# Controversy over Study of Diabetes Drugs Continues for Nearly a Decade

## *A bitter altercation raises major issues facing clinical scientists and regulatory agencies*

*In the next few weeks, the Food and Drug Administration will decide whether all oral anti-diabetes pills should carry warning labels saying they are toxic. And in the near future, the U.S. Supreme Court will decide whether to hear arguments that data from federally funded research should be publicly available. These are issues arising directly from a highly controversial clinical trial—a trial whose results may portend the kinds of difficulties facing supporters of the large crop of clinical trials now being conducted.*

The past decade has been a time of bitter debate and accusations within the diabetes community, a time when eminent scientists and physicians became sharply polarized in their opinions on a subject that is, at best, murky. The altercation has been so vituperative that an authority in the field calls it "the most shameful in the history of modern medicine."

The dispute is over the use of oral anti-diabetes drugs. These pills, which lower blood sugar, are popular with doctors and patients and are extremely profitable for the drug companies. But administrators of a major clinical trial, called the University Group Diabetes Project (UGDP), concluded 10 years ago that the drugs are not efficacious and that they are probably toxic as well. This conclusion has since been sharply attacked by one group of physicians and scientists and evangelically promoted by another and the trial itself is the focus of a heated debate.

The tale of the UGDP is more than just the story of an internecine fight. It raises major issues facing clinical scientists and regulatory agencies today. These include the way people behave when their beliefs are challenged by data that are themselves open to challenge, the role of the Food and Drug Administration (FDA) in taking a stand on controversial issues, the proper treatment of adult-onset diabetics, the public's right to access to data from government-funded studies, and the ultimate value of clinical trials.

The principal figures in the UGDP story are:

- The FDA, which has, by its actions, fanned the fires of the debate. In 1968, the FDA immediately endorsed the UGDP's conclusion that one of the oral anti-diabetes drugs might be toxic and decided to put warning labels on all such drugs. Although court challenges have thus far prevented the agency from going ahead with its requirement for warning labels, it has as yet refused to budge an inch in its position that the labels are necessary.
- The Committee for the Care of the Diabetic (CCD), a group of diabetologists who banded together to contest the FDA's endorsement of the UGDP. The CCD is an impassioned and sometimes strident group which is totally convinced that the UGDP must be discredited.
- Christian Klimt, a biostatistician at the University of Maryland Medical School in Baltimore, who was in charge of the computer coding and analysis of the UGDP results. He has thus far refused to make the study's raw data available and has been accused of manipulating them.
- Angela Bowen, a diabetologist now in private practice in Olympia, Washington, and formerly a principal coinvestigator in the UGDP. Bowen resigned from the study in part because of Klimt's failure to release patient records. She has played a key role in making and publicizing allegations about Klimt.

The UGDP began in 1961 as a major trial to answer questions of vital importance to the country's 2.5 million adult-onset diabetics: What is the value of lowering blood sugar concentrations? and, Are oral anti-diabetes agents a safe and effective way of doing it? These agents, which were introduced in the 1950's, were immediately welcomed by some physicians because they enabled patients to lower their blood sugar level without insulin injections and to avoid the unpopular and often unsuccessful diets prescribed for overweight diabetics. Other physicians questioned the usefulness of the drugs, arguing that it was not at all clear that lowering blood sugar prevents the complications of diabetes and that perhaps overweight patients whose only symptom is elevated blood sugar should just be urged to diet. (Most adult-onset diabetics are overweight and weight loss alone often controls their diabetes.)

The UGDP was to be the world's biggest and best-designed clinical trial. As one of the first large-scale trials ever conducted, it served as a model for the large crop of clinical studies that followed it. When the UGDP began, the general feeling in the scientific community was enthusiasm for its methods and goals. Only later was this enthusiasm to sour and the study to come under attack.

The trial was conducted at 12 university diabetes clinics* which recruited a total of 1027 volunteers. The study's design stipulated that the volunteers be adult-onset diabetics with expected lifespans of at least 5 years. The data from the clinics were sent to a coordinating center run by Klimt for analysis.

At the start of the trial, the patients were randomly divided into four groups: those who received a placebo, those who received a fixed dose of insulin, those who received a variable dose of insulin depending on their blood sugar level, and those who received a fixed dose of tolbutamide, an oral anti-diabetes drug. All patients were also given a low-calorie diet. Two years later, phenformin, another oral anti-diabetes drug that had just come on the market, was added to the study.

**Are oral anti-diabetes drugs a safe and effective way of lowering blood sugar?**

From 1961 to 1968, UGDP data were

*The clinical centers were: Appalachian Regional Hospital (West Virginia University School of Medicine), The Jewish Hospital and Medical Center of Brooklyn, The Johns Hopkins School of Medicine, Massachusetts General Hospital, Rush-Presbyterian-St. Luke's Medical Center in Chicago, University of Alabama Diabetes Hospital, University of Cincinnati Medical Center, University Hospitals of Cleveland, University of Minnesota Hospitals, University of Puerto Rico School of Medicine, The Virginia Mason Research Center in Seattle, and the Washington University School of Medicine.


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gathered and analyzed. At the same time, the oral anti-diabetes drug market boomed. According to Sidney Wolfe, head of Ralph Nader's health research group, American doctors wrote nearly 17 million prescriptions for the drugs in 1968. More than 50 percent of this market was captured by the Upjohn Company with its tolbutamide sold under the name Orinase. Thus the drug companies, and Upjohn in particular, had a great deal to lose if the anti-diabetes agents did not make a good showing in the clinical trial.

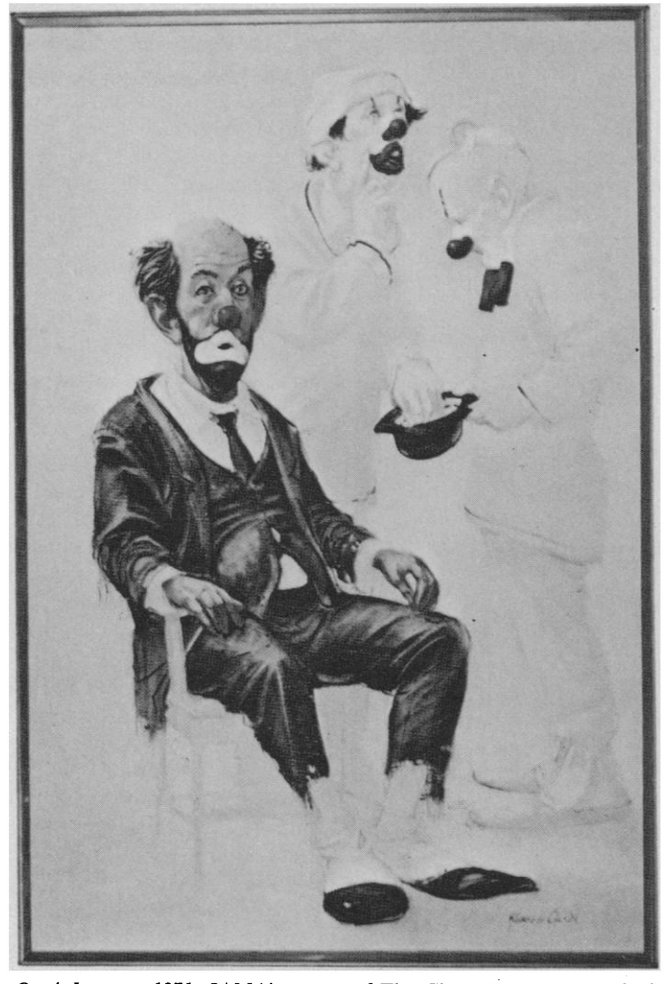
The first shock to the drug companies and to doctors who had been enthusiastically prescribing the oral drugs came in 1970. On 20 May, news was leaked to Wall Street that tolbutamide was to be withdrawn from the UGDP because it did not seem to be efficacious and because there was reason to suspect it caused cardiovascular complications. The reaction was immediate. The price of Upjohn's stock dropped dramatically and doctors switched patients from Orinase to Diabinese, a chemically similar drug made by Pfizer, Inc., or to DBI, the brand name for phenformin then made by Revlon, Inc.

The news from Wall Street puzzled the medical community. After all, tolbutamide was not a new drug and no one had ever before reported that it was toxic. Physicians with diabetic patients began to question the reasons for withdrawing the drug. The tolbutamide patients did not have a higher death rate than those in the other groups—they just had a higher proportion of deaths from cardiovascular causes. Physicians began to ask how the UGDP scientists determined the causes of death, and how the data were analyzed.

Despite these doubts about the validity of the UGDP's conclusions, the FDA, against the advice of its own advisory committee, acted swiftly on the study's results, even though it had not actually seen the UGDP data. Two days after the news about tolbutamide broke on the Dow-Jones ticker, the FDA endorsed the study's conclusions. Three days after that, the agency announced that warning labels would be put on all oral anti-diabetes drugs. Yet the UGDP results still had neither been published nor presented to a scientific audience.

Three weeks later, the UGDP data were presented and debated at an American Diabetes Association (ADA) meeting at which time the ADA endorsed the study's conclusions. But the results were not to be published for another 6 months.

By the time of the ADA meeting, the debate over the UGDP was focused on the question of whether tolbutamide was toxic. The question intended to be answered by the UGDP—whether control of blood sugar prevents the complications of diabetes—was ignored. It turned out that it was never to be answered because, in most of the patients, blood-sugar levels had been poorly controlled.



*On 4 January 1971,* JAMA*'s cover of* The Clown Doctors, *in which a dispute about therapy is resolved by a draw from a hat, captured the continuing quandary about treating diabetics. [Courtesy Robert Owen and Americana Galleries, Northfield, Ill.]*

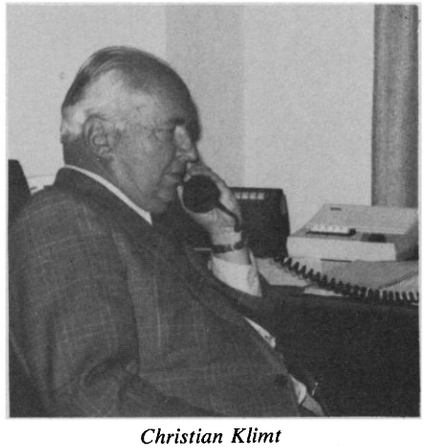
As months went by after the news about tolbutamide was reported, questions about the UGDP became louder and more persistent. The FDA stuck by its original decision to put warning labels on the drug.

Soon the simmering discontent of some UGDP investigators about the conduct of the trial and its conclusions came to the surface. In November 1970, Bowen and Robert Reeves, who were UGDP investigators at the Seattle clinic, resigned from the study. They explained that 7 of the 20 UGDP investigators had disagreed with the decision to withdraw tolbutamide. (None of the others resigned.) But Max Miller of Case Western Reserve University, who was chairman of the UGDP, insisted that the decision to withdraw the drug be made to appear unanimous, arguing that otherwise the conclusion would not be accepted by the medical community.

This demand for a false show of unanimity disturbed Bowen and Reeves. They were already suspicious of Klimt because, they said, he had at first denied and then admitted that at the time the study began he had been a paid consultant to U.S. Vitamin Pharmaceutical Corporation, a drug company with a stake in the trial's results, and had continued as a consultant until shortly before his appointment to the FDA. (Phenformin was originally sold by U.S. Vitamin. When tolbutamide was removed from the study, U.S. Vitamin more than quadrupled its sales of phenformin. Then U.S. Vitamin was taken over by Revlon.)

Klimt acknowledged to *Science* that he accepted $5000 from U.S. Vitamin during the years 1968 to 1970, but expressed astonishment that he could be accused of manipulating data for such a paltry sum.

Also in November of 1970, the CCD was formed by a group of 40 leading diabetologists who had decided to join forces in combating the UGDP. They retained a Boston lawyer named Neil Chayet, who specializes in medical-legal matters, to prevent the FDA from going ahead with its labeling proposal and to gain access to the UGDP's patient rec-



*Christian Klimt*

ords. Chayet has, by a number of legal maneuvers, been able to delay implementation of the labeling requirement for the past 8 years.

The CCD still exists, now numbering about 250 diabetologists. (In contrast, about 2500 physicians are members of the ADA.) Its efforts have played a large role in keeping the UGDP controversy alive—so large a role that the study's supporters commonly preface their remarks about the CCD's arguments by saying that the members of the CCD, and Chayet in particular, are funded by Upjohn. Chayet has denied under oath that Upjohn has ever paid him for any work he did for the CCD.

Within the first year after tolbutamide was withdrawn from the UGDP the scene was set for the continuing dispute. Klimt's integrity was impugned, the CCD was formed, and the study's critics and supporters began to be polarized. But the study was not over. On 17 May 1971, nearly 1 year to the day after the tolbutamide story broke, news was leaked to Wall Street that phenformin too was to be withdrawn from the study. The UGDP data indicated that the diabetics taking phenformin suffered excess mortality from all causes. When reports of phenformin's imminent demise came over the Dow-Jones ticker, investors rushed to unload their Revlon stock. Revlon took a beating and was forced to stop trading on its stock that day.

When phenformin was withdrawn from the UGDP, the furor over the study and its conclusions knew no bounds. Supporters of the study were becoming increasingly strident. The debate had turned ugly, had turned into a duel in which the weapon of choice was the ad hominem argument. Not only did the critics question Klimt's honesty, but the supporters accused the CCD and other critics of being drug company whores.

At least one critic of the UGDP was even warned that his criticisms and his associations with Upjohn might destroy his academic career. Stanley Schor, who at the time was head of the statistics department at Temple University, was paid by Upjohn to critique the UGDP. He says he quite honestly found faults in the study's design and analysis. Schor had much experience as a consultant, both for industry and for the government. "But this was the first time I ever agreed with a drug company and disagreed with the FDA," he says

As a result of his role in criticizing the UGDP, Schor was accused of having been bought by Upjohn. He reports that a UGDP administrator said to him, "You have an outstanding scientific reputation. You'd better divorce yourself from these people [the study's critics] or you'll be finished." Schor says that "a lot of peculiar things" happened after he criticized the study. He subsequently lost his consultantship at the FDA and left Temple University. He now works for Merck Sharp & Dohme.

The UGDP debate was largely limited to the United States. For example, Germany, which was just recovering from the thalidomide tragedy, was greatly concerned that the drugs might be toxic. Shortly after tolbutamide was withdrawn, a meeting was held in Dusseldorf to discuss the UGDP. After hearing both sides of the debate, the German government decided that no action was required to restrict sales of the drug or warn doctors of its toxicity. The Canadian, British, and Swedish governments also considered the UGDP report no basis for action.

In what turned out to be a futile attempt to answer the persistent angry questions about the UGDP, Robert Q. Marston, who was then director of the NIH, asked that the Biometric Society, which is a professional society of statisticians, appoint a committee to review the UGDP. The committee was appointed in 1971. For 4 years it deliberated, talking to the study's critics, journeying to the coordinating center and various UGDP clinics, and considering other studies that did not support the UGDP's conclusions. Finally it published a report more or less vindicating the UGDP.

The Biometric Society report is a carefully worded document that defended clinical trials in general and answered some questions about the trial but nonetheless failed to satisfy the study's critics.

One of the most troublesome accusations about the UGDP which the Biometric Society committee considered is that the patients given tolbutamide had more risk factors for heart disease than patients given placebos. These are conditions such as high blood pressure and high concentrations of cholesterol in the blood, that increase the likelihood that a person will have heart disease. If these patients were at greater risk to begin with, the increased incidence of cardiovascular deaths in this group could reflect that fact and not the effects of tolbutamide.

In response to this criticism, the committee used a statistical model to decide how many cardiovascular deaths would be expected in a population with the risk factors of the tolbutamide group. It determined that far fewer deaths would be expected than actually occurred.

A second problem involves data analysis. Critics object to the decision to consider each patient a member of the treatment group to which he was assigned, regardless of whether he adhered to that treatment. They point out that only 26 percent of the UGDP patients faithfully stayed with their originally assigned treatment.

In order to decide whether patients' lack of adherence to their assigned treatments altered the UGDP's results, the Biometric Society committee corrected for lack of adherence by two different statistical methods. Both methods yielded results that confirmed the original conclusion that tolbutamide causes excess cardiovascular deaths.

Still another often-cited criticism of the UGDP's findings is that there may have been some bias in assigning causes of death. As Alvan Feinstein of Yale University points out, many cases of cardiovascular disease are undetected during life and are only discovered at autopsy. Therefore, the more patients that are autopsied, the more likely it is that deaths will be assigned to cardiovascular causes. Fifty percent of the tolbutamide patients that died were autopsied as opposed to only 29 percent of the patients assigned to placebo or insulin. According to Feinstein, the statistical significance of the increased cardiovascular deaths in the tolbutamide group would vanish if only three deaths in each group were reassigned to different causes.

The Biometric Society conceded this point to the critics, saying that "some reservation about the conclusion that oral hypoglycemic agents are toxic must remain."

The Biometric Society report was published in the *Journal of the American Medical Association* along with an editorial by Thomas Chalmers, who is now dean of Mount Sinai Medical School and chairman of the UGDP advisory committee. (He was then at NIH.) In his editorial, Chalmers estimated that the oral anti-diabetes drugs cause an additional 10,000 to 15,000 deaths each year in the United States. He obtained this estimate by interpreting literally the statistically insignificant trend toward more deaths in the UGDP patients taking tolbutamide. Even though his figures are controversial, Chalmers sticks by them.

While the arguments over the UGDP's design and data analysis were going on, the CCD had stalled the FDA by bringing to court the issue of whether the agency could put its intended warning label on all oral anti-diabetes drugs. The committee's argument was that any warning label should present both sides of the issue. It should reflect the controversy over the UGDP and take note of other studies that do not confirm the UGDP's conclusions. Lawyer Chayet contended that the FDA's own fair balance regulation required it to do this. The fair balance regulation was designed to prevent companies from making wild and extravagant claims for their products in package inserts without explaining serious differences of opinion and qualifications when they existed. When the First Circuit Court of Appeals in Boston sent the case back to the FDA asking that the two parties resolve their differences, the FDA modified its fair balance regulation as it applied to the government. Now only the drug companies, and not the FDA, must comply with the regulation.

The FDA tried again to put warning labels on the drugs, holding a hearing in August of 1975 to discuss its proposed labels. At the hearing, two sensational issues were brought up—one legal and the other personal. The legal issue may now be the subject of a Supreme Court case. The personal issue is the subject of an FBI investigation.

The legal question was brought up by Chayet. He attempted, on behalf of the CCD, to obtain the patient records from the UGDP. He explained that the committee's request to look at the raw data had "been shuttled from agency to agency, ignored or denied." Finally, on 7 August 1975, Chayet received a letter from Theodore Cooper, then Assistant Secretary of HEW. Cooper wrote, "I have made further extensive inquiries of both the National Institutes of Health and the Food and Drug Administration. Neither agency has ever had the raw data in its possession."

Cooper went on to explain that the data apparently belong to Klimt. "I am informed," Cooper wrote, "that the raw data is [sic] now in the form of microfilm and is stored in a Maryland bank vault. . . . While I cannot, therefore, suggest it as a fruitful approach, it would appear that further efforts on your part should be directed to Dr. Klimt."

Chayet has as yet been unable to obtain the data from Klimt. Jerome Cornfield, a statistician at George Washington University who strongly defends the study, says it is only proper that Chayet be denied access to the UGDP data. The CCD, Cornfield explains, only wants to see the data to denigrate the study.

Nonetheless, Klimt explained to *Science* that it has always been his policy that the data should not be released until it had all been analyzed and the analyses published. Now that nearly all the UGDP reports are out, he says, the data are available. The only exceptions are the data pertaining to a monograph on insulin use, which is still being prepared.

Chayet maintains that all the data are not available. The patient records and the forms filled out at the clinics are still sequestered, he says. He says he is taking the issue of whether they should be available to the U.S. Supreme Court, explaining that he believes that in a government-funded study such as the UGDP in which major policy decisions hang on the data, it is inappropriate that neither NIH nor the FDA saw the data. (He says he has some qualms about whether all data from federally funded research should be publicly available, however, because if they are, researchers could be subject to harassment.)

The most inflammatory testimony at the 1975 hearing was Bowen's. She questioned the "personal integrity and scientific honesty" of Klimt, linking his consultantship at U.S. Vitamin to the UGDP's decision to withdraw tolbutamide. She explained that "it became increasingly difficult for investigators to voice legitimate scientific concerns in the semiannual meetings of the UGDP. The entire project sort of began to assume a vendetta-like quality against the manufacturers of tolbutamide."

Bowen's testimony stunned the audience at the FDA hearing and led the FDA to institute an audit of the beleaguered study. The audit results were recently made public. Once again, the UGDP was vindicated and once again the critics remain unsatisfied.

At the time the audit was being conducted, FDA officials asked the Inspector General of HEW to look into Bowen's suspicions about Klimt. Chayet explains that, in early 1978, J. Richard Crout, who is head of the FDA's Bureau of Drugs, asked Bowen to come to the FDA and discuss her suspicions. Bowen came, bringing Chayet with her. Following his conversation with Bowen and Chayet, Crout allegedly took steps that resulted in HEW's investigation. (Crout refused to comment on this matter.)

In January 1979, the Inspector General turned the case over to the FBI. William Rhodes of the Baltimore office of the FBI will only say that the statute under which the agency claims jurisdiction is bribery and that it is investigating whether there is any substance to allegations involving Klimt and the UGDP.

Klimt protests that he is innocent and that the FBI investigation is just one more example of the harassment he has been subjected to for the past 8 years. He says he did not even know of the FBI's involvement until *Science* mentioned the matter.

*Neil Chayet*

Critics say that their qualms about the sequestered data are increased by some patient records that have recently been released. These records, previously held by Klimt, were turned over to the FDA when the agency was investigating a charge by Wolfe that phenformin is an imminent hazard to human health. As soon as it learned the FDA had these records, the CCD obtained them through a Freedom of Information Act request. Then Nathaniel Horowitz, a writer for the *Medical Tribune*, publicized the records in the newspaper. (The *Medical Tribune* had been running a series of articles critical of the UGDP.)

The study's critics were horrified by

the evidence of patient mismanagement at the clinics, as revealed in the patient records. For example, some patients with malignant hypertension were untreated, a woman with a preexisting kidney failure and sickle cell anemia was given phenformin (the drug was specifically counter-indicated in her case), and a man with normal blood sugar was given insulin.

In addition to the patient mismanagement, the UGDP records reveal that data were frequently erroneously recorded. This sloppiness in treating patients and recording data is passed off by UGDP supporters who say that a few errors are inevitable in a study the size of the UGDP, and that it is necessary to consider the study as a whole. They point out that, according to the FDA audit, the errors and discrepancies in recording and analyzing data do not alter the UGDP conclusions.

Supporters of the UGDP commonly say that the study's critics are intellectually and emotionally unable to accept the fact that treatment of symptomless adult-onset diabetics does no good. Both Chalmers and Thaddeus Prout, a UGDP administrator from Johns Hopkins University, draw an analogy with a large-scale trial on treatment of high blood pressure that was conducted at about the same time as the UGDP. This study, directed by Edward Freis of the Veteran's Administration Hospital in Washington, D.C., purportedly showed that anti-hypertension drugs prevent deaths and complications of hypertension. But, say Prout and Chalmers, Fries' study was no better than the UGDP. Yet his study's results were immediately accepted and Freis won a Lasker Award.

The implication is that there is a widespread tendency in the clinical and research communities to accept findings that drugs are useful and to reject findings that drugs are useless. Freis, on the other hand, says his study is not at all comparable to the UGDP. It answered the original questions it was designed to answer and there was never any doubt about the statistical analysis and significance of its results.

Casting aspersions on the motives of the UGDP critics, however, cannot stem the increasing tide of objections to the study. Recently, Charles Edwards, the former FDA commissioner who accepted the first UGDP results and proposed the warning label, said that he made a mistake in listening to statisticians and not looking at the study's quality control. Edwards, who is now President of Scripps Clinic and Research Foundation, says, "The UGDP was a bad study. Why can't anyone admit that?"

On the other hand, Paul Meier of the University of Chicago, who was a member of the Biometric Society committee, says the UGDP is no worse than any other clinical trial. It's just that no one before had ever seen so much data from a trial. If Meier is correct, what does that say about clinical trials in general? Should their quality control be improved and, if so, how? How much money, time, and resources should be devoted to them?

The FDA has not yet given up its battle to put warning labels on all oral anti-diabetes drugs. It recently proposed a label and planned to accept comments until 15 January 1979. Now, at the request of the ADA, which recently took back its original endorsement of the study's conclusions, the FDA extended its comment period until 15 March. But the warning section of its proposed label still does not reflect the scientific controversy. Perhaps, as Edwards says, this is an issue in which the FDA should not intervene, should not try to decide in the face of such a dispute whether the UGDP's conclusions are valid.

It has been rumored that the FDA may compromise on its warning label by restricting the warning to tolbutamide. Prout believes such a restriction would be a sellout because it would allow drug companies to profitably market their new anti-diabetes drugs in this country. However, Edwards and others point out that it is hard to justify extending the warning to all anti-diabetes drugs. Even Klimt says he could not scientifically justify such an extension. ("It's not my fault if the FDA over-interpreted our data," he told *Science*.)

Some medical scientists think that the UGDP battle is winding down—that the ADA's change of mind about the study means it is discredited by all but its most strident supporters. They note that now the American Medical Association says it is reassessing its position in support of the UGDP and that the comments received by the FDA on its warning label proposal are overwhelmingly critical of the UGDP. Of course, the debate will not end until the warning label controversy is resolved. This will be the final decision in a fight that, like a bad boxing match, has no sharp punches, no telling blows, no display of finesse—just a lot of clinching, shouting, glancing punches and, finally, desultory pats.

—GINA BARI KOLATA

*Next week, a story on blood sugar and the complications of diabetes will appear in Research News.*

## OTA Director Resigns

After only a year in office, Russell W. Peterson, the director of the Office of Technology Assessment (OTA), has announced his resignation.

Peterson, OTA's second director in 5 years, is departing just as the embattled agency received a fresh wave of criticism (*Science*, 23 February). He will become president of the National Audubon Society on 1 April.

"I am reluctant to leave OTA," Peterson says, "but find an unsolicited offer to become president of the National Aubudon Society too attractive to resist. The varied experiences I have had in private and public life have led me to prefer an advocacy role rather than an advisory one."

Peterson also may have been dismayed by the reluctance of OTA's congressional advisory board to express full support for his grand list of research priorities first issued last September. The advisory board also refused to endorse his 1980 budget proposals, which called for major expansion and additional hiring in a time of fiscal austerity.

Finding a new director may not be that difficult, according to congressional staffers; the files of the last search committee are still warm.

## USC President Resigns Amid Campus Quarrel . . .

Buffeted by a controversy over ties between the University of Southern California (USC) and several nations in the Middle East, the president of the university, John R. Hubbard, has announced his resignation, to be effective in 17 months.

Hubbard, who has been president of USC since 1970, had pledged several years ago to step down after a decade in office, and said his announcement was unrelated to criticism of his role in questionable financial arrangements for a Middle East study center at USC. The arrangements would have permitted extraordinary outside control of the center by a group of businessmen that trade with Middle Eastern Arab nations (*Science*, 2 February). Other well-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