolbutamide and remains low for about 3 hours. A similar effect is not observed in other hypoglycemic states, and tolbutamide administration can thus be used as a diagnostic test. Serum immunoreactive insulin determinations should also be performed. Care is necessary, since fatal hypoglycemia has occurred.

In addition, reports have appeared of the successful treatment of reactive hypoglycemias due to a variety of causes with sulfonylureas (Anderson and Herman, 1971).

BIGUANIDES: PHENFORMIN

Chemistry and Preparations. The only commercially available preparation in the biguanide series of hypoglycemic agents is *phenformin.* Its structural formula is as follows:



Phenformin

Phenformin Hydrochloride, U.S.P. (DBI, MELTROL), is marketed as 25-mg tablets and as a 50- and 100-mg time-disintegration capsules.

Mechanism of Action. The biguanides differ significantly from the sulfonylureas in the mechanism of their hypoglycemic effect. Thus, phenformin does not act by stimulating secretion of insulin by the pancreas, hypoglycemia is not readily induced in normal human subjects, the concentration of insulin in the plasma is not increased, and the morphology of the β cell is uninfluenced. Basically, three actions have been described. *In vitro,* phenformin, in relatively large doses, increases glucose utilization by enhancing anaerobic glycolysis (*see* Williams and Porte, 1974). This is thought to occur as a result of, or coincident with, an inhibition of cellular respiration. As a result, adenosine triphosphate (ATP) concentrations fall and those of lactate increase. A second action of the drug is to decrease gluconeogenesis (*see* Gordon and de Hartog, 1973; Haeckel, 1973). The third and most recently recognized is inhibition of intestinal absorption of glucose and probably certain other substances as well; for example, decreased absorption of vitamin B_{12} has been observed (Berger *et al.,* 1972). Phenformin does not act in the normal subject (at least as readily as it does in the diabetic), presumably because the increase in peripheral glucose utilization is compensated for by an increase in hepatic glucose output.

Phenformin has been used experimentally to correct the hypoglycemia that may follow abnormally rapid intestinal absorption of glucose (Permutt *et al.,* 1973).

Absorption and Duration of Action. Phenformin is adequately absorbed from the gastrointestinal tract. The drug has a short half-life (3 hours) and a correspondingly brief duration of action. The hypoglycemic effect may be prolonged to between 6 and 14 hours with the use of timed-disintegration capsules.

Toxicity. Phenformin may cause a metallic taste, nausea, anorexia, vomiting, diarrhea, or cramps in some patients, particularly if the dose is greater than 200 mg per day. Reduction of the dose or withdrawal of the drug results in prompt disappearance of the untoward reactions. Weight loss and weakness may sometimes occur.

The cause of *ketonuria* during phenformin therapy has been the subject of debate. It is most common in patients with unstable juvenile-onset diabetes treated with a combination of insulin and phenformin. While it may at times reflect an insufficient insulin dosage, at other times it is associated with normal plasma glucose concentrations. Therefore, in patients taking both insulin and phenformin in whom ketosis develops, plasma glucose concentration should be measured before the insulin dosage is increased, to avoid hypoglycemic reactions.

The recommended treatment for ketosis with normal plasma glucose concentrations is a reduction of phenformin dosage or an increase of dietary carbohydrate intake. Increased concentration of lactic acid in the blood without ketosis has been reported to occur in patients with severe renal or cardiovascular impairment under phenformin treatment. However, the drug may not contribute to the lactacidemia, since such severely ill diabetic patients may exhibit lactacidemia even when treated with insulin. Results obtained with phenformin in the UGDP study are discussed above.

Diabetic subjects with severe hepatic or renal insufficiency or congestive heart failure are not suitable candidates for oral hypoglycemic therapy. Almost no data are available concerning the effects of phenformin in pregnancy, and its administration during pregnancy is currently not recommended.

Therapeutic Uses. Phenformin is used in the treatment of maturity-onset diabetes according to the principles presented above for the sulfonylureas.

The patient is started on two tablets, 25 mg each, one before breakfast and the other before supper. The dose is increased until control of the diabetic state is attained or until digestive disturbances limit further increase in dosage. The total daily dose is usually somewhere between 100 and 150 mg. However, doses as high as 400 mg per day are tolerated by some patients. A single 50-mg, timed-disintegration capsule may be substituted as the equivalent of two 25-mg tablets in divided doses.

It is claimed that about 70% of maturity-onset diabetic patients who are imperfectly controlled by either a sulfonylurea or phenformin alone respond favorably to the concurrent use of these agents (Beaser, 1960; Unger *et al.*, 1960). The fact that the sulfonylureas and the biguaniles act by different mechanisms to reduce hyperglycemia lends support to this contention (*see* Breidahl *et al.*, 1972). However, since the indications for the use of either phenformin or a sulfonylurea are now severely constricted, such combination therapy should represent the choice of the physician who has exhausted every other alternatitive.

SE WESTERN RESERVE UNIVERSITY • CLEVELAND, OHIO 44106

August 21, 1975

Hearing Clerk
Food and Drug Administration
Room 4-65
5600 Fishers Lane
Rockville, Maryland 20852

Dear Sir:

I regard it as a privilege to have this opportunity to discuss the proposed FDA labeling on the use of oral hypoglycemic agents. It is indeed appropriate that such direct action has finally being taken if the scientific basis for medical practice is to have any real significance. The heated discussions that followed the publication of the findings of the longest and largest prospective controlled clinical trial in the history of therapeutics serve only to point up the critical issues involved in the practice of medicine today. These issues involve the crucial question as to the basis for the judgement of the physician for choosing the optimum treatment for the patients entrusted to his care. Is the decision to be based on "clinical impression", anecdotal stories and wishful opinions, or will it be based on substantial evidence from adequate, well-controlled clinical investigations? If modern medicine is to have a firm foundation in basic and clinical science the wisdom of the Drug Amendments of 1962 resulting from the thalidomide disaster becomes crystal clear.

The scientific design, merit or validity of the UGDP study has been amply confirmed by the most intensive and extensive reviews in the history of medicine. When the evidence of excessive cardiovascular mortality first surfaced after several years of the trial, outside consultants were brought in to review the data independently. After the report was made public at the A.D.A. meeting in St. Louis in June of 1970, separate peer review committees appointed by the American Diabetes Association, the A.M.A. Committee on Drugs and the Medical Letter accepted the basic conclusions of the study. Because of the alleged contradictory findings from other studies, none of which approached in any way the magnitude or relevance of the UGDP study an elite committee of the internationally based Biometrics Society over a period of two years reviewed all these controlled trials and in their report published on February 10, 1975 the J.A.M.A. came up with essentially the same conclusions and recommendations. This report like the UGDP reports will stand as monumental and classical papers in the history of clinical medicine.

epartment of Medicine
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Whatever other fragmentary data that has appeared since 1970 have only served to support the general conclusions. It is interesting to me that the total efforts of the Committee on Care of the Diabetic has been directed to the criticism and denigration of the UGDP study and that no sound scientific evidence has been brought forth since the introduction of the oral hypoglycemic agents in 1955 to show any long-term benefit whatsoever. It is a sad commentary that despite the expenditure of some 10-15 billion dollars by the diabetic public throughout the world over these twenty years, the drug companies and their adherents have failed to come up with any studies that adequately prove that any reduction in morbidity and mortality has resulted from the long-term use of their drugs. If the logical concept of scientific proven benefit over risk as defined by the laws established by Congress in 1962 is to have any meaning for the twenty million to 30 million diabetic patients in the world the strongest possible warnings clearly stated should be implemented as soon as possible. The UGDP studies were published in 1970 and yet by August 1975 no clear labeling warning has as yet been issued by the government agency responsible by law to protect the American public.

I would appreciate having a transcipt of the hearings of August 20th, 1975 when they are available.

Very truly yours

Max Miller

Max Miller, M. D.
Professor

PRESENTATION OF
SIDNEY M. WOLFE, M.D. AND ANITA JOHNSON,
PUBLIC CITIZEN'S HEALTH RESEARCH GROUP,
to the
FDA HEARINGS ON PROPOSED LABELLING FOR DIABETES DRUGS

August 20, 1975

It is now more than 5 years since the findings of the University Group Diabetes Program (UGDP) were presented at the American Diabetes Association annual meeting. Despite the findings of increased cardiovascular mortality in patients taking oral diabetes drugs and their lack of efficacy, their use has continued. Over the last 5 years, however, several of the largest diabetes treatment centers have swung strongly away from using these agents.

The question is, why are 1 1/2 million American adult onset diabetics being given drugs costing more than 100 million dollars per year, killing an estimated 10-15,000 patients per year and not having any demonstrable benefits in treating diabetes?

There are three reasons which appear to explain this irrational state of affairs:

1. The pride of physicians

2. The inadequacy of most diet programs for diabetics

3. The profits of the drug industry

1) Pride

As candidly stated this year by Dr. Frank Davidoff -- Professor of Medicine and diabetes specialist for the University of Connecticut Medical School -- and probably unspoken but thought by thousands of other physicians, pride plays a major role in the continued prescribing of these drugs by doctors in the face of evidence to the contrary. (Testimony - Sept. 19, 1974, Senate Small Business Subcommittee).

"It is one thing to challenge the safety of a drug . . . . But to be told that the drugs we had been giving to diabetics for 12 years were unnecessary, beside the point, in a word ineffective, was, as I see it, a more serious blow to our professional pride." We submit that the pride of doctors is standing in the way of giving the best treatment to their patients and that this is irresponsible medicine if not malpractice.

2) Inadequate Diet Programs for Diabetics

According to Dr. Ethan Sims, diabetes specialist and Professor of Medicine at the University of Vermont Medical School,

"If we grant that there are 1 1/2 million patients reportedly taking oral agents and that 50% are grossly overweight, we have 750,000 patients with diabetes and obesity who are probably also less physically active than they should be. If we assume that 90% of them are not exposed to any vigorous and comprehensive regimen such as that at the Grady Hospital, 675,000 are left with their obesity essentially untreated and 4 out of 5 are taking an agent which increases their obesity. The taking of oral medication lulls both physician and patient into believing that something worthwhile is being accomplished, while the options which could

make a fundamental difference in a patients life and survival are being neglected." (ibid, Senate Hearings)

Dr. John Davidson, Director of the Grady Hospital (Atlanta) Diabetes Unit which has been very successful in getting diabetics off of the oral drugs, has said,

"Why do so many physicians have little success in treating it? [the problem of obese diabetics]. . . . In my experience, at least 80% of diet therapy failures are due to physician failure, not patient failure." (ibid, Senate Hearings)

3) Profits

In a letter to the FDA, requesting to speak at this hearing, H.R. Allen of Upjohn commented that:

"The proposed class labelling of oral diabetes drugs. . . . is, in our view, inappropriate, uninformative, and hence misleading. . . ."

Translated into English, Upjohn -- which has about 40% of the $100 million American market for oral diabetes drugs -- doesn't want its leading money-makers -- tolbutamide (Orinase) and tolazamide (Tolinase) -- to suffer in sales andprofits just because scientific studies show the drugs are ineffective and extremely dangerous.

That the extraordinary profits of Upjohn, Pfizer, Ciba-Geigy and Lilly -- who have cornered this several hundred million dollars per year worldwide market for these drugs -- has had a major effect on the irresponsible delay in ending the massive misuse of these drugs is not arguable.

In addition to sponsoring hundreds of "educational" symposia around the country -- with academic facades -- intended to assure doctors that these drugs are O.K., the drug industry has kept the AMA alive with infusions of advertising revenue and political contributions and, in return, the AMA has written reassuring letters (Dr. Sammons) to physicians about these drugs.

To demonstrate how much of a curtailment of profits would occur if the abuse of these drugs were ended, consider the experience at Cleveland Metropolitan General Hospital. At the peak of use of the oral diabetes drugs (1970) at that hospital, expenditures per year were as follows:

Tolbutamide (Orinase)	Phenformin (DBI)	Chlorpropamide (Diabinase)
$32,376	$7,857	$8,294

After use was restricted, the 1975 figures (projected by the hospital) were:

$6,966	$138.00	$3,371

a savings of $38,000 or 78% of the $48,527 1970 expenditures for these drugs.

In the face of pride, profits, and inadequate dietary management, aided and abetted by court delays, the FDA has somehow found it possible to delay for almost 5 years finalized labelling changes for these drugs.

Anita Johnson will discuss our specific criticisms of the present version of proposed labelling (the third in 3 years) but I would make the following addition.

It is not enough to have labelling -- albeit strengthened -- on a product which the patients' doctor has already decided to prescribe. Patients must be given information in the doctors office which will allow them to participate in the serious decision to use these drugs. Specifically, future use of oral diabetes agents should be preceded by a written informed consent form including, but not limited to the following information:

INFORMED CONSENT FOR USE OF ORAL DIABETES DRUGS

1. I have participated in a program of dietary control and physical exercise including at least 25 hours of instruction.

2. This program did not succeed in weight reduction or control of blood sugar and Dr._____ told me that insulin was the preferred drug if one had to be used.

3. I refuse (or am physically unable) to take insulin.

4. I am aware of the increased risk of cardiovascular death from taking oral diabetes drugs and of the animal study showing that one of them (Tolbutamide) causes a significant increase in coronary artery disease and that therapeutic efficacy has not been proven.

In light of the above, I agree to take _____ (oral diabetes drug).

_____ _____

Date Patient's Signature

Recommendations for the Label

1. The antidiabetic drugs should be indicated only for patients with symptoms from high blood sugar, whose symptoms cannot be controlled by diet or insulin. They should be used by patients who cannot be controlled by diet only if such patients also cannot inject insulin.

The label as proposed by FDA approves use in a broader group of patients -- those whose "symptoms cannot be controlled by diet alone and in whom insulin cannot be used because of patient unwillingness, erratic adherence to the injection regimen, poor vision, physical or mental handicap, insulin allergy, employment requirements or other factors." The FDA label essentially condones use in symptomatic patients when insulin is merely inconvenient to use. Mere inconvenience is not a legitimate reason, in our view, to sustain the known risks of these drugs. The FDA label also indicates use in patients without symptoms.

2. The label as proposed by FDA grants an indication to patients with high blood sugar who do not have symptoms. The Food, Drug and Cosmetic Act requires that all indications be supported by "substantial evidence," evidence from "adequate and well-controlled investigations, including clinical investigations." Obviously, since these patients have no short-term symptoms of diabetes, such

as dizziness, polyuria, etc. the drugs are not effective in treating short-term symptoms. Some diabetes doctors believe that they prevent long term symptoms of diabetes such as vascular deterioration. However, there is no scientific substantiation of this belief.

3. The label should state that there is substantial evidence that these drugs are not effective for the prevention of the long-term symptoms of diabetes. FDA has proposed new regulations for all prescription drug labels which contains the following requirement:

> If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for that condition, but the preponderance of evidence related to such use indicates that the drug is ineffective, the package insert shall state that there is a lack of evidence that the drug is effective for that use. s. 1.112 (3)(d). 40 Fed. Reg. 67, 15392ff.

The UGDP study demonstrated that these drugs are ineffective in preventing the long-term effects of diabetes.

4. The Warning section should state that these drugs are associated with increased cardiovascular mortality, without referring to the UGDP study. The proposed warning states that the drugs may be associated with increased cardiovascular mortality and that "This warning is based on the study conducted by the U.G.D.P." together with details of that study. If the UGDP reference is retained, the other studies which confirm the UGDP findings must also be cited. Otherwise, the warning will give the false impression that the UGDP findings are isolated and unique, which they are not.

Since the UGDP study, laboratory studies have pinpointed the mode of adverse action on the heart. This mode of action has been confirmed in humans by catheterization studies. Another study has described a significant rise in ventricular fibrillation in patients on these drugs. Two epidemiological studies have shown an abruptly increased mortality among diabetics since these drugs were introduced. Three retrospective clinical trials confirm the UGDP results, as do two cohort studies, the Kanarek study, based on patients at the Joslin Clinic, and the Palumbo study based on patients at the Mayo Clinic.

5. The Warning section should not include a statement that there is controversy as to the need for the warning. The FDA proposed warning says: "Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide adequate scientific basis for this warning," thereby including a statement of controversy. The 1972 lawsuit, Bradley v. Weinberger, raised this issue. Bradley, who had the habit of prescribing these drugs, sued to prevent FDA from putting a warning on the label, or, if that failed, to get a statement in the warning that there was a difference of opinion among experts concerning the need for a warning. The case was never decided on the merits. However, FDA contested Bradley, stating that warnings should not contain disclaimers which would encumber and dilute the warning. Now FDA is reversing its position and including a "controversy" statement. We agree with FDA's earlier view that this statement is unwarranted and from a health point of view, counterproductive.

Without these changes in labelling, the addition of informed consent and immediate finalizing of these improved regulations, the FDA, to the delight of the drug companies, will be condemning American diabetics to a continuation of the needless death and waste of precious health dollars.

Oral Hypoglycemic Agents Are Worthwhile

ROBERT F. BRADLEY

Joslin Clinic, Boston, Massachusetts

The controversy evoked by the University Group Diabetes Program (UGDP) results reported in December, 1970,[1] and a few months later,[2] has quite properly rekindled the interest of clinicians in the need for intensive dietary therapy of the adult maturity-onset diabetic and has provided another example of *possible* insidious effects of foreign compounds administered to humans. It has also exhumed the more basic controversy, namely, that relating to the benefits, if any, which can be gained from the rigid metabolic control of diabetes mellitus, as reviewed previously in the first edition of this text.[3]

The UGDP study by all odds had the best designed and the most laudable objectives of any yet undertaken. Unfortunately as they "eyeballed" the data week by week and month by month and saw first a cluster of deaths in patients treated with variable doses of insulin and then a somewhat larger cluster in those treated with tolbutamide, the biostatisticians held sway. Clinicians, shaken by their lack of expertise in biostatistics and forgetting that the study was not intended to evaluate mortality results,[4] bowed graciously to the intonations of those who extrapolated the data to the maturity-onset diabetic population at large. The tragedy of this issue rests both in the possibility that the implications of the UGDP study are entirely correct, and the equal possibility that they are completely invalid, i.e., that the observed cardiovascular events resulted from a repository of individuals treated with tolbutamide or phenformin who were greater cardiovascular risks at baseline.[5]

Regardless of the many arguments that have been presented pro and con, one must keep in mind the preliminary nature of the results, namely, that the total cardiovascular deaths occurring in the UGDP study represented only 5 per cent of those diabetic patients comprising the entire study population.

The sulfonylureas (carbutamide, tolbutamide, chlorpropamide, acetohexamide, tolazamide, glybenzcyclamide) and biguanides (phenformin, metformin, and buformin) lower blood glucose levels by differing mechanisms. Such an effect of these oral hypoglycemic agents used singly or in combination has been

well documented in appropriately selected hyperglycemic individuals and accounts for their widespread usage in the United States and other countries during the past 17 years. In many of the more responsive patients with maturity-onset diabetes, normal blood glucose levels are more readily attainable than with diet or insulin.

Despite numerous reports during the early years of their clinical use that these compounds would effectively lower blood glucose levels in 50 to 75 per cent of maturity-onset diabetics who were not insulin dependent or ketoacidosis-prone and whose diabetes began at age 40 or older, physicians familiar with insidious long-term problems of the diabetic have from the beginning been concerned that patients so treated might be less well controlled and more prone to premature development of these complications than individuals treated with insulin. Experience has provided ample evidence that for one reason or another oral hypoglycemic agents lose their effectiveness at varying but relatively short intervals of time after initiation of treatment. The rate of such "secondary failure" depends upon many factors, including patient selection and dietary cooperation, therapeutic objectives, and the manner in which the oral hypoglycemic agents are used. A lucid presentation of "primary" vs. "secondary failure" and the effect their definition has upon long-term "failure" has recently been published.[6] The element of convenience for middle-aged and elderly people is obvious, but always has had to be balanced against the increased cost for those who took more than minimal doses and the possibility that physicians and patients alike would rely too heavily upon their effectiveness, so that diet would be either ignored or less carefully followed.

If benefit is to be anticipated from lowering blood glucose levels as well as reversing lipid, protein, and other metabolic abnormalities associated with insulin deficit, what should be the blood glucose levels attained? From the early days of their use, many sets of criteria have been utilized by those involved in the study of diabetic patients. In general, these have fallen into two categories: (1) those who consider the oral hypoglycemic agents effective despite blood glucose levels in excess of normal, provided the symptoms of diabetes have been relieved and remain so, and (2) others, such as Marble and his associates,[7] including this author, whose objective has been normoglycemia and aglycosuria, in accordance with the criteria originally published by Camerini-Davalos et al. in 1957[8] (Table 1). In defense of the former is the fact that in many maturity-onset diabetic patients whose blood glucose levels remain elevated despite dietary adherence, the addition of oral hypoglycemic agents lowers blood glucose levels to a degree comparable to that readily obtained with insulin and relieves symptoms, so that little would be gained by insisting upon a more rigid standard of metabolic control. Recognizing that evidence for the benefits of tight metabolic control remains controversial, the adoption of such standards would seem to be reasonable. On the other hand, if it is true that protection from long-term complications is attainable only through the more rigid control of blood glucose levels, the latter criteria should be applied, and if the standards are not attained, more relentless application of diet and insulin if necessary is required. At present the fundamental controversy continues to be that related to the possible benefits of such control. Considerable new evidence is available today, unfortunately no

Table 1. *Joslin Clinic Standard for Blood Glucose Control in Diabetic Patients Treated with Oral Hypoglycemic Compounds: Standards of Control* and Degree of Control†*

RELATION TO FOOD	GOOD		FAIR		POOR
	Blood Sugar‡ (mg./100 ml.)	*Urine Sugar (per cent)*	*Blood Sugar‡ (mg./100 ml.)*	*Urine Sugar (per cent)*	
Fasting	110	Trace	130	0.1	All
1 hr. p.c.	150	0.3	180	0.5	other
2 hr. p.c.	130	0.1	150	0.3	cases
3 hr. p.c.	110	Trace	130	0.1	

*For purpose of classification as to degree of control 70 per cent or more of values must conform with standards listed in the table.
†These standard values are the highest acceptable.
‡Glucose as determined by the Somogyi-Nelson procedure.

more conclusive than the data of 20 years ago. Meanwhile the practicing physician is busily and assuredly attempting to lower blood cholesterol levels, but is not certain how assiduously to work toward lowering blood glucose levels, and if so, how much.

A major concern has been the possibility that these oral agents might produce or allow the earlier development of the following: (1) islet cell failure with consequent decompensation of endogenous insulin function and greater activity of the diabetes; (2) infections; (3) neuropathy; (4) cataracts; (5) onset or more rapid progression of microangiopathy; and (6) greater morbidity and/or mortality from accelerated macroangiopathy, particularly that involving the coronary, cerebral, and peripheral vasculature. Because no good evidence had ever been presented to suggest that oral hypoglycemic agents were "antidiabetic," which would mean that they were inherently capable of delaying or preventing these more serious problems, the only reasonable benefit to be expected would be consequent to a net increase in the effectiveness of endogenous insulin, as indicated by lowering of the blood glucose level over and above that obtainable with diet. Thus, if significant lowering of blood glucose levels could not be attained and then maintained, there would be no basis for using any of the currently available oral hypoglycemic agents. The extent to which oral hypoglycemic agents have succeeded or failed with regard to these potential problems will be briefly reviewed.

Islet Cell Function

That sulfonylureas lower blood glucose levels primarily by increasing insulin secretion from the pancreas has been definitely proved.[6] However, it has long been contended by some investigators that extrapancreatic effects of sulfonylureas, particularly those related to hepatic glucose release, contribute to the effects upon glucose.[6] Recently considerable data have confirmed extrapancreatic actions, which are demonstrable in the absence of insulin at cellular sites and with con-

centration of drug compatible with the clinical setting.[9] In addition, a portion of the effects of sulfonylureas may relate to inhibition of cyclic AMP phosphodiesterase, with a consequent net increase in cyclic AMP.[10]

One must also keep in mind the significant, and sometimes serious, hypoglycemia induced by sulfonylurea drugs. None of those currently available is an exception. Some of these enhanced hypoglycemic effects of the sulfonylureas have been related to the coincident use of other drugs such as salicylates, monamine oxidase inhibitors, phenylbutazone, sulfonamides, sulfisoxazole, sulfaphenazole, coumarin anticoagulants, and phenyramidol.

Occasional patients on sulfonylurea drugs are suspected of having a rapid loss of endogenous insulin function because it appeared necessary after a short period of treatment to give insulin to control the diabetes. Such observations obviously have suggested that the sulfonylurea might have accelerated the depletion of pancreatic insulin. However, studies in animals chronically treated with sulfonylureas have not supported this concept. Rather, there has been consistent histologic evidence of an increase in the number of beta cell mitoses, hypertrophy of the islets, and an increase in mass of islet tissue.[6, 9]

No data have been presented to suggest that biguanides "wear out" the insulin mechanism. The means by which biguanides lower blood glucose levels in diabetics, but not in normal humans, remains uncertain. By whatever means they act, these substances lower blood glucose levels in diabetic individuals having some available endogenous or exogenous insulin, albeit more gradually than is noted in responsive diabetic individuals following sulfonylureas. Available endogenous or administered insulin simply appears to be more effective when phenformin or other biguanides are administered. In the absence of any demonstrable effect of these compounds upon the pancreatic islet cell, it is not surprising there is no evidence thus far that diabetes is worsened metabolically by their administration.

A number of studies have suggested that sulfonylureas or biguanides may ameliorate "chemical" or "latent" diabetes[6] (as defined by the American Diabetes Association[11]). Although inconclusive, observations of no adverse effects have now accumulated for a sufficient number of years to allow one to assume that at least no worsening of the diabetes is likely to be produced.

Infection

At one time the increased susceptibility of the diabetic to invasive local and systemic infection accounted for an important portion of the morbidity and mortality among diabetics. With improved control of diabetes following the availability of insulin and the proper use of antibiotic treatment, infections in the diabetic now pose much less of a problem.

Recent studies have helped to clarify the issue as to whether the diabetic is indeed more susceptible to infection. Defects in host defense can be related to the degrees of hyperglycemia and/or ketoacidosis.[12, 13] Uncontrolled diabetes of short duration may not be associated with a great likelihood of infection, but when present over a period of weeks and months the patient becomes more susceptible. Thus far no studies have clearly defined the critical degree or duration

of uncontrolled diabetes, but metabolic control is well accepted as a fundamental part of the preventive program in avoiding fungal infection and active tuberculosis, as well as bacterial infection. Perhaps the most common and easily demonstrable example clinically is the persistence of Candida infections producing vulvovaginitis in the female and balanitis in the male, responding poorly to specific therapy such as nystatin or gentian violet but dramatically improving with the cessation of or marked improvement in excessive glycosuria and hyperglycemia. Such improvement is readily shown to occur in the diabetic patient responsive to oral hypoglycemic therapy, with rapidity of improvement comparable to that obtained with insulin. Similar responses can be obtained in certain patients with nearly normal endogenous insulin reserve upon application of diet and, of course, with the administration of insulin.

To date there has been no indication in patients responsive to oral hypoglycemic agents, when properly combined with reasonable dietary adherence, that new infection or aggravation of existing infection has occurred as a result of the use of oral rather than insulin therapy.

Neuropathy

No controlled studies have proved that metabolic control prevents the development of neuropathy. However, neuropathy, particularly the more severe types such as amyotrophy, anesthetic feet, Charcot joints, and so forth, classically develops in the adult who seems to have had a short duration of diabetes, but who was unknowingly hyperglycemic for a period of time, or in the patient with known diabetes of longer duration in whom therapy was inappropriate or inadequate. Although diabetic patients may at times have an exacerbation of symptoms due to neuropathy following treatment of any kind, and although on occasion hypoglycemia may itself induce neuropathy, the *usual* clinical observation is that following improved metabolic control by whatever means, many manifestations of neuropathy improve sooner or later.

Recent biochemical data demonstrating the presence of the polyol pathway in nerve suggest a mechanism by which increased ambient glucose concentrations in the Schwann cell activate the formation of sorbitol,[14] so that nerve function may be compromised. To date the critical circulating blood glucose levels for activation of this pathway have not been clearly demonstrated, but its possible major metabolic role in the production of neuropathy provides further evidence for the desirability of keeping blood glucose levels as close to normal as is readily obtainable.

Cataracts

At least two morphologic types of cataract occur in diabetes. These are: (1) the snowflake, flocculent, or metabolic cataract, occurring mainly in juveniles with grossly uncontrolled diabetes; and (2) the senile cataract due to sclerosis of the lens nucleus, indistinguishable from that seen in the nondiabetic and the commonest type observed in adult diabetic patients. The more rapid maturation of senile cataract in the diabetic than in the nondiabetic has recently been re-

emphasized by studies showing grossly poorer diabetic control in patients having cataract extraction than among the average patients attending a diabetic clinic.[15] These observations, and demonstrations of the appropriate enzymes in the lens of man for activation of the polyol pathway by existing hyperglycemia,[16, 17] lend considerable support to the long-held opinion that poorly controlled diabetes is a factor in the rate of maturation in senile cataract as well as in the development of metabolic or snowflake cataract.[15, 18]

Although of lesser importance, the well known relation of refractive changes in the eye of the diabetic to changing blood glucose levels would be still another basis for adequate blood glucose control, at least in terms of the quality of daily living.

Microangiopathy

The microangiopathy of diabetes involves small blood vessels, particularly capillaries supplying many tissues. The possible value of careful metabolic control in protecting the individual from clinically important retinal and/or renal vascular disease has been the subject of major controversy for 25 years. The UGDP study was directed in major part toward seeking an answer to this question. Thus far, neither the prospective UGDP study nor other studies, all wholly or in part retrospective in nature, have proved conclusively that significant benefit is to be gained from any tighter control of the metabolic components of diabetes than is necessary to avoid the symptoms of diabetes, ketoacidosis, and so forth. Detailed reviews of this subject have either supported no relationship between careful metabolic control and the prevention of microangiopathy,[19] or indicated that such control improves the chances of preventing severer grades of clinical microangiopathy, such as retinitis proliferans and/or nephropathy with renal failure.[20]

Despite the lack of unanimity concerning this controversy, recent biochemical data tend to shift the weight of evidence in the direction of favoring tight metabolic control. In particular, the observations of Spiro regarding the role of hyperglycemia as a stimulus to the biosynthesis of basement membrane material of the renal glomerulus,[21, 22] and observations of basement membrane thickening showing an apparent correlation with duration of insulin deficit,[23] appear to bolster the practice of those physicians who strive for normoglycemia.

Meanwhile, although not specifically related to effects upon microangiopathy, sufficient data have accumulated to support the role of striving for normoglycemia as assiduously as possible in assuring survival of the fetus of the diabetic mother.[24, 25]

Macroangiopathy

Although neuropathy, increased susceptibility to infection, and microangiopathy are the most specific manifestations of diabetes mellitus and are of particular concern because of their adverse effects upon many younger patients, the overall greatest problem in terms of morbidity and mortality is that related to involvement of medium and larger vessels, especially the coronary, cerebral and lower extremity arteries. The prevalence of such vascular lesions is high in the

Table 2. *Causes of Death in 912 Diabetics (Per Cent of Total Deaths) 1966–1969*[*]

Vascular disease, total	74.3
Cardiac	54.6
Renal	8.0
Cerebrovascular	10.0
Gangrene, "circulatory"	1.7
Cancer	12.8
Infectious, Non-TBC	5.9
All others	6.0

[*]Experience of the Joslin Clinic.

general population, but cardiovascular disease as a cause of death is nearly doubled in the diabetic. Table 2 shows that cardiovascular causes account for at least two thirds of the mortality in the diabetic population as a whole. With such a high frequency and with so many factors other than diabetes playing a potential role, any attempts to assess the possible benefits of diabetes treatment are extremely difficult to evaluate. An additional problem in trying to judge the effects of therapy directed toward improved diabetes control is that in the adult maturity-onset diabetic the duration of hyperglycemia is extremely difficult to ascertain, except in those individuals who have been subjected to blood glucose measurements from early in life either because of a family history or as part of routine examinations.

Many observations relate vascular disease of medium-sized arteries to the presence of hyperglycemia.[26] Perhaps the earliest, and certainly one of the most striking, has been derived from the huge autopsy series of Bell at the University of Minnesota[27] (Table 3), which points out the extraordinary prevalence of peripheral vascular disease and gangrene in the hyperglycemic individual. Such associations appear to justify efforts of physicians within reason to provide "metabolic control" of diabetes.

In the clinical use of oral hypoglycemic agents, the assumption has been that lowering blood glucose would reverse the metabolic abnormalities related to insulin deficits, such as those in protein and lipid metabolism, much as such defects are reversible with comparable degrees of blood glucose lowering following insulin. As has been summarized elsewhere,[28] various types of circulating lipid abnormalities are reversible with sulfonylureas in those patients who have sufficient endogenous insulin, such that blood glucose levels fall to normal following the administration of one of these oral agents. On the other hand, a number of

Table 3. *Results of Autopsies Following Atherosclerotic Gangrene*[*]

	NONDIABETIC (59,733) (PER CENT)		DIABETIC (2130) (PER CENT)		RATIO OF FREQUENCY
Age	M	F	M	F	Diabetic/Nondiabetic
20–40	0	0	3.4	0	All Ages > 40
40–60	0.1	0.08	14.7	14.0	M 53:1
60–80	0.45	0.46	24.3	24.6	F 71:1

[*]From Bell, E. T.: Amer. J. Clin. Path. 28:27, 1957.

reports have demonstrated persisting abnormalities in cholesterol, free fatty acids, and triglycerides in individuals who were receiving a sulfonylurea, but on close inspection of the data, "control" was determined only by measurements of fasting blood glucose levels, and even these were persistently elevated. However, abnormalities in circulating lipids associated with imperfect management of diabetes using oral hypoglycemic agents have been shown to be reversible by the addition of sufficient insulin to improve blood glucose levels.[28] This observation has been one of the factors which have supported the use of more rigid blood glucose criteria as an objective in treatment with oral hypoglycemic agents, be they sulfonylureas or biguanides. Thus far there is no clear-cut evidence that blood lipid abnormalities due to relative insulin deficit are more or less likely to be preventable or reversible at comparable blood glucose levels whether insulin or oral hypoglycemic agents are used.

A real problem has been the tendency for physicians to use oral hypoglycemic agents not in an ideal manner, but rather for the sake of convenience, with too little emphasis upon diet, adequate choice or dosage of the agent used, or proper selection of the patient. In such situations, obviously, the performance of oral hypoglycemic agents should be less effective than that of insulin, assuming that control of blood glucose and lipid abnormalities are indeed important in slowing down progression of macroangiopathy.

The above observations are critical in evaluating studies such as the University Group Diabetes Program (UGDP), which recorded more cardiovascular deaths in patients receiving tolbutamide or phenformin than in those treated with diet and placebo, diet and standard dose of insulin, or diet and a variable dose of insulin. The results may be interpreted as follows: (1) If it is true that tolbutamide, as a result of an inotropic effect upon the myocardium[29] or via some other mechanism, and an unrelated compound such as phenformin, through some unidentified mechanism, actually contribute to cardiovascular death, the seriousness of this particular end point would weigh so heavily that the use of these oral hypoglycemic agents should be summarily discontinued. (2) On the other hand, if these oral agents were seemingly less effective because of their improper use, the question is whether the results would be improved by correct usage and what the criteria should be for such usage. (3) The third possibility is that inadvertent significant differences in baseline cardiovascular risk factors accounted for the less favorable cardiovascular mortality experience in those treated with tolbutamide or phenformin and that the study does not prove or disprove lack of effectiveness for tolbutamide up to the time it was discontinued from the study (October, 1969) or for phenformin (discontinued January, 1971). The latter is more than a mere possibility, for the interpretations of UGDP results by the investigators, the American Diabetes Association,[30] the Council on Drugs of the American Medical Association,[31] and the U.S. Food and Drug Administration[32] are based upon statistical grounds that do not take into account the clinical background of knowledge concerning coronary heart disease in the diabetic. The many flaws in the UGDP study make any extrapolation of the results to the diabetic population at large extremely hazardous, and a number of objections remain apparent to the clinician:

1. In placebo treated patients not a single myocardial infarction was recorded among the cardiovascular deaths.

2. A characteristic feature of cardiovascular mortality in the diabetic is the female predisposition to dying, equaling or exceeding that observed among males.[26] UGDP findings of fewer than one half as many cardiovascular deaths in females as compared to males in placebo treated diabetics indicated a lack of full expression of the effects of diabetes upon cardiovascular mortality in this group; i.e., the diabetes was milder and/or of shorter duration, or the numbers were too small.

3. Cardiovascular risk factors at baseline were present wtih greater frequency in patients on tolbutamide than in those treated with placebo or with small fixed doses of insulin ("insulin standard"). Although only one factor, blood cholesterol levels equal to or greater than 300 mg./100 ml., reached statistical significance in its greater frequency in tolbutamide treated patients, out of a total of 10 baseline risk factors, nine occurred more often in the tolbutamide treated than in the placebo group. On comparison with "insulin standard" treated patients, seven cardiovascular risk factors were present at baseline with greater frequency in tolbutamide treated patients as compared to three affecting more patients in the "insulin standard" group.

4. The prevalence of coronary heart disease as evidenced by "significant ECG abnormality" at baseline was extremely low in all treatment groups (Table 4), especially in view of the higher frequencies of digitalis usage, of angina pectoris, and of ECG abnormalities in diabetics of comparable age reported in the literature.[26, 33] When the original baseline findings were reported by the UGDP investigators in 1967, different criteria for ECG abnormality were used, so that on the basis of the electrocardiogram, a distinctly greater prevalence of coronary heart disease was reported in the tolbutamide as compared to placebo, insulin standard, or insulin variable groups of patients.[34]

5. The duration of diabetes among patients entering the UGDP study were indeterminate. However, elevated fasting blood glucose and greater increments of post glucose blood levels were found in more tolbutamide treated patients at baseline than in any other treatment group. Therefore, more tolbutamide treated patients had severer and/or longer durations of diabetes mellitus.

6. For an end point (cardiovascular mortality) having an extremely high prevalence in the diabetic population in which a number of risk factors, both

Table 4. *UGDP Study—1967* vs. 1970†*
Selected Baseline Cardiovascular Risk Factors

	PLACEBO		TOLBUTAMIDE		INSULIN STAND.		INSULIN VARIABLE		TOTAL	
	No.	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*	*No.*	*Per Cent*
Significant ECG abnormality 1967	30	(15.2)	48	(24.0)	40	(19.3)	39	(19.3)	157	(19.4)
Significant ECG abnormality 1970	6	(3.0)	8	(4.0)	11	(5.3)	8	(4.0)	33	(4.1)
History of digitalis use	9	(4.5)	15	(7.6)	12	(5.8)	10	(5.0)	46	(5.7)
History of angina pectoris	10	(5.0)	14	(7.0)	16	(7.7)	7	(3.5)	47	(5.8)

*Reference 34.
†Reference 1.

known and unknown, were present, the number of individuals reaching that end point was too small to permit a definitive conclusion.

Summary

The benefits of oral hypoglycemic agents are limited to those diabetic patients who are responsive, in that symptoms of diabetes are absent and blood glucose levels are significantly and consistently lowered (20 per cent or more) below pretreatment values. Under these conditions, benefits may be summarized as *definite* or *qualified.*

DEFINITE

1. Convenience.
2. In those with diminished vision, arthritis, or other problems, who find injection of insulin difficult or impossible.
3. For individuals whose diabetes is not controllable by diet and whose employment and/or economic status might be jeopardized by the taking of insulin.
4. In certain patients with allergy to insulin, in whom desensitization is difficult or cannot readily be maintained.
5. In truly responsive diabetics in whom normoglycemia is more readily attained than with insulin.

QUALIFIED

If lowering of lipid and other metabolic abnormalities related to insulin deficit are important in protecting the diabetic from earlier progression of vascular lesions and neuropathy, as well as from infection, the use of oral hypoglycemic agents is of benefit in patients who attain "significantly" lower blood glucose values than are attainable by use of diet alone. My criteria for such blood glucose values are that on two out of three occasions the blood glucose, whenever drawn, is normal.

Data from the UGDP study have thus far contributed nothing to the controversy regarding the effectiveness of blood glucose control and are sufficiently in doubt as to the apparent lesser benefits of tolbutamide and phenformin as compared to diet alone or diet and insulin, so that the results cannot at present be extrapolated to the diabetic population at large. They do not warrant discontinuation of the appropriate routine clinical use of oral hypoglycemic agents.

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[From the Washington Post, July 9, 1975]

AMA Official Let Company Use Name

(By Stuart Auerbach)

A top official of the American Medical Association allowed drug company salesmen to use a letter from him as part of their effort to persuade doctors to continue prescribing a controversial drug that has been blamed for as many as 15,000 unnecessary deaths a year.

Dr. James H. Sammons, AMA executive vice president, gave his permission to Upjohn Co. salesmen in March despite an opinion from an AMA lawyer that it is against the association's policy to use its name for business purposes.

The letter from Sammons downplayed questions about the safety of widely prescribed anti-diabetic drugs that had been raised in the AMA's magazine, the Journal of the American Medical Association.

His letter and the opinion of AMA lawyer Betty Jane Anderson were made available to newspapers by a man who was identified himself as a former AMA employee dismissed in a staff cutback. The documents were verified by AMA officials.

In a Jan. 28 letter, Sammons warned about 400 medical society executives around the country that the Feb. 10 issue of JAMA would contain a confirmation by the Biometric Society of a 10-year study that showed that some anti-diabetic drugs, known as hypoglycemics, cause more people to die of heart disease than they save from dying of diabetes. The society is an impartial group of statisticians dealing with medical issues.

The original study, done by the University Group Diabetes Program (UGDP), was hotly contested by many diabetes specialists when it was released four years ago.

But a large number agreed with the UGDP findings, and the U.S. Food and Drug Administration last week ordered that advertising for the drugs must contain the warning that they may cause death from heart disease.

The drugs are used by an estimated 1.5 million Americans to lower their blood sugar, and represent an estimated $100 million-a-year business for the pharmaceutical industry. Upjohn sells two leading brands of the drugs—Orinase, for years the most widely prescribed oral hypoglycemic pill, and Tolinase.

Upjohn said it wanted to use Sammons' letter "as a result of the confusion from the Feb. 10 JAMA story." It would be used by Upjohn salesmen in discussions with doctors "should the subject arise."

Sammons' letter reported that an editorial in JAMA would say the drugs are probably associated with "10,000 to 15,000 unnecessary deaths" a year in the United States.

The editorial was written by Dr. Thomas C. Chalmers, dean and president of the Mt. Sinai Medical College in New York and former director of the National Institutes of Health's Clinic Center in Bethesda.

Nevertheless, Sammons wrote:

"A considerable body of expert scientific opinion contradicts these published findings. Diabetic patients should not be influenced by press reports, and should continue on whatever diabetic management program their own physician has prescribed."

When Upjohn asked to distribute the letter to its salesmen, AMA attorney Anderson wrote Sammons, "The policy of the AMA is that the association's name may not be used for trade purposes.

"Permission to reprint AMA materials has not been granted if there is any indication that the name of the association or its materials will be used in any manner that might directly be construed as an endorsement by the AMA of a particular product or manufacturer."

Later in the memo, she warned Sammons that the use of the letter of Upjohn salesmen "may cause embarrassment to him personally or to the AMA."

"Upjohn's purpose could be better accomplished by having an article presenting the other side of the controversy published in JAMA," she said.

On March 17, JAMA published a letter by Dr. M. Hubbard Jr., Upjohn's president opposing the AMA editorial and the Biometrics study, and on May 26 it published a series of letters and articles from other doctors who believe in the drugs.

THE UNIVERSITY OF CHICAGO
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17 February 1975

Senator Gaylord Nelson
Chairman, Monopoly Subcommittee
Senate Small Business Committee
424 Russell Senate Office Bldg.
Washington, D.C. 20510

Dear Senator Nelson:

I have reviewed the transcript of my testimony before your Committee on 31 January and I think it may be useful to restate the position I was supporting in our exchange.

First, it was entirely proper for the UGDP investigators to withdraw Tolbutamide from the study as soon as they had substantial doubts about its safety. However, as a consequence, they could not reach a firm conclusion about it. Their own conclusion was stated as follows:

> "... the findings of this study indicate that the combination of diet and tolbutamide therapy is no more effective than diet alone in prolonging life. Moreover, the findings suggest that tolbutamide and diet may be less effective than diet alone or than diet and insulin at least insofar as cardiovascular mortality is concerned."

I think that statement should be taken at face value, and not as a polite substitute for a more forceful condemnation of Tolbutamide.

Second, in the light of all available evidence, a decision must be made about the appropriate legal or regulatory steps to be taken about the distribution of Tolbutamide. The suggestion made by Dr. Ricketts seems to me appropriate. Enough doubt about its effectiveness in ordinary use and concern about toxicity exists to warrant imposing some additional reporting burden on the physician who prescribes it.

Finally, of far more importance than the decisions to be made about Tolbutamide is the continuing lack of procedures for accumulating reliable information about the effects of drugs for which the balance of risk and benefit is uncertain. The answer cannot be entirely a matter of adding more and more requirements before a drug is released for marketing. I am not convinced that present regulations have substantially impeded the adoption of valuable drugs, but pushed too far,

they certainly could. I should prefer to see drugs made available on the basis of reasonable evidence of safety and efficacy, and to require that appropriate studies should be carried out until the matter of risk vs. benefit is settled beyond reasonable doubt.

Sincerely yours,

Paul Meier

Paul Meier

P.S. I enclose a recent curriculum vitae, in accordance with your request.

PM/tk

February 1975

PAUL MEIER

Personal: Born 24 July 1924, New York City.

Education:

B.S.	Oberlin College	Physics, Mathematics	1941-45
	Brown University Intersession Program in Applied Mathematics		1945
M.A.	Princeton University	Mathematics (Mathematical Logic)	1945-47
	Study and Research in Statistics		1947-48
Ph.D.	Princeton University	Mathematics (Statistics)	1951

Professional Career:

1948-49 Assistant Professor of Mathematics, Lehigh University.

1949-51 Research Secretary, Philadelphia Tuberculosis and Health Association (part-time).

1951-52 Research Associate, Analytical Research Group, Forrestal Research Center, Princeton University.

1952-57 Department of Biostatistics, School of Hygiene and Public Health, The Johns Hopkins University
(1952-53, Research Associate; 1953-55, Assistant Professor; 1955-57, Associate Professor).

1957- Department of Statistics and Division of Biological Sciences, University of Chicago
(1957-62, Associate Professor; 1962- Professor of Statistics; 1960-66, Chairman, Department of Statistics; 1962-69, Director, Biological Sciences Computation Facilities; 1968-74, Professor of Theoretical Biology; 1970-71, Acting Chairman, Department of Statistics; 1973-74, Chairman, Department of Statistics; 1975- Ralph and Mary Otis Isham Professor of Statistics and of the Pharmacological and Physiological Sciences).

1966-67 National Institutesof Health Special Fellow at the University of London (School of Hygiene and Tropical Medicine, and Imperial College), on leave from the University of Chicago.

Professional Memberships:

American Statistical Association, Fellow; Board of Directors; Vice-President, 1965-67; Chairman, Committee on Computers in Statistics, 1967; Chairman, Section on Training, 1974.

Biometric Society, Executive Committee, ENAR, President, ENAR, 1967.

Institute of Mathematical Statistics, Chairman of Editorial Board, IMS-University of Chicago Press Monographs in Statistics, 1961-64 and 1968- .

Royal Statistical Society, Fellow.

American Association for the Advancement of Science, Fellow.

American Mathematical Society.

Mathematical Association of America.

Association for Symbolic Logic.

Society for Industrial and Applied Mathematics.

Association for Computing Machinery.

American Public Health Association, Fellow.

American Thoracic Society, Fellow.

American Heart Association, Fellow, Council on Epidemiology.

Consultant Activities and Special Appointments:

1955	Consultant on Statistical Problems in the Pharmaceutical Industry.
1959	Consultant on Sampling and other Statistical Problems in Transportation.
1959-62	Member, Committee on Lung Cancer, American Cancer Society.
1960-66	Consultant, The RAND Corporation.
1965-70	Member, Special Study Section, Biomathematics and Statistics, National Institute of General Medical Sciences (NIH).

1967-71 Member, Therapeutic Evaluation Committee, National Heart Institute (NIH).

1968 Member, Diet-Heart Feasibility Study Review Committee, National Heart Institute (NIH).

1970- Member, National Academy of Sciences Committee on Biological Effects of Atmospheric Pollution.

1971- Member, Advisory Board, Environmental Health Resource Center.

1972- Member, Task Force on Health Considerations of a National Energy Policy, American Public Health Association.

1973- Member, Advisory Board of Veterans Administration Cooperative Study of the Pathogenic Effects of the Sickle Cell Trait.

1973- Member, ASA Advisory Committee to Statistical Policy Division — Office of Management and Budget, Executive Office of the President.

1973- Member, Committee for the Assessment of Biometric Aspects of Controlled Trials of Hypoglycemic Agents.

1974- Member, Panel on Airborne Particles and Panel on SO_x, Assembly of Life Sciences, National Research Council.

1974-75 Sigma Xi Lecturer.

1974- Member, Advisory Council for the Department of Statistics at Princeton University.

1974- Member, Computer and Biomathematical Sciences Study Section, National Institutes of Health.

Honorary Societies:

Phi Beta Kappa

Sigma Xi

Publications:

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(19) "Fluorospectrophotometric analyses of endometrial and endocervical epithelial cells" (with George L. Wied, Anita M. Messina, Jose I. Manglano and Richard R. Blough), Acta Cytologica, 8 (1964), 408-415.

(20) "DNA-assessments on fuelgen stained endometrial cells and comparison with fluorometric values" (with George L. Wied, Anita M. Messina and Ethel Rosenthal), J. Lab. Investigation, 14 (1965), 1494-1499.

(21) "Statistical evaluation of the effect of hormonal contraceptives on the cytological smear pattern" (with George L. Wied, M. Edward Davis, Richard Frank, Peter B. Segal, and Ethel Rosenthal), Obstet. and Gyne., 27 (1966), 327-334.

(22) "Analysis of morbidity and mortality of children irradiated in fetal life" (with M. L. Griem and Glen D. Dobben), Radiology, 88 (1967), 347-349.

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(26) "Hazards in oral contraception: The case for further tests," Midway, (1970), 87-95.

(27) "The biggest public health experiment ever: The 1954 field trial of the Salk poliomyelitis vaccine," in Statistics: A Guide to the Unknown, Frederick Mosteller, et al, eds., Holden-Day, Inc., (1972), 2-13.

(28) "Air Pollution and Pulmonary Cancer" (with Bertram Carnow), Arch. Environ. Health, 27 (1973), 207-218.

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HERBERT H. McDADE, JR.
PRESIDENT
CHIEF OPERATING OFFICER

March 11, 1975

The Honorable Senator Gaylord Nelson
Chairman - Monopoly Subcommittee
on the Senate Small Business Committee
The United States Senate
Washington, D. C. 20510

Dear Senator Nelson:

As the discoverer and developer of phenformin, USV Pharmaceutical Corporation has been following the controversy regarding the UGDP study; and, at your invitation, on October 21, 1974 we submitted to your Subcommittee the Company's general policy concerning the appropriate use of hypoglycemic agents, various criticisms of the UGDP study and comments concerning the reports of other groups which have studied these agents.

Our comments, as expressed in that letter, remain the same; however, in reading the transcript of the testimony before your Subcommittee on January 31, 1975, we feel compelled to amplify our previous letter.

The testimony of The Chairman of The Committee for the Assessment of Biometric Aspects of Controlled Trials of Hypoglycemic Agents reflected the following statement:

> "The findings on phenformin, if one can judge from the absence of criticism, appear to have been accepted by medical scientists, even if they have not so far been translated effectively into medical practice. Yet these findings also

were made by the UGDP using the methods that have come under heavy criticism when applied to tolbutamide."

A similar implication of absence of criticism of the UGDP with respect to phenformin appears at the end of section 3.1 (Findings) of the Biometric Committee's Report published in the February 1975 issue of the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION.

We believe it is necessary to dispute any implication that the criticisms leveled against the UGDP study are concerned with the drug, tolbutamide, alone. To the contrary, the substantive criticisms made, although perhaps naming tolbutamide specifically, apply equally with respect to phenformin inasmuch as the structuring of the two trials under the UGDP was nearly identical. Further, it should be pointed out that because of the nature of phenformin, the rather late introduction of its trials, and a variety of other material factors, the phenformin portion of the UGDP necessarily becomes the subject of additional criticisms.

There are several reasons why criticism of the UGDP study most generally is publicized in terms of tolbutamide. Tolbutamide was the first of the two drugs to be studied by the UGDP - in fact, tolbutamide preceded phenformin in the study by 18 months. Likewise, the first data generated by the studies were those on tolbutamide. Second, and just as importantly, the final Report of the UGDP on phenformin had yet not been published as of the date of the Biometric Committee's review. Since it is not generally recognized as scientifically proper to comment upon, or criticize, work presented only in preliminary form, it is natural that there had been less formal criticism on the phenformin aspect of the UGDP

study. Under these circumstances, it was to be expected that criticism of the UGDP study was more likely to be framed in terms of tolbutamide; however, this should not, in our opinion, be interpreted to mean that as to phenformin, the results of the UGDP study "have been accepted by medical scientists."

The Biometric Committee obviously considered important the fact that the final UGDP Report on phenformin had not yet been published and, in fact, the Committee did not consider the basic data on the effects of phenformin treatment. This is clearly reflected in the following quotation from Section 1 (Introduction) of the Biometric Committee's Report:

> "The preliminary report on phenformin was considered in September of 1973, but in view of the fact that the final report on that subject was still unpublished, the Committee did not request the basic data on the effects of this treatment."

In addition, the Biometric Committee recognized in its Report that the introduction of phenformin to the UGDP ..."greatly complicated an already difficult study." [See Section 7.1 (Conclusion, Protocol)].

Based upon these and other factors, it is our conclusion that the Report of the Biometric Committee does not resolve the controversy surrounding the UGDP study. It does not resolve the general criticisms of the UGDP study set forth in our letter of October 21, 1974, nor does it resolve the specific issues relative to phenformin.

We greatly appreciate this opportunity to present these