Pictured left to right: Tom Chalmers, Jerry Cornfield, Thad Prout, Chris Klimt, Max Miller

The UGDP

The project that was to become the University Group Diabetes Program (UGDP) was born of a question to Max Miller (University Hospitals of Cleveland; UGDP study chair) by a Congressman in the late 1950s.

The Congressman's daughter had just been diagnosed with type 2 diabetes and placed on Orinase® (tolbutamide) for control of blood sugar. The Congressman wanted to know if blood sugar control was beneficial in reducing the complications of diabetes. Miller's answer was that no one knows because there have not been any trials to address the question.

The question galvanized a small cadre of people to set about organizing the UGDP.

The trial spanned 21 years. Funding started in 1960 and ended in 1981. The first patient was enrolled February 1961. Enrollment ended five years later; February 1966. The last followup examination was done August 1975.

The trial was placebo-controlled, partially masked, and randomized. The treatments tested and numbers enrolled are as below.

Enrollment and study treatments

No. enrolled	Treatment	Dosage
204	Insulin variable (IVAR)	As much insulin (U-80 Lente Iletin or other insulins) per day, as required to maintain "normal" blood glucose levels
210	Insulin standard (ISTD)	10, 12, 14, or 16 units per day, depending on person's body surface
205	Placebo (PLBO)	Placebo (lactose) tablets or capsules similar to those used for the tolbutamide or phenformin treatments
204	Tolbutamide (TOLB)	3 tablets per day, 0.5 gms of tolbutamide/tablet
204	Phenformin (PHEN)	1 capsule per day during first week of treatment, thereafter 2 capsules per day; 50 mgs phenformin per capsule
1,027	**Total**	

The first results came in 1970 in relation to a decision to stop the use of tolbutamide (Orinase®):

the findings of this study indicate that the combination of diet and tolbutamide therapy is no more effective than diet alone in prolonging life. Moreover, the findings suggest that tolbutamide and diet may be less effective than diet alone or diet and insulin at least insofar as cardiovascular mortality is concerned. For this reason, use of tolbutamide has been discontinued in the UGDP. (Diabetes **1970**; 19(Suppl 2):789-830)

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All told the group produced eight publications:

1. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes: I. Design, methods, and baseline characteristics. Diabetes **1970**;19 (suppl 2):747-783.
2. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes: II. Mortality results. Diabetes **1970**;19 (suppl 2):785-830.
3. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes: III. Clinical implications of UGDP results. JAMA **1971**;218:1400-1410.
4. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes: IV. A preliminary report on phenformin results. JAMA **1971**;217:777-784.
5. A Study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes: V. Evaluation of Phenformin therapy. Diabetes **1975**;24 (suppl 1):65-184.
6. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes: VI. Supplementary report on nonfatal events in patients treated with tolbutamide. Diabetes **1976**;25:1129-1153.
7. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes: VII. Mortality and selected nonfatal events with insulin treatment. JAMA **1978**;240:37-42.
8. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes: VIII. Evaluation of insulin therapy: Final report. Diabetes **1982**;31(suppl 5):1-81.

Before the smoke settled there were Congressional hearings, audits, court cases, and a request for raw data from the trial under the Freedom of Information Act that eventually wound its way to the U.S. Supreme Court.

The UGDP was a defining event in my professional life. It was my first trial. When it was over years later, it was what soldiers say when returning from battle, “I wouldn't care to do it again, but I wouldn't have missed it for anything!”.

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The UGDP, as prevention trials go, was relatively small – only 1,027 patients about evenly divided across five treatment groups – but what it lacked in size it made up by being in the forefront of prevention trials. In the end the principal trouble with the trial was that it produced results the world did not want to hear. When that happens the assumption is that there is something wrong with you, because the world cannot be wrong.

The controversy surrounding the UGDP has been covered by Harry Marks in his book *The progress of experiment: Science and therapeutic reform in the United States, 1900-1990* (Chapter 7: Anatomy of a controversy: The University Group Diabetes Program Study). Details of the study and the controversy are also featured in Chapters 7 and 49, respectively, of the 1st and 2nd editions of my textbooks and chronicled in the Lind Library and the Royal Society of Medicine Journal.

Ask people who have been involved in trials and they almost always mark their involvement as a great learning experience. No exception for me. The UGDP was my first venture into trials. The only thing I knew about trials when signing on with Chris Klimt was what I read in textbooks and the little I learned about them in classrooms.

If you are going to be in a leadership position in a coordinating center you would be well-advised to take courses in understanding group dynamics. I took lots of courses as an undergraduate and while in graduate school, but none having to do with group dynamics. Whatever I knew about that I learned on the farm.

As a boy, I had the job in the summer of rounding up the cows for milking. Without fail, they were in the furthest corner of the pasture.

It did not take long to recognize that my job was easier if I got the boss cow heading home because the others would follow. There was order to how they marched home and how they came in the barn. First the boss then the others in descending order of seniority.

If you come into trials via a coordinating center you will be a stranger in the group and will have to figure out how the group works. To make matters worse in 1960,

biostatisticians were still oddities and coordinating centers were at the dawn of their creation.

So there I am, a shy country boy from Sleepy Eye at my first investigators meeting. A complete set of strangers save for my boss, Chris Klimt. The clinicians were buddies, hobnobbing with one another and there I am on the outside looking in. My immediate challenge is to figure out the dynamics of the group, so I apply what I learned on the farm.

I pay attention to who talks to whom at coffee breaks. Note the order in which people return to the meeting room after breaks and where they sit. Who they look at when they talk, their body postures and facial expressions.

The UGDP investigator group was an unruly bunch. The best that could be hoped at meetings was for no more than three people talking at the same time. If anyone was familiar with Robert's Rules of Order it was not readily apparent and, indeed, when someone attempted to restore order by citing one of his rules, the citation was more likely to produce debate about the rule than order. Yet this same group, when convened by conference telephone, was polite and conversations were orderly, with only one person speaking at a time. This difference in behavior led me to suggest, during a particularly chaotic debate at a meeting of the investigators, that the group retire to their respective hotel rooms and have the hotel operator arrange a conference call.

As often happens, new treatments come along while a trial is ongoing. Indeed, usually the last treatment out of the gate is the "best". So it was when phenformin came into use in the late 1950s. Its mode of action was different than that of tolbutamide and was widely regarded as being virtually "side effect" free. It was seen by a few key players in the UGDP as having great promise. They argued that it was imperative that the study be expanded to include phenformin. Failure to do so, they argued, would render the trial "irrelevant".

The only trouble was that the trial was already underway. Hence, if the treatment was to be added, the sample size would have to be increased and the randomization scheme modified to accommodate the new treatment.

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The accommodations were made, but the treatment was a loser.

The drug has the distinction of being the first and only one removed from the market (1977) by the "imminent hazard provisions" power vested in the Secretary of Health, Education, and Welfare.

Be wary of "miracle" treatments!

A trivial pursuit question: What does Henry Kissinger and the UGDP have in common? Answer later.

The Committee on the Care of the Diabetic (CCD) was formed as a counter to the efforts of the FDA to relabel tolbutamide and other members of the sulfonylurea class of drugs with a black box warning after publication of the tolbutamide results. The committee was organized in the fall of 1970; several months after the tolbutamide results were presented and about when results were published. The Committee's initial effort was to block the label change proposed by the FDA. Later, efforts centered on trying to block removal of phenformin from the market and on efforts to gain access to raw data from the UGDP under the Freedom of Information Act (FOIA).

Chronology of events in the CCD battle

1969	June 6	UGDP investigators vote to discontinue tolbutamide treatment
1970	May 20	Tolbutamide results on Dow Jones ticker tape
1970	May 21, 22	*Wall Street Journal*, *Washington Post*, and *New York Times* articles on tolbutamide results
1970	June 14	Tolbutamide results presented at American Diabetes Association meeting, St Louis
1970	October 30	Food and Drug Administration (FDA) publishes bulletin supporting findings
1970	November	Tolbutamide results published
1970	November	Committee on the Care of Diabetic (CCD) formed
1971	April	Feinstein criticism of UGDP published

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1971	May 16	UGDP investigators vote to discontinue phenformin treatment in UGDP
1971	June	FDA outlines labeling changes for sulfonylureas
1971	August 9	UGDP preliminary report on phenformin published
1971	September 14	Associate Director of National Institutes of Health (NIH) (Tom Chalmers) asks the president of the International Biometrics Society to appoint a committee to review UGDP
1971	September 20	Schor criticism of UGDP published
1971	September 20	Cornfield defense of UGDP published
1971	October 7	CCD petitions FDA commissioner to rescind proposed label change
1972	May	FDA reaffirms position on proposed labeling change
1972	June 5	FDA commissioner denies CCD 7 October 1971 request to rescind proposed label change
1972	July 13	CCD requests evidentiary hearing before FDA commissioner on proposed labeling changes
1972	August 3	Commissioner of FDA denies 13 July 1972 CCD request for evidentiary hearing
1972	August 11	CCD argues to have the FDA enjoined from implementing labeling change before the United States District Court for the District of Massachusetts
1972	August 30	Request to have the FDA enjoined from making labeling change denied by Judge Campbell of the United States District Court for the District of Massachusetts
1972	August	Biometrics Society Committee starts review of UGDP and other related studies
1972	September	Seltzer criticism of UGDP published
1972	October 17	Second motion for injunction against label change filed by CCD in the United States District Court for the District of Massachusetts
1972	October	Response to Seltzer critique published
1972	November 3	Temporary injunction order granted by Judge Murray of the United States District Court for the District of Massachusetts

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1972	November 7	Preliminary injunction against proposed label change granted by United States District Court for the District of Massachusetts
1973	July 31	Preliminary injunction vacated by Judge Coffin of the United States Court of Appeals for the First Circuit. Case sent back to FDA for further deliberations.
1973	October	FDA hearing on labeling of oral agents
1974	February	FDA circulates proposed labeling revision
1974	March-April	FDA holds meeting on proposed label change, then postpones action on change until report of Biometrics Committee
1974	Sept 18-20	Testimony taken concerning use of oral hypoglycemic agents before the United States Senate Select Committee on Small Business, Monopoly Subcommittee
1975	January 31	Additional testimony concerning use of oral hypoglycemic agents before the United States Senate Select Committee on Small Business, Monopoly Subcommittee
1975	February 10	Report of the Biometrics Committee published
1975	February	UGDP final report on phenformin published
1975	July 9, 10	Additional testimony concerning use of oral hypoglycemic agents before the United States Senate Select Committee on Small Business, Monopoly Subcommittee
1975	August	End of patient followup in UGDP
1975	September 30	CCD files suit against David Mathews, Secretary of Health, Education, and Welfare, et al., for access to UGDP raw data under the Freedom of Information Act (FOIA) in the United States District Court for the District of Columbia
1975	October 14	Ciba-Geigy files suit against David Mathews, Secretary of Health, Education, and Welfare, et al., for access to UGDP raw data under the FOIA in the United States District Court for the Southern District of New York
1975	December	FDA announces intent to audit UGDP results

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1976	February 5	United States District Court for the District of Columbia rules UGDP raw data not subject to FOIA
1976	February 25	CCD files appeal of February 5 decision in United States Court of Appeals for the District of Columbia Circuit
1976	October	FDA Endocrinology and Metabolism Advisory Committee recommends removal of phenformin from market
1977	March 8	United States District Court for the Southern District of New York rejects Ciba-Geigy request for UGDP raw data
1977	April 22	Health Research Group (HRG) of Washington, DC, petitions Secretary of HEW to suspend phenformin from market under imminent hazard provision of law
1977	May 6	FDA begins formal proceedings to remove phenformin from market
1977	May 13	FDA holds public hearing on petition of HRG
1977	July 25	Secretary of HEW announces decision to suspend New Drug Applications (NDAs) for phenformin in 90 days
1977	August	CCD requests that United States District Court for the District of Columbia issue an injunction against HEW order to suspend NDAs for phenformin†
1977	September 20	FDA audit report
1977	October 21	CCD request to United States District Court for the District of Columbia for injunction against HEW order to suspend NDAs for phenformin denied†
1977	October 23	NDAs for phenformin suspended by Secretary of HEW under imminent hazard provision of law
1977	December	UGDP announces release of data listings for individual patients
1978	January	Appeal of October 21, 1977 court ruling filed by the CCD in United States Court of Appeals for the District of Columbia Circuit
1978	July 7	Preliminary report on insulin findings published

1978	July 11	Judges Leventhal and MacKinnon of the United States Court of Appeals for the District of Columbia Circuit rule that public does not have right to UGDP raw data under the FOIA. Judge Bazelon dissents'
1978	July 25	CCD petitions United States Court of Appeals for the District of Columbia Circuit for rehearing on July 11 ruling
1978	October 17	Petition for rehearing at the United States Court of Appeals for the District of Columbia Circuit denied
1978	November 14	Results of FDA audit of UGDP announced
1978	November 15	FDA Commissioner orders phenformin withdrawn from market
1979	January 15	CCD petitions the United States Supreme Court for writ of certiorari to the United States Court of Appeals for the District of Columbia Circuit
1979	April 10	Appeal of October 21, 1977 ruling denied†
1979	May 14	Writ of certiorari granted
1979	October 31	UGDP case of Forsham et al., versus Harris et al., argued before the United States Supreme Court
1980	March 3	United States Supreme Court holds that HEW need not produce UGDP raw data; 7 to 2 decision
1982	April	Expiration of NIH grant support for UGDP
1982	November	UGDP deposits patient listings plus other information at the National Technical Information Service for public access'
1984	March 16	Revised label for sulfonylurea class of drugs released'

†Personal communications with Robert F Bradley, Joslin Diabetes Center, Boston (1st chair of the CCD).

It was 13 years after relabeling by the FDA was proposed before it was accomplished.

Special Warning on Increased Risk of Cardiovascular Mortality: *The administration of oral hypoglycemic drugs has been reported to 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 non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (Diabetes, 19 (Supp.2):747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2 ½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of tolbutamide and of alternative modes of therapy. Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure. (Physicians' Desk Reference (PDR); 39th edition; 1985; pg 2,130)

The relabeling was a Pyrrhic victory. By the time it was incorporated in the label, the diabetes world had moved onto other drugs, not of the sulfonylurea class.

The answer to the trivial pursuit question above is that both cases for access to data under the Freedom of Information Act (raw patient data in the case of the UGDP and telephone logs of Henry Kissinger when he was Secretary of State) wound their separate ways to U.S. Supreme Court and were heard together (argued 31 October 1979; decided 3 March 1980). The ruling was that the Act did not apply and, hence, access to Kissinger's telephone logs and to raw data of the UGDP were denied by the Court.

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If you do something like the UGDP, you are going to make mistakes. One that comes to mind is the mixup in clinics as to how they make a key measure – glucose levels.

Persons enrolled into the UGDP had to have a blood glucose sum of fasting, one, two, and three hour values ≥ 500 mg/100 ml to be eligible for enrollment.

Glucose determinations were done locally at the study clinics.

The issue to be settled was whether determinations should be done using blood or serum. After a fair amount of discussion the issue was decided in favor of blood.

Things proceeded uneventfully until, about three years into the study, when an investigator made an offhand remark regarding their method for determining glucose levels during an investigators meeting. Since the method cited was one requiring use of serum, another investigator questioned how the method could be used on whole blood.

"Whole blood? We use serum."

"The protocol specifies whole blood."

"It does?"

And so unfolded the "glucose story" with, ultimately, the discovery that four of the twelve clinics were using serum instead of blood. When the smoke settled, the mistake affected determinations for 280 patients.

The mistake required converting serum values to whole blood equivalents. Since serum glucose values are higher than whole blood values, the conversion resulted in 57 of the 280 patients enrolled at those four clinics having corrected sum GTTs below the diagnostic cut point of ≥500 mg/100 ml for enrollment. (They were counted in results with an explanatory footnote.)

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The tolbutamide mortality excess emerged over time. At first, the difference was just a matter of curiosity, but eventually there were investigators suggesting that the tolbutamide treatment should be stopped because ill-effects.

The trend was evident in results presented at the 1969 spring meeting of study investigators. After considerable discussion, a motion was made to stop tolbutamide. A vote was taken. The motion carried (13 stop; 12 continue).

The voting policy was two votes per center – two for each of the twelve clinics and two for the coordinating center (one vote for the center director; one for the deputy director) – but without any clear policy on proxy votes, “stand in” voters in the absence of the director or deputy director, or even the designation, “deputy director.” The ambiguities were noted when the policy was drafted, but considered not important because voting would be unnecessary in the expectation that major decisions would be by “consensus”. (The only time one can be certain of consensus is in groups of size one.)

After the vote by show of hands, there followed a debate as to who had voting rights, sort of a precursor to the “hanging chad” problem of the 2000 presidential election in Florida.

In the end, the vote was considered too close for action. Investigators agreed to reconvene after additional analyses about a month hence.

Again investigators voted, this time with a slightly larger fraction for stopping than at the first meeting. But still investigators felt uneasy stopping tolbutamide so they opted to meet again a month later.

They voted again, this time only 2 against stopping. With that they stopped the tolbutamide treatment. But the biggest mistake was what happened after voting.

Investigators, early on, agreed to a "publish first, present later" policy in regard to study results. The first test of that policy came after the decision to stop tolbutamide. As often happens with such policies, there was backsliding, with investigators wanting to have their cake and eat it too.

Ultimately, investigators decided in favor of presentation with the expectation of having results published by the time they were presented.

Abstracts were submitted for the 1970 American Diabetes Association (ADA) meeting early in 1970. The pair of papers comprising a separate supplemental issue of Diabetes were submitted about the same time as abstracts to the ADA.

For a time it looked as if the strategy was working but things fell apart in late spring when the manuscripts were returned for revision.

In the end, the two papers appeared in print in November, about five months after the presentation in St. Louis. The intervening time meant that study investigators stood helpless in answering the deluge of criticism following the presentation. The time gap was problematic. Diabetologists were deluged by calls from worried patients concerning the drug they were on. The fact that they had to answer patient's questions without benefit of a publication made them hostile to the study and disposed to ignore the results when they were finally published.

Never made that mistake again – but made new ones. Oh well.