2. Further delay occurs because of the need for clinical testing.

3. When the information is finally released there are varying degrees of receptivity and understanding. Here we deal with a variety 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 mostly 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 post graduate 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 post graduate 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 throw aways" 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 post graduate 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.

TABLE I

COMPARATIVE USAGE OF ORAL HYPOGLYCEMIC AGENTS
CLEVELAND METROPOLITAN GENERAL HOSPITAL

The use of Tolbutamide, Chlorpropamide, and Phenformin for the years which there are accessible records are as follows:

TOLBUTAMIDE

Year	Tablets Used	Cost	Total Cost
1968	270,800	$62.00/Thousand	$16,789.00
1969	525,300	$62.00/Thousand	$32,562.00
1970	522,200	$62.00/Thousand	$32,376.00
1971	320,600	$62.00/Thousand	$19,877.00
1972	286,600	$62.00/Thousand	$17,769.00
1973	144,200	$64.00/Thousand	$ 9,228.00
1974	83,500	$69.62/Thousand	$ 5,813.00
1975 (To date)	46,100	$75.56/Thousand	- - - - - -
1975 (Projected)	92,200	$75.56/Thousand	$ 6,966.00

PHENFORMIN

Year	Capsules Used	Cost	Total Cost
1968	74,300	$73.50/Thousand	$ 5,461.00
1969	93,200	$73.50/Thousand	$ 6,850.00
1970	97,000	$81.00/Thousand	$ 7,857.00
1971	95,700	$80.00/Thousand	$ 7,656.00
1972	61,300	$80.00/Thousand	$ 4,904.00
1973	42,800	$69.10/Thousand	$ 2,957.00
1974	15,600	$69.00/Thousand	$ 1,076.00
1975 (To date)	1,000	$69.00/Thousand	- - - - - -
1975 (Projected)	2,000	$69.00/Thousand	$ 138.00

CHLORPROPAMIDE

Year	Tablets Used	Cost	Total Cost
1968	76,000	$67.64/Thousand	$ 5,140.00
1969	110,000	$67.64/Thousand	$ 7,440.00
1970	127,600	$65.00/Thousand	$ 8,294.00
1971	116,900	$65.00/Thousand	$ 7,598.00
1972	113,500	$65.00/Thousand	$ 7,377.00
1973	104,500	$81.51/Thousand	$ 8,517.00
1974	34,200	$81.51/Thousand	$ 2,787.00
1975 (To date)	18,800	$89.66/Thousand	- - - - - -
1975 (Projected)	37,600	$89.66/Thousand	$ 3,371.00

June 25, 1975

TABLE II

Yearly Use of Insulin Stocked in Pharmacy Cleveland Metropolitan General Hospital
Based on Accessible Records

Year	10 ml. Vials	Total Cost
1968	7,250	$ 6,587.15
1969	6,594	$ 8,119.90
1970	6,522	$ 7,675.00
1971	7,125	$ 8,405.45
1972	8,065	$ 9,927.00
1973	9,803	$12,130.96
1974	9,814	$15,232.00
1975 (Projected)	9,192	$12,437.00

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Statement Before Subcommittee on Monopoly

Senate Small Business Committee

July 10, 1975

Mr. Chairman and Members of the Subcommittee

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: (1) 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. (2) The impact which the findings of the UGDP study have had on medical practice. (3) 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 life saving 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. It is thus clear that these drugs are useful in a very limited number of patients with adult-onse 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 1) these agents are drugs of convenience, 2) they are widely overprescribed, 3) they may increase cardiovascular mortality, and 4) 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% between 1972 and 1973. This represents a total of over 19 million prescriptions costing over $100,000,000 and involving over 1½ million patients.

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:

1. 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. 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.

2. 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.
3. Research should be undertaken on developing improved methods of assuring patient conpliance and success in adhering to weight-reducing diets.
4. Most importantly, the labeling of oral hypoglycemics should be changed to include:
   a. A warning that evidence has been reported that these agents may increas cardiovascular mortality; and
   b. That use of these agents should be restricted to adult-onset diabetics in whom dietary measures have failed and insulin is refused or impractical.

Mr. Chairman, 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 life span in adult-onset diabetics.

(STATEMENT BY
(JOSEPH LARNER M.D., PhD., PROFFESSOR AND CHAIRMAN
(DEPARTMENT OF PHARMACOLOGY AND DIRECTOR OF THE DIABETES AND
(ENDOCRINOLOGY CENTER, UNIVERSITY OF VIRGINIA SCHOOL OF MEDICINE,
(CHARLOTTESVILLE, VIRGINIA
(BEFORE SUBCOMMITTEE ON SMALL BUSINESS
(JULY 10, 1975)

Honorable Gaylord Nelson and members of the Subcommittee:

Senator Nelson:

My name is Joseph Larner, I am a scientist (pharmacologist, biochemist) and physician who has been interested in problems of diabetes for many years, and who has been working on the mechanism of insulin action for 15 years. I was called and asked to testify before this committee, and am pleased to do so. In connection with the five points raised in your letter of June 19, 1975, I respond as follows:

1. 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, 5th 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.

2. 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 analogues 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.

3. 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 non-diabetic through the use of an insulin delivery system yet to be developed, would there still be vascular complications?" Or, 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. Since no answer exists for insulin, which is a direct hormone replacement therapy, obviously no answer exists for the oral hypoglycemic agents. For this reason, I feel there is no direct evidence that these oral agents are beneficial, i.e., life-saving or life-preserving.

4. 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 unknown. 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.

5. Any 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 effects 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: 1) the summary statement of the work of Wissler et al. which states that in rhesus monkeys fed an average American diet for 74 weeks containing 20 mg/kg 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. 2) 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 autonomic 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.

STATEMENT BY
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BEFORE MONOPOLY SUBCOMMITTEE
SENATE SMALL BUSINESS COMMITTEE
31 JANUARY 1975

Mr. Chairman. I speak as a member of the Biometric Society Committee on Biometric Aspects of Controlled Clinical Trials whose report is under discussion today.

Professor White has outlined our problem and our findings, and Professor Zelen will speak about some of the particular criticisms made of the U.G.D.P. 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 Thrombo-embolism 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. My explanation for the lack of substantial research on this important problem was as follows:

> "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, 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 U.G.D.P., but they could scarcely have been more apt.

It is true that the U.G.D.P. 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 U.G.D.P. 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, the evidence is sufficient to abandon the drug. Or, on the contrary, as in the U.G.D.P. 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.

Statement by

P. J. Palumbo, M.D.

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Before Subcommittee on Monopoly

Senate Small Business Committee

January 31, 1975

13668 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

DIABETIC TREATMENT AND SURVIVORSHIP

P. J. Palumbo, M.D.

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, Minnesota between 1945 to 1970 contains some hints that survivorship may be lower in diabetics on oral antidiabetic agents, but group differences preclude any firm conclusions regarding this observation. 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 five or more years. These data have been reviewed and the conclusions have been found to be sound.

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 an adverse effect of the oral antidiabetic agents on survivorship in the diabetic. The use of these oral agents, therefore, should be curtailed.

STATEMENT BY
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BEFORE THE SUBCOMMITTEE
OF THE SELECT COMMITTEE,
ON SENATE SMALL BUSINESS,
JANUARY 31, 1975

I have studied diabetes mellitus, cared for diabetic patients, and conducted researches in this specialty for 34 years. I have been president of the American Diabetes Association and co-founder 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.

My connection with the Committee of the Biometric Society was that of a consultant diabetologist, and I attended most of their 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 were 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.

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, perforce, 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 conclusion 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 four 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 (Diabetes, Supplement No. 2, Vol.19:747-830, 1970). I quote:

> "...The UGDP mortality study shows that death rates were essentially the same in the IVAR group, which maintained more nearly normal fasting blood glucose levels, as in the more poorly controlled groups of PLBO and ISTD. This would appear to mean that efforts

to establish "good"control of hyperglycemia 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 TOLB 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 exluded, 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, 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 sulfonyurea 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 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.

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, 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.

STATEMENT BY
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BEFORE MONOPOLY SUBCOMMITTEE
SENATE SMALL BUSINESS COMMITTEE
JULY 10, 1975

Mr. Chairman, Members of the Committee: I am glad to have the opportunity to testify before this Committee relative to the proper labeling of oral hypoglycemic agents in the light of recent studies, and on the problems of translating the results of research to the practice of medicine. I plan to center my remarks on the optimal management of the overweight, non-insulin-dependent diabetic as this relates to the recommendations included in the proposed labeling. My qualifications include care of diabetic patients at Yale-New Haven Hospital and in Vermont over the past 30 years and former direction of a Metabolic Unit and of an NIAMD training program in diabetes. I have served on special study sections of the NIH for review of proposals for Diabetes and for Obesity Centers. I am a member of the advisory and editorial group for the Fogarty International Center Conferences on obesity and of the workshop on Obesity of the National Diabetes Commission.

SUMMARY

I. Obesity is now recognized as a factor predisposing to non-insulin-dependent diabetes in a genetically susceptible person. Untreated obesity may pose a greater long-term risk in relation to cardiovascular and other disease than the use of oral agents.

II. Insulin, in addition to its well known function of lowering blood glucose, is a storage hormone. The use of insulin, or of oral agents

which stimulate release of insulin promote fatness.

III. Intense preoccupation with one aspect of the UGDP study has blurred our perceptions of other vitally important data in the study. These data indicate adverse effects of therapy both with sulfonylureas and with insulin in promoting further development of obesity. This is a recognized risk factor for cardiovascular disease.

IV. One should not go on writing package labeling recommendations based on data comparing the five treatment modes chosen by the investigators of the UGDP in the 1960s, when these options are now out of date. They do not include preventive and rehabilitative measures available in 1975.

V. Lifestyle changes in eating and in physical activity are essential components of the management of non-insulin-dependent diabetes, as well as of cardiovascular disease and are often sufficient in themselves to restore near normal function. Initiated early they may provide effective prevention.

VI. The proposed FDA package labeling for oral agents should reflect these considerations. They should also be written in a form conducive to the education of the patient.

VII. The schedule of peer review and publication of the results of randomized prospective clinical trials requires modification, if the results of future studies are to be accepted by interested parties.

VIII Efficacy of a drug must be considered in the light of other available options for management. On this basis there is little evidence of acceptable efficacy of the sulfonylureas, except under special circumstances which preclude other therapeutic options. In the case of phenformin the efficiency:efficacy ratio is not acceptable.

I. PROPER LABELING OF THE ORAL HYPOGLYCEMIC DRUGS IN THE LIGHT OF RECENT STUDIES

I believe that the intense preoccupation with the increase in cardiovascular mortality from use of the oral agents has drawn attention away from matters of even greater importance in the management of the non-insulin-dependent diabetic. These include the facts that 1) Obesity is now recognized to be a predisposing factor for diabetes in a person genetically susceptible. 2) Insulin, in addition to its well-known function of lowering blood glucose, is a storage hormone and its use and the use of oral agents which promote release of insulin promote obesity. 3) Lifestyle changes in eating and in physical activity are essential components of good management of non-insulin-dependent diabetes and of cardiovascular disease as well. These changes are often sufficient in themselves to restore near normal function.

We should not classify diabetes into juvenile and maturity onset, since the correlation of types with age is poor. Diabetes occurs in two forms, each requiring entirely different management: i. e. insulin dependent, usually lean and hungry, and non-insulin-dependent, usually obese and also insulin resistant. Our studies in Vermont have shown that normal volunteers who deliberately gain 20 to 30 per cent above their basal weight develop insulin resistance similar to that seen in the spontaneously obese. They also had a diminished ability of muscle and fat cells to utilize glucose. Their fat cells enlarged, but did not increase in number, again similar to those who spontaneously develop obesity in adult years. These results suggest that in the naturally obese patient at least a part of the insulin resistance that places a stress upon the pancreatic reserve of insulin is secondary to weight gain and is reversible.

The UGDP investigators chose their five treatment regimens because

they replicated the commonly accepted options of the early 60s, but they do not represent the best options available now. Epidemiologists and cardiologists have defined the risk factors for cardiovascular disease, which include more than just elevated blood sugar and fats, i. e. obesity, smoking, and physical inactivity. Of the 1,500,000 patients now taking oral agents, probably 50 per cent are more than 25% over weight (54% of those entering 6 of the 12 clinics of the UGDP study). When these patients are treated with "diet alone", it is generally little more than a token gesture in the direction of a low-caloric diet. The success rate for weight loss is notoriously poor. There is important data in the UGDP study the significance of which is overlooked. With qualified dieticians available, there was an initial drop of slightly under 3 % in all groups. Only those taking placebo or phenformin maintained their weight throughout the 16 followup periods, and there was no difference between placebo and phenformin. On the other hand, those taking either tolbutamide or insulin lost less weight initially and regained weight above their baseline values so that in all there was an 8 per cent difference between the mean rate of the placebo group. This was to be expected since when the patient receives either a sulfonylurea drug or insulin plasma insulin is increased, thus increasing the tendency to store fat. The Indications listed in the latest FDA recommendation for package labeling calling for use of insulin if diet fails runs counter to our current concepts of the pathophysiology of non-insulin-dependent diabetes when it is associated with overweight and when there are other valid options.

OTHER OPTIONS FOR TREATMENT. There are other options in addition to the five of the UGDP study. These differ from the UGDP treatment modes in that they have the potential for reversing the patient's diabetic state. They include vigorous and comprehensive

regimens which include education and increase in physical activity. Now adjuncts include behavioral self-modification and protein-sparing starvation.

a) Withdrawal of Oral Agents and Intensive Weight Reduction. An important result of the UGDP study was the decision of Dr. John Davidson in Atlanta to discontinue oral agents for 1500 patients at Grady Hospital in Atlanta, as reported on Sept. 18, 1974 to this Committee. I suggest that his recent paper (JAMA 232:853, '75) on his experience be incorporated in the record of this hearing. 60% of these patients have been controlled without drugs or insulin by an intensive regimen of dietary treatment and exercise, which includes 25 hours of instruction and the use of special manuals. 50-90 % have lost significant amounts of weight, and it has been possible to discontinue insulin therapy in all patients who were initially above ideal body weight. The short term costs for education of the patient are considerable, but so are the long-term costs to the patient of oral agents, which are also susceptible to secondary failure. Dr. Davidson's important experiment, a pilot study which still requires reporting in full detail, demonstrates not only that patients may do as well with no medication as with oral agents, but also that their overt diabetic state may be at least temporarily reversed.

b) Protein-Sparing Starvation. We are becoming more experienced in the use of brief and occasionally long periods of semi-starvation to initiate weight reduction without consuming essential body protein s well as fat stores. This can be accomplished not by by providing carbohydrate to spare protein, which was the dictum in the past, but by providing optimal protein and minimal carbohydrate to minimize insulin stimulation. Such a temporary Spartan aid to acute weight loss is often surprisingly well tolerated by patients, who may report

loss of appetite plus a feeling of well being. (Genuth JAMA 231: '74). But it obviously cannot represent a panacea and must be carried out under close supervision. To sustain weight loss other measures are needed.

c) Increase in Physical Activity. I have left to the last what may well be one of the most important, even if the least tried and the most poorly documented adjuncts for the prevention and treatment of non-insulin-dependent diabetes, namely increase in physical activity. The only reference to exercise to date in these hearings was on Sept. 18, 1974 (p 10880). Mr. Gordon questioned Dr. Schmidt regarding the suggestion of Dr. Jesse Roth of the NIAMD that "vigorous exercise lowers blood sugar and that there seems to be a persistent beneficial effect in addition to the immediate effect". In answer Dr. Schmidt gave short shrift to exercise as a major factor in the management of diabetes. I disagree with him in this, and have support in the recommendations of the White House Conference on Food, Nutrition, and Health (Panel II-3 p 51 Adults in an Affluent Society: The Degenerative Diseases of Middle Age). A relevant study is that of Dr Per Bjorntorp in Sweden, who has measured the insulin response of obese middle-aged men before and after a course of physical training. Even though he encouraged them to maintain their excess weight, their resting insulin and insulin response to glucose was strikingly reduced (Metabolism 19:631 '70). This is not surprising, as any insulin-dependent diabetic learns that exercise lowers the requirement for insulin. Some formerly obese persons find that susteined increase in physical activity is the only way they can maintain weight loss.

A lifestyle incompatible with good health often lies behind many patients with non-insulin-dependent diabetes. A change in lifestyle with respect to composition of the diet and level of activity

is the first and sometimes the only measure required for many such diabetics. For those patients who definitely are insulin-dependent insulin is a necessary and logical adjunct to diet therapy. These include 1) the acutely decompensated diabetic (even those above ideal weight) 2) the hyperglycemic maturity onset diabetic at or below ideal weight 3) the hyperglycemic pregnant diabetic and of course 4) the young insulin-dependent diabetic. However, for the overweight diabetic, use of oral agents or insulin is both illogical and unnecessary, if the measures indicatec above can restore metabolic balance.

Many patients enter the health care system too late in the course of their diabetes or of their lives to modify their lifestyle effectively, and the therapeutic options are limited. Our profession should make maximum efforts to reach younger members of high-risk families with education and programs for effective prevention.

If all the above is true, one might indulge in an extrapolation regarding the results of using oral agents in the non-insulin dependent diabetic. Such an extrapolation is obviously highly conjectural since solid data is not yet available, but I believe that it points in the direction of important truth. If we grant that there are approximately 1,500,000 patients reputedly 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 patient's life and survival

are being neglected. This to my mind is an important consideration which dwarfs even the serious concerns about the toxicity of the agents. Even if the oral agents were proven to have no toxic action, their detrimental role as a substitute for other safe and potentially rehabilitative measures would remain.

To change the way we are doing things today is not a simple matter, and it is inappropriate to blame the physician or the patient for the result of large forces at work in our economy. A considerable reallocation of resources over a period of time would be required to bring about a shift from a symptomatic to a rehabilitative form of therapy. Dr. Leon White, Commissioner of Health and Hospitals in Boston, recently listed the destructive lifestyle habits in this country and the diseases and disorders they produce. Social excess of alcohol, overeating, and lack of exercise contribute to obesity and cardiovascular disease. These habits also contribute to diabetes in the genetically predisposed. As reported in the Harvard Medical Newsletter (1:no 39, June '75) Dr. White stated that if the battle to modify lifestyle is to be fought, a major enemy is advertising. But advertising is not the only enemy. Lifestyle modification, if it is to be successful, will adversely affect the pharmaceutical industry, the tobacco industry, the alcohol products industry, the food products industry, and the auto industry. The real challence is to improve health without wrecking the economy.

THE RESPONSIBILITY OF THE FDA REGARDING LABELING

The question remains as to whether the Commissioner of the FDA should indicate priorities or treatment or treatment options and whether these represent a constraint on the freedom of the responsible physician or mak him liable to suit if he does not follow such priorities. Since there is a stated responsibility

under the Federal Food, Drug, and Cosmetic Act, section 505 for the FDA to assure efficacy as well as safety of a drug, I believe that the FDA has a responsibility to make such indications, since they affect the relative efficacy of a drug. Considered alone a drug might be rated as effective, but if a superior alternative becomes available, its relative effectiveness is changed. Since the types and stages of diabetes vary, it seems to me appropriate for the FDA to suggest priorities for the use or non-use of drugs at these various stages. The physician retains the ultimate responsibility of deciding how his particular patient relates to the general guidelines. He should not be medicolegally vulnerable for electing any particular option provided that he can justify his decision and also makes his patient an informed partner in the choice, whenever possible.

SUGGESTED CHANGE IN PROPOSED LABELING FOR SULFONYLUREA DRUGS

In line with the above considerations I suggest that the section on Indications for the use of sulfonylurea drugs submitted for the Federal Register (page 40 of the copy available for the hearings) be modified as follows. (Changed wording is underlined).

Diabetic patients with non-insulin-dependent diabetes who are overweight commonly exhibit insulin resistance and have elevated fasting insulin concentrations and increased, though relatively inadequate insulin response to glucose. Such patients can frequently be rehabilitated and their overt diabetes reversed by a vigorous and comprehensive regimen of dietary restriction, increased physical activity and weight loss. Thus neither treatment with (drug) nor insulin is indicated, unless application of such measures is totally impractical. (Drug)is indicated in maturity onset non-ketotic diabetics of normal or subnormal weight whose hyperglycemia*cannot be controlled by carbohydrate restriction and increased activity and

in whom insulin cannot be used because of ....similar factors.

When used in asymptomatic patients whose elevation of blood glucose cannot be controlled by the above measures and in whom insulin .....unanswered scientific question."

* I have substituted the word hyperglycemia for asymptomatic here because I do not consider that the UGDP study, with its limited range of population and limited measurements is decisive in determining whether hyperglycemia is related to microangiopathy. Also with a high renal threshold for glucose prolonged hyperglycemia of major degree may be present without symptomatic glucosuria.

II THE EFFECT OF THE STUDIES OF THE USE OF ORAL AGENTS ON MEDICAL PRACTICE AND PROBLEMS OF TRANSLATING RESULTS OF RESEARCH TO PRACTICE

Judging by the prescription rates for the various oral agents, the impact of the UGDP study on general practice has been negligible. It is ironic that the sale of phenformin, the agent which has been most clearly shown to produce tachycardia, hypertension, and a significant increase in both cardiovascular and overall mortality has ncreased in sales (up 5% from '72 to '73). There are suggestions, however, that the use in the vicinity of large medical centers has decreased. The study has provoked a great deal of inquiry into the use and limitations of prospective randomized clinical trials. The Reasons for the minimal impact have been discussed by others in detail before this Committee, and I will mention only a few:

1) Both physicians and patients look for quick solutions in the form of pills or injections. This is understandable because correction of our many health problems today calls for alterations in life style which are not easy to accept and which often call for resources which most physicians do not have available. It is the large problem of

symptomatic vs. preventive and rehabilitative medicine.

2) The disagreement, wrangling, and finally name calling (scandal, coverup, drughouse whore, etc.) that has develooed out of the controversy over one single, though important, aspect of the UGDP study has tended to weaken public confidence in the medical profession and has obscured our ability to perceive the factors of most critical importance to the patient.

The Planning of future randomized, controlled Clinical Trials.

To avoid some of the features which have detracted from the impact of the UGDP I suggest the following:

1) That direct financial support of particular studies by vested interests be avoided.

2) That agreement be obtained in advance regarding both the conduct of the study and the release of data.

3) That the final data and that at any critical point in the study be reviewed by a third party unaware of the identity of the experimental groups.

4) The customary piecemeal process for review and publication of medical work is inappropriate and impractical in the case of a randomized clinical trial which may involve ingrained traditions of clinical practice and academic theory on the one hand and multimillion dollar commercial interests on the other. It seem to me that the first release should be of a full report which vitally interested parties have had an opportunity to review prior to definitive issue.

5) We are entering a period when patients will take a more active role in deciding their own options for treatment of chronic health problems. In parallel with this I hope that we will see informed, cooperative patients in the early stages of their disease or disorder taking part in clinical studies.

6) Medical advertising often tends to neutralize the impact of randomized clinical trials, if the results from a particular product are unfavorable. Our profession has a responsibility to see that advertising accepted for our professional publications does not undermine or weaken the impact of research

and government regulations. As an example, the medical journal which published the full report of the experience of the UGDP with phenformin has continued to print advertisements for phenformin which give no warning regarding hypertension, tachycardia, and cardiovascular death as adverse reactions.

7) Teaching in medical schools and in post-graduate courses should emphasize methods of evaluation of therapeutic agents to a greater extent. At the University of Vermont during several years we have used the UGDP study and its problems as the basis for an interdepartmental teaching exercise. The excellent short book by A. L. Cochrane in England, Effectiveness and Efficiency (Nuffield Provincial Hospitals Trust 1972) should be available in this country as required reading for all health professionals.

III. AVAILABILITY OF SCIENTIFIC EVIDENCE DEMONSTRATING BENEFIT OF ORAL AGENTS

The UGDP demonstrated no increased effectiveness of tolbutamide as opposed to placebo with respect to mortality or gross evidence of vascular disease in the groups of maturity onset diabetics of the type now receiving oral agents in today's practice. As in other studies there was also evidence of secondary failure. Thus,on the issue of efficacy, were the drug up for initial review today, it doesn't seem likely that it would be approved. The UGDP study also showed that, in this group of largely overweight non-insulin dependent diabetics, lowering the blood glucose concentrations alone gave no objective benefit, altho the techniques for evaluating microangiopathy were insensitive. Therefore, the one justification for continued approval of the sulfonylureas appears to be that there is a very small percent of patients who can't take or will not take insulin, do not respond to other measures, and are severely symptomatic and hyperglycemic. However, to give blanket approval for use of the drug to accomodate this relatively minute fraction of the diabetic population leaves the door wide open for continuation of widespread inappropriate use, with all the disadvantages indicated above. It is unrealistic to believe that package labeling with suitable warning and suggested priorities will alter the patterns of prescription.

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It therefore seems to me to be justifiable and appropriate to classify the sulfonylurea compounds, along with other drugs with circumscribed uses and significant adverse effects, to sharply limited clinical situations by placing them in a restricted category and requiring written justification for their use in a particular situation. This would not curtail their use where there is strong indication, but would limit much uninformed or ill-considered use.

The justification that is advanced for continued use of phenformin is that it does not stimulate insulin release while lowering blood glucose and therefore is ideal, as the advertisements say, for releasing patients from entrapment in their fat cells. The UGDP study showed that the patients who took phenformin maintained their initial weight loss, and had approximately 8 % lower body weight at the close of the study than those taking tolbutamide or insulin. There was, however, no difference from those taking the placebo and the clearcut evidence of tachycardia, hypertension and increased total and cardiovascular mortality seen in the UGDP study in addition to the potential of producing lactic acidosis indicates a price in toxicity too great to pay for any relative advantage over oral agents with respect to weight loss. Therefore I believe that it is past time that this agent should be disapproved.

Statement of

Colin White

Professor of Public Health
Yale University School of Medicine
New Haven, Connecticut 06510

Before the

Sub-committee on Monopoly of the
Small Business Committee
U. S. Senate

January 31, 1975.

Mister Chairman and Members of the Sub-committee:

I am the chairman of a committee which was appointed by the Biometric Society and funded by the National Institutes of Health to carry out the following mission:

i. 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;

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

The committee consisted of six members:

John P. Gilbert, Harvard University

Paul Meier, University of Chicago

Chris L. Rümke, Free University, Amsterdam

Rodolfo Saracci, Pisa, Italy

Marvin Zelen, State University of New York at Buffalo

Colin White, Yale University

Two officers of the Biometric Society attended several of the meetings as observers: Peter Armitage, London School of Hygiene and Tropical Medicine; and Berthold Schneider, Hannover, West Germany.

The research associate for the committee was Theodore Holford, and the consultant diabetologist was Henry T. Ricketts.

The full committee met on six occasions over a two 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 U.G.D.P. 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, and 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 U.G.D.P. 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 U.G.D 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 U.G.D.P., was the study in Bedford, England, organised by Dr. H. Keen and Dr. R. J. Jarrett. It should be said at once, however, that the Bedford study, based on 125 patients in each of two treatment groups was not comparable in size or in detail to the U.G.D.P. 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:

1. Visits were made to the U.G.D.P. co-ordinating Center and to two of the co-operating clinical centers to study methods used in the trial.

2. The methods and findings of the U.G.D.P. study were discussed with several authors who had written about them, and the Bedford study was discussed with Dr. Keen and Dr. Jarrett.

3. The published criticisms of the U.G.D.P. were reviewed in detail. Comparable criticisms of the Bedford study do not exist, though several of the major criticisms made about the U.G.D.P. would apply a fortiori to the Bedford study.

4. New analyses were made of the data from the U.G.D.P. and Bedford studies, the data being kindly made available by the directors concerned.

Critics have pointed out that in the U.G.D.P. 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 cirticism has some weight but is not convincing. Criticisms that have been commonly made but which, in our view, are not correct are:

(1) the excess mortality in the tolbutamide group was due to the data obtained from just a few clinics:

(2) the studies of Keen et al and of Paasikivi contradict the U.G.D.P.

(3) 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 critics, to my knowledge, has given serious consideration to the multiple logistic method that was used by the U.G.D.P. to take the effect of baseline risk factors into account. Until they do they have not carried out an adequate review of the U.G.D.P. analysis.

(4) the findings on the effect of tolbutamide are flawed by the failure to adapt dosage to individual need.

(5) the evidence was not adequate to justify the discontinuation of the oral drugs.

In our analysis of the U.G.D.P. data we have used the same multiple logistic model as was employed by the U.G.D.P. 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% 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 U.G.D.P. 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.

Statement of Dr. Marvin Zelen, Director
Statistical Laboratory, State University of
New York at Buffalo

Mr. Chairman and Members of the Committee. Thank you for this opportunity to appear before this Committee. My comments will be divided into two parts.

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.

Let us 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 (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 record keeping on a large number of patients would a changed cardiovascular death rate of 2-3 be detected. The analysis of such multi-faceted data requires more sophisticated data analytic methods than those in common usage by clinicians.

Next, I wish to discuss 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. 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 follow-up.

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 into our final report. Our conclusion is that the weight of evidence points to tolbutamide as being responsible for excess cardiovascular mortality.

EXHIBITS PROVIDED BY THE FOOD AND DRUG ADMINISTRATION

STATEMENT

BY

ALEXANDER M. SCHMIDT, M.D.

COMMISSIONER

FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

BEFORE THE

SUBCOMMITTEE ON MONOPOLY

SELECT COMMITTEE ON SMALL BUSINESS

UNITED STATES SENATE

JULY 9, 1975

Mr. Chairman:

I am pleased to appear today before this subcommittee to discuss current Food and Drug Administration (FDA) actions relating to 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. The Food and Drug Administration (FDA) has now published a proposed regulation providing new labeling for this class of drugs, which appeared in the Federal Register of July 7, 1975, and has invited comments on this labeling. A public hearing will be held on August 20, 1975 to afford interested persons a further opportunity to comment.

On September 20, 1974, I summarized before this subcommittee the actions of the FDA that followed the report of the results of the University Group Diabetes Program (UGDP) study. Today I will review the events that have taken place since my previous testimony and I will discuss in some detail important aspects of our proposed labeling changes.

REVIEW OF BIOSTATISTICAL ISSUES BY THE COMMITTEE OF THE BIOMETRIC SOCIETY

Because of the controversy concerning the UGDP study and the oral hypoglycemic labeling previously proposed by FDA based on the findings of that study, we decided that publication of proposed labeling should await completion of a detailed review of the UGDP study by the Biometric Society, a distinguished international organization of biostatisticians. The Society's report was published in the February 10, 1975 issue of the

Journal of the American Medical Association. Testimony before this subcommittee on January 31, 1975, by the members of the Biometric Society who had conducted the review, had provided a preview of their conclusions.

The Biometric Society Committee assessed the scientific quality of the UGDP study, particularly the design, conduct, and analysis of the trial, and evaluated other controlled trials involving oral hypoglycemic agents. The committee discussed in detail the published criticisms of the UGDP study and found that "most of the criticisms unpersuasive." Specifically, the committee concluded that:

1. The criticism that patient selection had been inappropriate was "largely irrelevant" to the validity of the evidence for the toxicity of the oral agents.

2. The criticism that total mortality in the tolbutamide group 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."

3. Excess mortality in tolbutamide-treated patients was not confined to a few clinics, as critics had claimed.

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

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

6. Although the committee acknowledged that, "It would have been easier to interpret the findings if there were more data on mortality." [that is, if the study had been carried on longer], it did "* * * not criticize the UGDP investigators for having made the decision when they did." The committee further 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."

7. Other studies said to contradict the findings of the UGDP study do not in fact do so.

In addition to evaluating criticisms of the UGDP study, the Biometric Society Committee conducted extensive new analyses of the UGDP data, taking into account the effect of various base-line variables and cardiovascular risk factors. The committee's analyses confirmed that cardiovascular mortality was increased in the tolbutamide group. The 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 study demonstrated 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 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 the survival modeling method, which takes into account the proportion of time each patient received the assigned medication, women in the tolbutamide group showed statistically significant increase in both cardiovascular and total mortality.

The Biometric Society Committee summarized conclusions in the final section of its report as follows:

"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 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, 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.

ADDITIONAL INFORMATION PERTAINING TO ORAL HYPOGLYCEMIC DRUGS

In addition to the Biometric Society report, other information has become available recently.

1. The UGDP recently published its detailed report of the results of the phenformin study (Diabetes, 24 (suppl 1): 65-184, 1975). 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.

2. At hearings before this Subcommittee on January 31, 1975, 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 oral hypoglycemic agents, compared to those patients treated with insulin or diet. Dr. Palumbo's full study has not yet been published.

3. A retrospective study of diabetic 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 full review by statistical and epidemiologic experts. 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 difficulties in interpretation because of doubts

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regarding comparability of the 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.

4. Drs. Tan, Bradley, Gleason, and Soeldner reported on the long-term (4 years) effects 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 indicated that there was no significant difference in the improvement in glucose tolerance in patients receiving oral hypoglycemic agents compared with patients receiving 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.

5. Dr. R. W. Wissler, et al., in an FDA-supported study, examined the chronic effects of tolbutamide in the rhesus monkey. He found that coronary artery lesions were almost two times more frequent and three times more severe in the tolbutamide-treated animals than

in the control animals. The FDA recently received the final report on this study, which has not yet been published in the literature. At Dr. Wissler's request, FDA is supporting a further review of the pathologic findings by several independent pathologists.

6. 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 on May 3, 1975 (abstract in Clinical Research 22:215A, 1975). The investigators found that, after one year of treatment with tolbutamide, left ventricular function was reduced and cardiac morphology altered compared to the control groups.

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

PROPOSED LABELING FOR ORAL HYPOGLYCEMIC DRUGS

Mr. Chairman, as you know, it has been the position 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 bast examination of the long term effects of oral hypoglycemic agents yet undertaken -- and 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 warning is necessary to assure the safe and effective use of the drug by physicians.

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.

The proposed labeling contains 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 drug 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. Let me discuss each of these sections in greater detail; they are reproduced in full in an attachment.

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 "fair balance." We have concluded, however, and made clear in revised section 1.3 of our regulations (also published July 7, 1975), 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.

The 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 all other products in each category. The Warning is thus identical for all the sulfonylurea drugs; only one biguanide drug is marketed in this country.

Finally, the warnings section makes explicit the clear implication of the finding that tolbutamide and phenformin may carry a risk not associated with insulin: "(Drug) 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 (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 as safe and effective. We have also concluded, however, that this patient population is a limited one. The proposal to limit the treatment population to patients in whom insulin cannot be used has been opposed in the past on the ground that it interfered with the practice of medicine. We recognize that drug labeling has an impact on the practice of medicine. For this reason the Food and Drug Administration has an obligation to ensure that labeling is as correct and accurate as possible. It must, however, meet the statutory standard of describing the conditions of use under which a drug may be considered safe and effective. If a known hazard or potential risk leads to the conclusion that a drug may be used safety only in certain patients, this limitation on use must be expressed in labeling.

The indications section, in addition to describing the population in whom these drugs are 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 problematical.

Mr. Chairman, you asked that I comment on the promotion of these drugs. Advertising for these products has not violated general legal requirements, but it has been based upon labeling that has been in need of modification. It is clear that promotional materials must change radically to reflect the new warning and the restricted indications. You can be assured that we will be monitoring the promotion of these products closely after the new labeling becomes final, to see that they do so.

It is important to recognize that the use of the oral hypoglycemics remains widespread despite the UGDP findings and despite the rather limited capability 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 (a survey of IMS America) have been stable between 19 million and 21 million since 1967 (except for an apparent dip in 1969). There is thus a great deal of common practice to overcome before use of the oral agents will recede to its proper lebels.

It is anticipated that publicity attendant upon our publication of proposed labeling and announcement of the upcoming public hearing

as well as public interest in today's hearing will bring the new labeling to the attention of physicians and help begin to persuade them that the UGDP findings should change the way they treat diabetic patients. In addition, the FDA plans 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 final labeling.

I will be pleased, Mr. Chairman, to answer any questions.

PROPOSED LABELING INDICATIONS, CONTRAINDICATIONS AND WARNINGS SECTIONS FOR ORAL HYPOGLYCEMIC DRUGS OF THE SULFONYLUREA CATEGORY.

INDICATIONS

(Drug) is indicated to control symptoms due to hyperglycemia in patients with maturity-onset nonketotic diabetes mellitus 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 similar factors.

(Drug) may also be used to lower blood glucose in asymptomatic patients whose blood glucose elevation cannot be controlled by diet alone and in whom insulin cannot be used for any of the above reasons. 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.

The use of (drug) may be associated with an increased risk of cardiovascular mortality as compared to diet alone or diet plus insulin; see WARNINGS. For this reason, it should be used only

when the advantages in the individual patient justify the potential risk. The patient should be informed of the advantages and potential risks of (drug) and of alternative modes of therapy and should participate in the decision to use this drug.

The foundation of therapy in the obese maturity-onset diabetic is caloric restriction and weight loss. Proper dietary management alone is often effective in controlling the blood glucose and eliminating symptoms of polydipsia and polyuria. Use of (drug) must be considered by both the physician and patient as a treatment in addition to diet and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint.

Many patients who are initially responsive to oral hypoglycemic drugs become unresponsive or poorly responsive over a period of time, usually 1 to 5 years. (Drug) should be given only to patients demonstrated to be responsive to it; see DOSAGE AND ADMINISTRATION for discussion of secondary failure. Short term

administration of (drug) may be sufficient during periods of transient loss of control.

Concomitant Therapy with a Biguanide:

(Drug) may be used in conjunction with phenformin to control symptoms due to hyperglycemia in patients with maturity-onset nonketotic diabetes mellitus whose symptoms cannot be controlled by diet and maximum recommended doses of either drug alone and in whom insulin cannot be used for any of the reasons cited above.

In considering the use of concomitant therapy, it should be noted that both a sulfonylurea drug (tolbutamide) and a biguanide drug (phenformin) have been reported to be associated with increased cardiovascular mortality; see WARNINGS. In addition, phenformin can

produce lethal lactic acidosis in some patients. Thus the use of (drug) in association with phenformin carries a greater risk than the use of (drug) alone.

If a judgment is made that (drug) and phenformin are to be used together in a particular patient, it should be established that the patient is responsive to both drugs. This may be accomplished either by a trial of each drug separately or by adding the second drug and then tapering the dosage of the first, observing for diminished control of blood glucose. Once the need for both drugs is established, the desired control of blood sugar may be obtained by adjusting the dose of either drug. The possibility of hypoglycemia should be anticipated and appropriate precautions taken. See package insert for phenformin hydrochloride for CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.

CONTRAINDICATIONS

(Drug) is contraindicated in patients with:

1. Known hypersensitivity or allergy to the drug.

2. Diabetic ketoacidosis, with or without coma. Such patients should be treated with insulin.

WARNINGS

SPECIAL WARNINGS ON CARDIOVASCULAR MORTALITY

(This subsection of labeling to be boxed, set in boldface type, and placed at the beginning of WARNINGS section of labeling.)

The administration of oral hypoglycemic drugs may be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin.

This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with maturity-onset nonketotic diabetes. The study involved 1,027 patients who were randomly assigned to one of five treatment groups (Diabetes, 19 (supp. 2): 747-830, 1970; Diabetes, 24 (supp. 1):65-184, 1975).

The UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) or diet plus a fixed dose of phenformin (100 milligrams per day) had a rate of cardiovascular mortality approximately twice that of patients treated with diet alone or diet plus insulin. Total mortality was increased in both the tolbutamide- and phenformin-treated groups, but this increase was statistically significant only for phenformin. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide adequate scientific basis for this warning.

Although only one drug in the sulfonylurea category (tolbutamide) and one in the biguanide category (phenformin) were included in this study, it is prudent from a safety standpoint to consider that this result may also apply to other oral hypoglycemic drugs in these categories, in view of the close similarities in mode of action and chemical structure among the drugs in each category.

(Drug) 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 (drug) and of alternative modes of therapy and should participate in the decision to use this drug.

(Drug) is not effective in patients with juvenile diabetes or insulin-dependent diabetes at any age. Such patients should be treated with insulin. The concomitant long term use of insulin and (drug) in an individual patient is, in view of the potential risk of increased cardiovascular mortality with (drug), less safe on a benefit-risk basis than the use of insulin alone.

The effectiveness of any oral hypoglycemic drug, including (drug), in lowering blood glucose to a desired level decreases in a large number of patients as the drug is administered over a period of months or years, in part because the patient's blood glucose tends to rise over time and in part because of diminished responsiveness to the drug. This phenomenon is known as secondary failure to distinguish it from primary failure in which the drug is ineffective in an individual patient at the time of its initial administration. See DOSAGE AND ADMINISTRATION.

Renal or hepatic insufficiency may cause elevated blood levels of (drug) and increase the risk of serious hypoglycemic reactions.

Pregnancy: (Data and interpretation related to reproduction and teratology studies to be supplied by manufacturer).

Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. Neonatal hypoglycemia has been reported more frequently following use of the longer-acting agents. If (drug) is used during pregnancy, it should be discontinued (time period to be supplied by manufacturer) before the expected delivery date.

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