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COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

(Present Status of Competition in the Pharmaceutical Industry)

WEDNESDAY, SEPTEMBER 18, 1974

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 subcommittee) presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; and John O. Adams, minority counsel.

Senator NELSON. The Monopoly Subcommittee of the Senate Small Business Committee is resuming its hearings on competitive problems in the drug industry, and during the next few days we shall be hearing testimony specifically on the safety, efficacy, and use of oral antidiabetic drugs.

Diabetes is considered the fifth leading cause of death in the United States, predominantly because of chronic "complications," about 75 percent from vascular disease in general and about 50 percent from coronary artery disease in particular. Kidney disease in diabetes is 17 times more common than in the population at large. Diabetes is at least second and possibly the leading cause of blindness in the United States.

It is estimated that over 25 percent of the U.S. population has a family history of diabetes. There are approximately 10 million diabetics in the United States, half of whom are undetected.[1] Of the known diabetics, about 2 million take oral antidiabetic drugs, and 1 million are on insulin. Sales of the oral antidiabetic drugs at the manufacturers' level amount to about $100 million annually.

In 1970 a 10 year federally financed study conducted in 12 university clinics throughout the country concluded that the oral antidiabetic drugs, which had been widely prescribed since the late 1950's, not only were ineffective in preventing fatal complications from diabetes, but also appeared to shorten the lives of patients taking them over a long period of time. The Food and Drug Administration, the American Diabetes Association, and the Council on Drugs of the American Medical Association analyzed the findings and endorsed them. Neverthe-

[1] Drug Alert, vol. 2, No. 1, July–August 1972, University of Vermont Medical Center Hospital.

less, a large number of prestigious names in the diabetes field have attacked the study and have cited other studies to support their position. The general purpose of these hearings, then, is to try to sort out and analyze what scientific information we have about these drugs and the implications for medical practice.

The Subcommittee on Monopoly of the Senate Small Business Committee has had a long-standing concern with the development, marketing, and distribution of a wide variety of drugs. It is, therefore, appropriate that we turn our attention to the oral antidiabetic drugs which are widely used, particularly by the middle aged and older people of this country.

The aims of these hearings are to present for the general public's benefit the best and most objective information available about these drugs. First, whether they are as safe and effective as the medical profession and the public have been led to believe, and second, whether physicians who prescribe them may have sufficient information to weight the benefits against the risks.

The ultimate interest of the subcommittee is, of course, policy and we have asked the Food and Drug Administration, which has the responsibility of protecting the public, to discuss its actions since 1969 with respect to the oral antidiabetes drugs; the current status of, as well as the plans for, the new and more powerful drugs of the same class and possible further controlled studies of oral antidiabetic agents.

As I have said on many occasions in the past, every viewpoint on all subjects before this committee is sought. These hearings are no exception to that rule. The companies manufacturing these oral antidiabetic drugs are welcome to appear as witnesses upon their own request at any time.

Our first witness is Dr. Max Miller, chairman of the University Group Diabetes Program, professor of medicine at Case Western Reserve University, Cleveland, Ohio.

We welcome you here this morning, Dr. Miller. You may present your statement and proceed however you desire.

If you wish to speak extemporaneously, you are free to do so.

Please proceed.

STATEMENT OF MAX MILLER, M.D., CHAIRMAN, UNIVERSITY GROUP DIABETES PROGRAM, PROFESSOR OF MEDICINE, CASE WESTERN RESERVE UNIVERSITY, CLEVELAND, OHIO

Dr. MILLER. Mr. Chairman, I am grateful for the privilege and opportunity of testifying on the problem of the use of oral hypoglycemic agents for the treatment of diabetes.

I would like to make a plea that we strike from the record now and henceforth the word "antidiabetic", for there is no evidence that these agents do anything but lower blood sugar to only a slight to moderate degree. I would prefer the word, "hypoglycemic", which means simply "to lower the blood sugar". The word, "antidiabetic", implies that it has other beneficial effects on the disease, for which there is absolutely no evidence.

My qualifications are as a professor of medicine with primary interests in the field of diabetes and metabolism, as a researcher, as a

teacher, and as a clinician in a university clinic responsible for care of patients in this area.

I have been chairman of the University Group Diabetes Program, UGDP, since its inception in 1960. Between 1950 and 1960 I was instrumental in setting up and working with a diabetes research program at Western Reserve University supported in part by an area grant from the National Institutes of Health. I have been an active participant on several committees of the American Diabetes Association, particularly the Committee on Therapeutic Agents and have served in the past for 15 years on the editorial board of "Diabetes", the official journal of the American Diabetes Association. In addition, I have served on one of the review research study sections of the National Institutes of Health and have been a special consultant in diabetes for the National Institute of Arthritis and Metabolic Diseases and the National Eye Institute. I have served also as a consultant for the Veterans' Administration in the midsixties for a comparative study of the effect of two of the oral hypoglycemic agents in a controlled clinical trial. Recently I was appointed as a member of the Policy Advisory Board of the NEI (National Eye Institute) cooperative study of the effect and value of photocoagulation in the treatment of diabetic retinopathy. It is thus clear that I am qualified by experience, both scientifically and clinically to judge the status of our present modes of therapy for diabetes and to evaluate the needs of the several million diabetic patients in this country.

THE IMPORTANCE OF DIABETES IN THE TOTAL PICTURE OF HEALTH CARE

With the increasing life expectancy of our people, the problem of diabetes has been pushed to the foreground in the last quarter of a century. Before 1921, the year of the discovery of insulin, diabetes was a uniformly fatal disease except for the mildest of cases. A youngster who developed diabetes before 1921 could be expected to live an average of only 1½ years. Even in the older age group, where diabetes tends to be less severe, mortality was significantly increased. The availability of insulin eliminated the symptoms and disabilities due to the defect in sugar, glucose, metabolism and despite the slight inconvenience of taking a daily injection enabled the vast majority of diabetics to lead a reasonably normal and active life. We can state that diabetics who develop this disease in their younger years, under 30, almost always require insulin to achieve a state of comparative well-being, but approximately only one half of older patients need insulin for control of symptoms. With the discovery of simpler and more economical means of detecting diabetes more of the early and milder cases, particularly in the older age groups, have been diagnosed. It should be emphasized that 90 percent of all diabetics are over the age of 40 when first found and that the majority of this older group are obese by any standards.

With the prolongation of life due to the availability of insulin it became evident after a period of 10 to 20 years that very serious problems were emerging in the diabetic population. Directly proportional to the duration of the disease vascular complications involving the small vessels of the eye and kidney and the larger vessels in the heart and periphery became the vexing problem for both patients and

physicians. The small vessel disease led to blindness to such an extent that diabetic retinopathy is now the second leading cause of nontraumatic blindness in the United States; the renal damage is now the cause of death in 10 percent of all diabetics and 50 percent of the younger onset patients. With regard to the larger vessels, coronary artery disease, myocardial infarction, occurs two to four times as frequently in diabetics compared to age-sex matched nondiabetic populations. Peripheral vascular disease leads to gangrene with all its dire consequences. Today the major problem in diabetes is not the ability to control the blood sugar level but one of failure in preventing the development or amelioration of these crippling and death-dealing vascular complications.

CONCEPTION, INCEPTION AND RECEPTION OF THE UNIVERSITY GROUP DIABETES PROGRAM, UGDP

For the first three or four decades after insulin was discovered, many physicians believed that stricter control of the blood sugar level was the key to preventing or ameliorating these vascular problems. It became increasingly clear, however, that these complications were occurring in all diabetic populations, regardless of the success or failure of blood sugar regulation. By the end of the fifties it became evident to me and to several of my colleagues who were expert in this field that the question of the relation of blood sugar control to the vascular complications could only be resolved by carrying out a controlled clinical trial. After 2 years of planning the UGDP was launched with the financial support of the NIH. Since the oral hypoglycemic agents had just been introduced for clinical use in 1957 in this country it seemed also appropriate to include these agents to determine whether they had some inherent property that might be beneficial for the vascular disease. I must say for the record that the NIH seemed to be particularly concerned with the need for evaluating the long term effects of using a noncurative chemical in the treatment of a chronic disease. FDA approval at that time meant only that no significant short term deleterious side effects were detectable, but it was quite obvious that the use of foreign chemical agents for the rest of one's life required careful study of possible long term side effects.

Dr. Klimt will describe in brief detail the design and execution of the UGDP study so that I will not dwell on this aspect.

It should be pointed out that in the early pharmacologic studies on these drugs it was obvious that lowering of the blood sugar represented only a small part of the total effects, and that many organs and tissues responded, sometimes unfavorably, to the oral agents. Once the drugs were made available for clinical use, however, these other effects were essentially forgotten, or worse still, disregarded. Dr Prout will undoubtedly discuss in detail this aspect.

It took 6 years before the last of the approximately 1,000 patients were entered into the study. Two or 3 years later it became clear that those patients in the tolbutamide group were suffering from an increased mortality rate compared to the other three treatment groups, placebo and the two insulin groups. This trend was monitored carefully, and as the differences approached statistical significance, outside statistical consultants were invited to review and assess all the

available data. These discussions went on for approximately 9 months before the final decision was made to discontinue the use of tolbutamide in the study. It was clear that the decision was made to a large extent on the rules laid down in the Kefauver amendment to the Food and Drug Laws in the early sixties which was passed as a result of the thalidomide disaster. This simply stated that drugs should be used by the public only if the benefits exceeded the risks, and that this evaluation should be made on the basis of scientific studies rather than anecdotal clinical reports or impressions. For this reason we could not in all good conscience continue to treat patients in the study with oral agents until a larger excess of deaths developed. As you have heard, the decision was not made hastily but after long and careful deliberation.

All of our material was turned over to the FDA as soon as the trends became evident. There was no action by that agency for almost a year until 1½ months before the official presentation of our data to the American Diabetes Association in St. Louis in June 1970. I personally called the FDA early in May 1970, and called attention to the fact that they had not acted on the results of the study and that the American public would look to them for some guidance. It should be evident to all that we, as scientific investigators, had no right or power to determine the clinical use of these agents; our only function was to provide the scientific foundation for making the final decision.

In closing, I must say that the system now operating in this country is not optimal for translating scientific research into clinical usefulness for the benefit of our people. Factors such as the profit motive of drug companies and the problem of postgraduate medical education, which is now largely dominated by the so-called educational programs of the drug industry, using detail men and throwaway literature, certainly account for the fact that the results of the UGDP study have not been accepted by the practicing medical profession. Even worse, without any regulation by the FDA, with not even a descriptive labeling, the use of these agents has not been significantly lessened except perhaps in some university centers. Dr. Chalmers, Dr. Prout, and Dr. Davidson will document in more detail this most serious problem in American Medicine.

Senator NELSON. Thank you, Doctor.

Were the New Drug Applications for these agents, tolbutamide in particular, approved before or after the University Group Diabetics Program study?

Were they submitted after or before?

Dr. MILLER. Before.

Senator NELSON. But I thought you said in your statement they did not come into use until 1957.

Dr. MILLER. In 1957 the sulfonylurea agent, tolbutamide (Orinase), was approved by the FDA, based on the fact that short-term clinical trials demonstrated a blood-sugar lowering effect (albeit small) in adult-onset stable type diabetics; 90 percent of these older diabetics are obese, and a large fraction are without symptoms. Before the introduction of the oral hypoglycemic agents half were treated with diet alone while the other half required insulin for control. At that

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

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

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

Senator NELSON. What study was that?

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

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

Thank you very much for your presentation.

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

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

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

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

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

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

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

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