The Trials and Tribulations of the University Group Diabetes Program

The UGDP

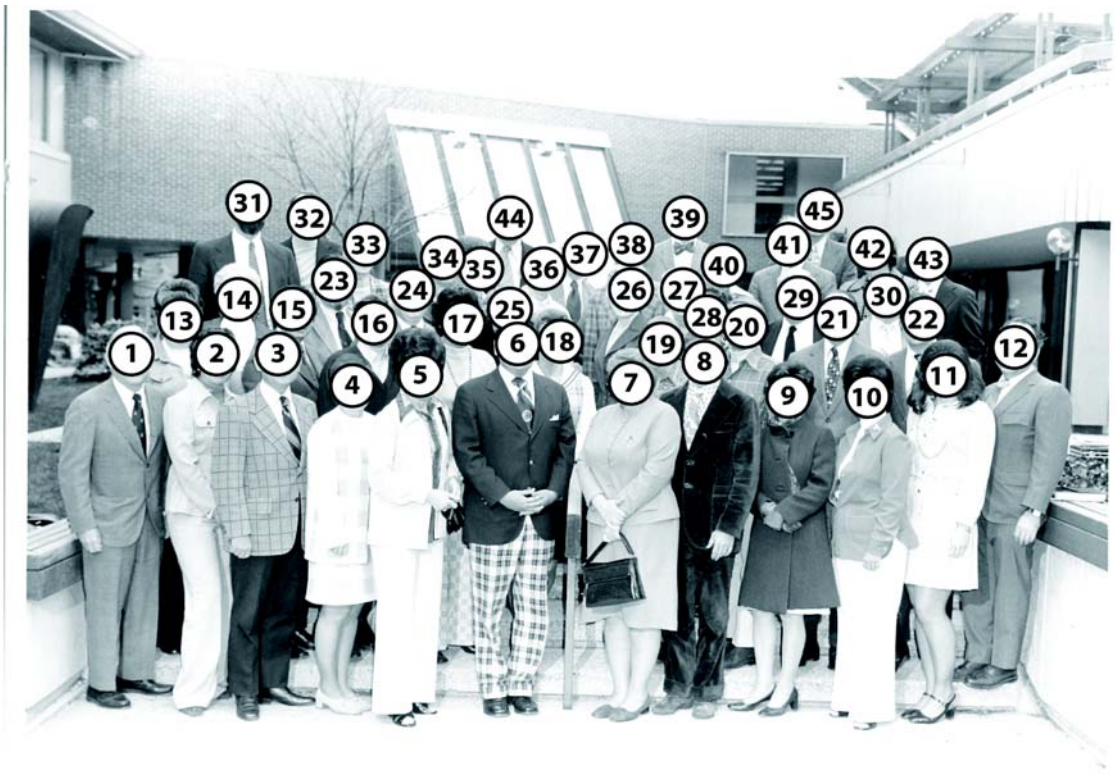
The Trials and Tribulations of the University Group Diabetes Program

The UGDP

Curtis L Meinert

Printed on 24 lb acid free paper

Binding by
The Kelmscott Bookshop
Baltimore



1. Harvey C. Knowles, Jr, MD - Cincinnati
2. Joan Grote - Cincinnati
3. Marvin Levin, MD - St. Louis
4. Suzan Slater - St. Louis
5. Vivian Martin - Cincinnati
6. Kenneth Kreines, MD - Cincinnati
7. Naomi Trauber - New York
8. Maynard Jacobson, MD - Minneapolis
9. Rose Marie Petrucelli, PhD - NIAMDD
10. Lillian Haddock, MD - San Juan
11. Barbara S. Hawkins - Coordinating Center
12. Charles Kilo, MD - St. Louis
13. Barbara Womack - Cincinnati
14. Margarita Valderama - San Juan
15. Paul Sweeney, MD - St. Louis
16. Frank Becker, MD - Chicago
17. Eloise Pernell - Chicago
18. Edith McCulloch - Birmingham
19. Virginia Belcher - Minneapolis
20. Robert K. Osborne, MD - Boston
21. Max Miller, MD - Cleveland
22. Thaddeus E. Prout, MD - Baltimore
23. William Newberry, MD - Cleveland
24. Christian R. Klimt, MD, DrPH - Coordinating Center
25. Shirley Weisenfeld, MD - New York
26. Pat Swanson - Seattle
27. June Pulvermacher - Cleveland
28. Marie Classon - Baltimore
29. Martin G. Goldner, MD - Retired
30. David I. Miller, MD - Baltimore
31. Curtis L. Meinert, PhD - Coordinating Center
32. Gabriel Spergel, MD - New York
33. Margaret J. Albrink, MD - Morgantown, Lipids Laboratory
34. Francisco Aguilo, MD - San Juan
35. Jackie Nash - Coordinating Center
36. Genell L. Knatterud, PhD - Coordinating Center
37. Jacob E. Berman, PhD - University of Minnesota
38. P.C. Kansal, MD - Birmingham
39. Samuel Biem, MD - West Virginia
40. Pat Morris - Boston
41. Thomas Vecchio, MD - Upjohn Company
42. Keatha K. Krueger, PhD - NIAMDD
43. Robert Nielsen, MD - Seattle
44. John Galloway, MD - Eli Lilly
45. Paul C. Davidson, MD - West Virginia

(From left to right) Tom Chalmers, Jerry Cornfield, Thad Prout, Chris Klimt, and Max Miller testifying at Congress on 18 September 1974

Foreword

Way back before there was electricity, when I graduated from Sleepy Eye High, I decided that the farm was the place for me, like Oliver Douglas in Green Acres. So I left the farm and went off to University of Minnesota to become a civil engineer. So I got a BS in psychology.

Fresh with my degree I hired on with Proctor and Gamble to sell toothpaste - until people in biostatistics came calling. The Department of Biostatistics in the School of Public Health at the University of Minnesota had money they were handing out. So, I ended up with a fellowship in biostatistics.

Before I graduated, Chris Klimt, the soon to be head of the Coordinating Center for what was to become the University Group Diabetes Program, came to town on the prowl for a "young biostatistician". My chair, mentor, and professional father, Pete Bearman, gave him four names, mine being one of them.

But I was not interested in jobs until I finished my dissertation, so I did not bother going for an interview, until, that is, I caught hell from Pete Bearman. I said "There is no point in wasting Dr Klimt's or my time interviewing for a job I do not want" - so I went to work on the UGDP.

Before long Klimt and the chair of Epidemiology in the School of Public Health – the academic home for the UGDP coordinating center when the study was formed – had a "meltdown" over a telephone cord. The next thing I know Klimt is moving to the University of Maryland and he wants me to come with him. I say no because I want to finish my PhD - so I go to the University of Maryland.

Being a Midwesterner, I did not find Maryland to be "Home Sweet Home" so I say to my wife "We will stay a few years, but I do not want to wake up dead in Baltimore" - so we stayed.

Foreword

The UGDP begot the Coronary Drug Project and after that there were other begots.

My career as a trialist is accidental, starting with the good fortune of being born so as to grow up with the emergence of clinical trials as a household word. A growth propelled by post WW II prosperity and expanding NIH budgets.

Contents

Preface

The UGDP, or the GD UP as its opponents came to call it, was an investigator-initiated, secondary prevention trial funded by grants from the National Institute of Arthritis & Metabolic Diseases. The purpose was to determine if any of the commonly used treatments for type 2 diabetes were useful in preventing the morbidity associated with the condition.

The trial spanned 21 years. Funding started in 1960 and ended in 1981. The first patient was enrolled February 1961 and the last followup examination was done August 1975. The first publication of results came in 1970 in relation to a decision to stop the use of tolbutamide (Orinase®) in the trial:

> *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)

Before the smoke settled there were Congressional hearings, audits, court cases, and a request for raw data 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 life as a trialist. It was my first trial. When it was all over years later, it was what soldiers say when returning home from war, "I wouldn't care to do it again, but I wouldn't have missed it for anything!".

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 and when that happens the assumption is that

Preface

there is something wrong with you and your trial because, surely, 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).[42] 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.[48,46]

I chose to write this essay before memory fades to blank and as a reminder to budding trialists, running across this down the road, that doing a trial is different than reading about results from a trial in a scientific journal.

Curtis Meinert
Towson Maryland
3 March 2015

To my UGDP colleagues

Center directors (as of January 2015)

Clinic directors

Thaddeus Prout	(1932-2007)	Johns Hopkins School of Medicine, Baltimore
Robert Osborne	(1931-2007)	Massachusetts General Hospital, Boston
Harvey Knowles	(1915-1984)	University of Cincinnati Medical Center, Cincinnati
Frederick Goetz	(1922-2012)	University of Minnesota Hospitals, Minneapolis
Martin Goldner	(1902-1987)	Jewish Hospital and Medical Center of Brooklyn
Max Miller	(1911-1978)	University Hospitals of Cleveland, Cleveland
Charles Jones	(?-1974)	Appalachian Regional Hospital, Williamson, W Va
Buris Boshell	(1926-1995)	University of Alabama Medical Center, Birmingham
Theodore Schwartz	(1918-2008)	Presbyterian-St. Luke's Hospital, Chicago
William Daughaday	(1918-2013)	Washington University School of Medicine, St. Louis
Lillian Haddock	(1929-)	University of Puerto Rico School of Medicine, San Juan
Robert Reeves	(1926-)	Virginia Mason Research Center, Seattle

Coordinating center

Christian Klimt	(1918-1984)	University of Maryland Medical School, Baltimore

Acknowledgments

A special thanks to Betty Collison and Jill Meinert for help in this work.

Betty (aka Watson) has been my right hand for 30 years. She has been like a wife, even complete with nagging and spats, but I would be lost without her. Talk about someone who can find things? Watson has no equal. How she does it is a mystery to me. Those skills have been invaluable in this effort what with having to dig into dusty boxes and filing dating back to the 1960s. The marvelous thing about a relationship as long as ours is that I do not have to spend a lot of words on instructions. Now that we no longer have adjoining offices, I cannot rely on "yelling out" (her words, not mine). Now I am reduced to mostly e-mail. Most of those are wordless except for the subject line. It works quite well.

Jill, who happens to be my daughter, has been my go to person when things blow up. "Hey Jill. I cannot get this program to work. Can you figure it out?" Or "Hey Jill. I think I have lost my files. Can you get them back (please, Dear God)?" Endless questions but always dealt with good grace and patience (she could not have gotten that from me). She has also been a deputy finder when Watson strikes out. Thank you Jill.

Thanks to Dave Shade, Esq, for help in finding and reading legal documents related to court cases involving the UGDP.

1. Diabetes

Diabetes* has been recognized as a debilitating condition for centuries but its cause remained a mystery until the 20th century. It would be late in the 19th century before von Mehring and Minkowski discovered that removal of the pancreas in dogs produced diabetes-like symptoms.[90] Early in the 20th century Sharpey-Schafer suggested that diabetics were missing a chemical from the pancreas; named by Sharpey-Schafer "insuline";[61,31] after insula (meaning island in reference to the islets of langerhans in the pancreas).

Before the discovery of insulin, the only way to "control" diabetes was through a diet low in carbohydrates and sugar and high in fat and protein. The diet allowed diabetics to live longer - but not a lot longer.

Frederick Banting and a student assistant, Charles Best, are credited with extracting insulin from dogs in 1921 in a laboratory at the University of Toronto provided by J.J.R. Macleod. Macleod recruited James Collip to work with Banting and Best to purify the pancreatic extract to make it suitable for human use; accomplished in 1922. The three (Banting, Best, and Collip) shared patent rights for insulin (ultimately sold to the University of Toronto for one dollar). Banting and Macleod were awarded the Nobel Prize in Physiology/Medicine in 1923. (For a detailed account of the actors in the discovery of insulin and interpersonal tensions see Hazlett.[32])

Treatment for diabetics was limited to diet and insulin until the advent of oral hypoglycemic agents in the late 1950s with FDA approval of Orinase® (tolbutamide) in 1957. Tolbutamide is a member of the family of sulfonylurea compounds. It has its origins in Germany during WW II and efforts to develop sulfa antimicrobial drugs (code name 2254-RP). One of the first tests of the compound in humans was in the treatment of typhoid fever. The use proved disastrous resulting in the deaths of two young women. Speculation was that the deaths were due to low blood sugar caused by the drug; proven quickly in animal experiments. (See article by Silverman for a good account.[60]) Compound 2254-RP lost its

1. Diabetes

appeal as an antimicrobial with the advent of penicillin and other antibiotics.

Eli Lilly brought a related compound (BZ-55) to the U.S. in the early 1950s for testing (carbutamide), but ultimately abandoned it because of disappointing results.

At about the same time Upjohn undertook preliminary trials with tolbutamide with good results; approved in 1957 and characterized by Upjohn as ushering in a "new era of therapy in diabetes".

When the UGDP started the characterization of diabetics was "juvenile" and "adult-onset"; juvenile because of early onset and usually insulin-dependent; adult-onset because of onset in the 20s and beyond and because usually not insulin-dependent. Those terms in the late 1970s gave way to type 1 and type 2 diabetes, respectively.

The number of people in the U.S. living with diabetes has increased steadily since 1960.
(http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf).

Year	% of US pop with db	US pop with db (millions)
1960	0.91	1.59
1985	2.62	6.13
2000	4.40	12.05
2010	6.75	21.13

The majority are type 2 diabetics.

1. Diabetes

The CDC estimates that of the 21 million diabetics in the U.S. in 2010 and on treatment, over half were on oral drugs alone; 14% insulin alone. (http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf)
In 1980, prescriptions in the U.S. were around 13 million.[48] In 1990 there were 23.4 million such prescriptions and 91.8 million in 2001.[91] Glipizide and glyburide, sulfonylurea compounds, accounted for 77% of all prescriptions in 1990 and 33.5% in 2001.

---

* For a comprehensive collection of works by experts in the field of diabetes see volume by JK Davidson[12] and chapter by Davidson and DiGirolamo.[13]

2. The 64 dollar question

Broadly speaking, there are two classes of clinical trials: treatment and prevention. The lion's share of trials are of the treatment type.

A **treatment trial** is one in which test treatments consist of drugs or procedures used for treatment of a disease or health condition by cure or amelioration.

A **prevention trial** is one done to assess the efficacy of a treatment aimed at preventing the development or progression of a disease or adverse health condition.

Prevention trials are of two types: primary or secondary.

A **primary prevention trial** is one involving the use of treatments intended to prevent or delay the onset of disease; persons enrolled are selected for the absence of disease and the test treatment is one that ostensibly has the ability to prevent the disease.

A **secondary prevention trial** is one involving people with a disease in which the test treatment is administered to prevent or delay further development or progression of the disease (for example, a trial involving the use of aspirin for the prevention of myocardial infarctions in people with a prior history of myocardial infarctions).

The UGDP was a secondary prevention trial because it involved people with disease (type 2 diabetes) and was done to determine if blood sugar control is effective in reducing the morbidity and mortality associated with the disease.

The reality is that much of what is extolled in medicine for preventing or delaying disease is based on supposition rather than fact.

2. The 64 dollar question

Consider Fosamax® and Boniva® (bisphosphonates) given to prevent bone fractures. Use is based on studies showing that the drugs increase bone density (the drugs are widely prescribed for prevention of bone fractures in post-menopausal women with osteoporosis). But does increased bone density translate to reduced risk of bone fracture with use of the drugs? The evidence for that is weak as seen in a meta-analysis of eleven randomized trials representing 12,068 women. Authors of the study conclude:

> *At 10 mg per day, both clinically important and statistically significant reductions in vertebral, non-vertebral, hip and wrist fractures were observed for secondary prevention. We found no statistically significant results for primary prevention, with the exception of vertebral fractures, for which the reduction was clinically important.*

Some of the first randomized trials of hypertensives were done in the 1960s by the Veterans Administration Cooperative Study Group on Antihypertensive Agents (Edward Freis, chair). Results reported in 1967 involved 143 male hypertensive patients (73 assigned to active treatment and 70 assigned to receive placebo; administered double-masked).

There were twenty-seven severe, complicating events in the placebo-assigned group compared to two in the drug-assigned group. The authors concluded that their:

> *report leaves little doubt as to the value of antihypertensive drug therapy in essential hypertension associated with clinic diastolic blood pressures of 115 mm Hg or more*.[89]

There have been scores of blood pressure trials reported since the VA trials. One of the biggest in the U.S. was the Hypertension Detection Followup Program (HDFP). It involved 11,000 men and women randomized to stepped care (hypertensive treatment provided via study

2. The 64 dollar question

clinics) and referred care (care provided by family physicians). The authors reported:

> *Five-year mortality from all causes was 17% lower for the SC group compared to the RC group (6.4 vs 7.7 per 100, P less than .01) and 20% lower for the SC subgroup with entry DBP of 90 to 104 mm Hg compared to the corresponding RC subgroup (5.9 vs 7.4 per 100, P less than .01). These findings of the HDFP indicate that the systematic effective management of hypertension has a great potential for reducing mortality for the large numbers of people with high BP in the population, including those with "mild" hypertension.*[33]

The usual approach in prevention is to focus on a known risk factor and then intervene to reduce the risk. In the case of diabetes, the risk factor is elevated blood sugar. The supposition is that reduction of blood sugar levels will reduce the risk of morbidity associated with elevated blood sugars.

Typically, drugs administered to reduce a risk factor such as hyperglycemia are approved if the manufacturer can show the drug to be safe and effective in reducing the risk factor. There is no requirement to show that the reduction confers benefit in reduced morbidity or mortality. The UGDP raised doubts as to the relationship.

So what do we know now about the answer to the 64 dollar question in regard to blood sugar control and type 2 diabetes? Not a lot.

The Diabetes Complications Control Trial (DCCT), started in 1983 and published in 1993 and involving 1,441 people, was an outgrowth of the controversy caused by the UGDP, but the trial is only of marginal relevance to the question addressed by the UGDP. DCCT investigators excluded type 2 diabetics and the trial involved only insulin treatments (tight control via insulin pumps or by three or more injections of insulin

2. The 64 dollar question

based on frequent blood monitoring versus conventional insulin treatment involving one or two insulin injections per day).[15] The investigators concluded that:

> *Intensive therapy effectively delays the onset and slows the progression of diabetic retinopathy, nephropathy, and neuropathy in patients with IDDM.*

Of more relevance is the UK Prospective Diabetes Study (UKPDS).[63] It involved 3,867 people with type 2 diabetes. People were randomly assigned to a sulphonylurea (chlorpropamide, glibenclamide, glipizide), insulin, or diet. Investigators concluded that

> *Intensive blood-glucose control by either sulphonylureas or insulin substantially decreases the risk of microvascular complications, but not macrovascular disease, in patients with type 2 diabetes. None of the individual drugs had an adverse effect on cardiovascular outcomes. All intensive treatment increased the risk of hypoglycaemia.*

The results of meta-analyses of type 2 diabetes trials are mixed. Boussageon and coworkers[3] did a meta-analysis of 13 randomized trials involving 34,533 type 2 diabetics with 18,315 receiving intensive glucose lowering treatment and 16,218 receiving standard treatment. They concluded:

> *results of this meta-analysis show limited benefits of intensive glucose lowering treatment on all cause mortality and deaths from cardiovascular causes.*

Ray and coworkers,[54] in a meta-analysis of five randomized trials involving 33,040 type 2 diabetics assigned to intensive control or standard control, concluded that:

> *Overall, intensive compared with standard glycaemic control significantly reduces coronary events without an increased risk of death.*

2. The 64 dollar question

However, the optimum mechanism, speed, and extent of HbA1c reduction might be different in differing populations.

Heart disease has been the leading cause of death in the US since 1921. Diabetes showed up as the 10th leading cause of death in 1932 and stayed in the top 10 thereafter, 8th in 1960, 7th in 2010.

Deaths due to heart disease have fallen dramatically since 1960. The age adjusted death rate in 1960 was 559 per 100,000 population. In 2011 it was 174. The dramatic drop is consistent with improved treatments aimed at preventing deaths from heart disease.

The picture is not as encouraging for diabetes. The death rate has remained unchanged over the time period; 22.5 per 100,000 population in 1960 and 21.5 in 2011.

3. The UGDP

1. Initiation

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® for control of her 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 that question. The answer came as a shock to the Congressman.

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

2. Purpose

The UGDP was an investigator-initiated multicenter randomized trial funded by the NIH. It started with five clinical centers and ultimately grew to twelve to achieve the enrollment goal. The coordinating center was located at the University of Minnesota in Minneapolis when the trial started. It was moved to the University of Maryland in Baltimore in 1963.

3. The UGDP

The aims were:

1. Evaluation of the efficacy of hypoglycemic treatments in the prevention of vascular complications in a long-term, prospective, and cooperative clinical trial;
2. Study of the natural history of vascular disease in maturity onset, non-insulin dependent diabetes;

and

3. Development of methods applicable to cooperative clinical trials.[87]

3. The name

Naming a study is like naming a child. All of sudden the child arrives and parents need a name. Maybe they had one before the birth but it can go by the wayside when the child arrives. Chances are that most reading this have no idea how they ended up with the names they have.

Likewise there is no record of how the UGDP got its name.

The name has only four words and just 33 characters and hence reasonably compact as names go. The words *University Group* communicates something about where the study is done (though not all sites were university-affiliated) and that it is multicenter. *Diabetes* communicates focus, and *Program* denotes an activity that is planned to achieve a specified end. The acronym *UGDP* was largely immune from mischief, except critics who referred to the study as the GD UP.

The downside of the name is that it is like the name of a child where you are left guessing if it refers to a boy or girl. *Program* as a currency word is nondescript. The preferred word is *Trial* but that word, at least when the study was formed was viewed as anxiety inducing for patients and usually avoided.

3. The UGDP

If we were starting over today and still limited to four words I would be arguing for names like the:

Blood Sugar Control Trial (BSCT)

or

Diabetes Morbidity Prevention Trial (DMPT).

4. Treatment groups

The treatment groups are as listed below. The phenformin treatment was added after the trial started.

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 patient's body surface
205	Placebo (PLBO)	Placebo (lactose) tablets or capsules similar to those used for 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 the first week of treatment, thereafter 2 capsules per day; 50 mgs phenformin per capsule
1,027	**Total**	

* All persons were prescribed antidiabetic diets in addition to their assigned treatments.

3. The UGDP

5. The randomization scheme

The randomization scheme is as described below as taken verbatim from reference 30.

The UGDP study was arranged as a balanced design, stratified by blocks of 16 or 14 successive patients with-in clinics but without other restrictions on the pattern of assignment of treatment to subjects. Initially, during 1961 in each of seven clinics, the four treatments – variable-dose insulin (IVAR), standard-dose insulin (ISTD), tolbutamide, and placebo were allocated randomly to patients in blocks of 16–four subjects to each of the four treatments in random order. In 1962-1963, phenformin was added to the treatments at five new clinics as well as at one of the original seven and, in order to achieve overall parity in the total number of patients assigned to each treatment, the block size was fixed at 14, with each block containing six subjects receiving phenformin, and two receiving each of the four other treatments.

For purposes of administrative efficiency, individual patients receiving tolbutamide or placebo were not assigned uniquely identified medication, but were supplied as follows: For the tolbutamide assignments, numbers 1 to 24 were split at random into two groups of 12, one group of numbers being assigned to placebo and the remainder to bottles that would be used for tolbutamide. Each of the first 24 subjects receiving placebo or tolbutamide in a given clinic was allotted a separate bottle number, the sequence then being repeated. Bottles 25 through 48 were used for patients assigned to tolbutamide in the clinics that also used phenformin.

As a consequence of this arrangement for the distribution of medication, sometimes two and at most three subjects in a given clinic were supplied with identical bottle numbers. The administrative advantage of this scheme is that each clinic could be given an initial supply of 48 uniquely labeled medications and could order additional supplies, as need arose, without

burdening the central pharmacy with responsibility for more than 800 separately labeled medications.

The orally given medications in the tolbutamide study were in tablet form. The introduction of phenformin in the second part of the study required a change in the method of administration, since phenformin is supplied as granule-filled capsules. In this part of the study all control medication for new patients was given as capsules. Tolbutamide was still supplied as tablets but, unknown to the participating clinics, placebo in the form of tablets was not given in the phenformin clinics. New bottle numbers (49 to 72) were used for the capsules, but the same method of resupply was employed.

In executing this plan, lists of ordered treatment assignments were prepared in advance for each clinic by the Coordinating Center. Random permutations of 16 from the tables given by Cochran and Cox[15] were used for the treatment allocations in the first six clinics, and the Rand tables[16] were employed for those clinics in which phenformin was administered. The assignments were entered in a log book, and space was left on each list for entry of the name and identifying number of the patient and the date of assignment. To facilitate initiation of treatment, assignment requests could be made by the clinic to the Coordinating Center and filled by telephone, in which case a limited number of individuals had authority to record the name of the patient on the appropriate line of the log book, and report back the preselected therapy as shown on the list, that is, either ISTD or IVAR or a bottle number. Confirmatory letters were exchanged subsequently. Alternatively, the assignment requests might come by mail, and the response be reported in like manner. All treatment assignments were made in the sequence laid out in the randomization list.

Once treatments were assigned, therapy was initiated by the clinic. Insulin therapies, not being "blind," required no further consideration. In

the case of orally given medication, however, the treatment was identified only by a bottle number.

6. Data collection schedule

The data collection visit schedule consisted of a baseline visit and then a randomization visit one month after the baseline visit. Persons were maintained on antidiabetic diets in the interval.

After enrollment, patients were seen every three months. Each visit involved a general physical examination and an organ specific examination; eye exam in quarter 1, heart exam in quarter 2, kidney exam in quarter 3, and peripheral vascular and neural examination in quarter 4 plus a glucose tolerance test (GTT). The sequence was repeated for each subsequent year of followup.

Baseline and enrollment visit

Baseline visit

Randomization (enrollment) visit

Followup visits

1st quarter (3, 15, ... mos after randomization): Physical and eye exam

2nd quarter (6, 18, ... mos after randomization): Physical and heart exam

3rd quarter (9, 21, ... mos after randomization): Physical and kidney exam

4th quarter (12, 24, ... mos after randomization): Physical and peripheral vascular and neural exam and GTT

3. The UGDP

7. Centers (as of January 1970)

Clinics	Directors
1 The Johns Hopkins School of Medicine, Baltimore (1960-81)	Thaddeus Prout, MD
2 Massachusetts General Hospital, Boston (1960-81)	Robert Osborne, MD
3 University of Cincinnati Medical Center, Cincinnati (1960-81)	Harvey Knowles, MD
4 University of Minnesota Hospitals, Minneapolis (1960-81)	Frederick Goetz, MD
5 The Jewish Hospital and Medical Center of Brooklyn, Brooklyn (1960-81)	Martin Goldner, MD
6 University Hospitals of Cleveland, Cleveland (1961-81)	Max Miller, MD
7 Appalachian Regional Hospital Williamson, West Virginia (1961-81)	Charles Jones, MD
8 University of Alabama Medical Center, Birmingham (1962-81)	Buris Boshell, MD
9 Presbyterian-St. Luke's Hospital, Chicago (1962-81)	Theodore Schwartz, MD
10 Washington University School of Medicine, St. Louis (1962-81)	William Daughaday, MD
11 University of Puerto Rico School of Medicine, San Juan (1963-81)	Lillian Haddock, MD
12 The Virginia Mason Research Center, Seattle (1963-81)	Robert Reeves, MD

3. The UGDP

Coordinating Center Christian Klimt, MD, DrPH
University of Minnesota School of Public Health Minneapolis (1960-63)
University of Maryland School of Medicine Baltimore (1963-74)
Maryland Medical Research Institute (1974-81)

Project Office (National Institute of Arthritis & Metabolic Diseases)
John Sherman, PhD (1959-60)
James Pratt, PhD (1960-64)
Edward Offutt, PhD (1964-65)
Rose Petrucelli, PhD (1965-68)
LeMar Remmert, PhD (1968-81)

8. Investigators and consultants
(Through January 1977 or date in parentheses)
Investigators

Aguilo, Francisco, MD	San Juan
Albrink, Margaret J, MD	Morgantown
Barrett, James C, MD	Birmingham (1972)
Becker, Frank O, MD	Chicago
Biern, Samuel, MD	Williamson
Boshell, Buris R, MD	Birmingham
Bowen, Angela J, MD	Seattle (1970)
Cammarn, Maxine R, MD	Cleveland (1965)
Crampton, Joseph H, MD	Seattle (died 1966)
Daughaday, William H, MD	St Louis
Davidson, Paul C, MD	Williamson
Field, Richard A, MD	Boston (1966)
Goetz, Frederick C, MD	Minneapolis
Goldner, Martin G, MD	Brooklyn
Haddock, Lillian, MD	San Juan

3. The UGDP

Jacobs, William H, MD	Williamson (died 1971)
Jacobson, Maynard E, MD	Minneapolis
Jones, Charles A, MD	Williamson (died 1974)
Kansal, P C, MD	Birmingham
Kilo, Charles, MD	St Louis
Klimt, Christian R, MD, DPH	Baltimore (CC)
Knatterud, Genell L, PhD	Baltimore (CC)
Knowles, Harvey C, Jr, MD	Cincinnati
Kreines, Kenneth, MD	Cincinnati
Leon, Eloina, MD	San Juan (1971-1975)
Levin, Marvin E, MD	St Louis
Mackenzie, Malcolm S, MD	Cleveland (1969)
Martin, Donald B, MD	Boston
Maslansky, Robert A, MD	Minneapolis (1973)
Meinert, Curtis L, PhD	Baltimore (CC)
Metz, Robert J, MD	Seattle
Miller, David I, MD	Baltimore (Cl)
Miller, Max, MD	Cleveland
Newberry, William B, Jr, MD	Cleveland
Nibbe, Albert F, MD	Chicago (1969)
Nielsen, Robert L, MD	Seattle
Osborne, Robert K, MD	Boston
Prout, Thaddeus E, MD	Baltimore (Cl)
Recant, Lillian, MD	St Louis (1967)
Reeves, Robert L, MD	Seattle (1970)
Rovira, Gabriel Martinez, MD	San Juan (1971)
Schwartz, Theodore B, MD	Chicago

Spergel, Gabriel, MD	Brooklyn
Steenrod, William J, MD	Seattle
Tucker, Randolph, MD	Chicago (1966)
Vega, Luis A, MD	San Juan (1970)
Villavicencio, Elena, MD	San Juan (1967)
Weisenfeld, Shirley, MD	Brooklyn

Consultants

Jacob E Bearman, PhD, statistics	University of Minnesota
Henry Blackburn, MD, electrocardiography	University of Minnesota
Byron W Brown, Jr, PhD, statistics	Stanford University
Jerome Cornfield, statistics	George Washington Univ
Matthew Davis, MD, ophthalmology	University of Wisconsin
Alan Freemond, MD, ophthalmology	Univ of Cincinnati (1968)
Philip M LeCompte, MD, pathology	Faulkner Hosp, Boston
Alexander Lewitan, MD, radiology	Kingsbrook Jewish Med Center, Brooklyn
Irving M Liebow, MD, electrocardiography	University Hospitals of Cleveland (1966)
J. Wallace McMeel, MD, ophthalmology	Retina Assoc, Boston
Frederick A Rose, MD, radiology	University Hospitals of Cleveland

9. Organizational structure

The leadership body was the steering committee (SC). It met semi-annually; more often if necessary. Voting was limited to the director and deputy director of the clinics and coordinating center.

The administrative arm of the SC was the executive committee (EC). It was comprised of five voting members and three ex-officio non-voting members. Its membership in 1970 was:

3. The UGDP

Max Miller (study chair; permanent)
Buris Boshell (3 yr term)
Christian Klimt (study coordinator; permanent)
Robert Osborne (3 yr term)
Theodore Schwartz (3 yr term)

Genell Knatterud (non-voting)
Harvey Knowles (non-voting)
Curtis Meinert (non-voting)

The EC met primarily by conference phone; in person at SC meetings.

There were several subject matter committees, comprised of three to seven members from the investigatorship. The committees, as listed in the Diabetes supplement of 1970, were:

Diabetic Control Committee
Editorial Committee
Eye Committee
Heart Committee
Kidney Committee
Medical Technology and Quality Control Committee
Mortality Committee
Neurology Committee
Peripheral Vascular Committee
Statistics Committee
Weight Committee

3. The UGDP

10. Chronology

1959 First investigators meeting
1960 NIH funding initiated
1961 First patient enrolled
1961 Two clinics added
1962 Phenformin treatment added
1962 Three clinics added
1963 Two clinics added
1966 NIH funding renewed
1966 Patient enrollment finished
1969 Tolbutamide treatment stopped
1970 Tolbutamide results published
1971 Phenformin treatment stopped
1971 Phenformin preliminary results published
1975 Phenformin final results published
1975 Patient followup ended
1981 NIH funding ended
1982 Insulin treatment results published

11. Synopsis

Purpose

To determine if blood sugar control in type 2, non-insulin dependent, diabetics is beneficial in preventing the morbidity associated with the disease

Trial type

Randomized, multicenter, secondary prevention

Funding

Investigator-initiated; NIH funded via grants to study centers
Start: 1960
End: 1981
Funding agency: National Institute of Arthritis and Metabolic Diseases

3. The UGDP

Cost: $30 million (estimate); Orinase®, DBI-TD®, and matching placebos supplied by the Upjohn Company and USV Pharmaceutical Corporation, respectively; insulin supplied by Eli Lilly; test strips supplied by Ames Company

Centers

Number: 13

Clinics: 12

Coordinating center: 1

Central labs

ECG reading center: University of Minnesota; Henry Blackburn

Lipid labs

University of Minnesota; Henry Blackburn

University of West Virginia; Margaret Albrink

Randomization design

Permuted blocks of 16 or 14, stratified by clinic

Stratification variable

Clinic

Assignment ratio

1:1:1:1 Tolb:IStd:IVar:Plbo in six of the seven original clinics and through 16th assignment in original seventh clinic

6:2:2:2:2 Phen:Tolb:IStd:IVar:Plbo in the last five clinics enrolled and starting with 17th person enrolled in the seventh clinic (Boston clinic)

Concealment

Assignments issued by coordinating center on request by clinics after determination of eligibility and willingness of person to enroll

Masking

Tolb and Phen administered double-masked via use of matching placebos and administration schedules for Tolb and Phen; IVar and IStd unmasked

Treatment groups

Five

3. The UGDP

Test treatments: Three (Tolb, Phen, IVar)
Control treatments: Two (Plbo, IStd)

Enrollment
Start: 1961
End: 1966

Number enrolled

IVar:	204
IStd:	210
Plbo:	205
Tolb:	204
Phen:	204

Total: 1,027

Data collection
Start: 1961
End: 1975

Primary publications
Eight (1970, 1970, 1971, 1971, 1975, 1976, 1978, 1982)

Early stops
Tolbutamide; 1969
Phenformin; 1971

Eligibility
Diabetes diagnosed within one year of enrollment; absent history of ketoacidosis; minimum life expectancy of five years; sum of fasting and 1, 2, 3 hour post challenge GTT ≥ 500mg/100ml

Data collection schedule
Baseline visits: Two, one month separated; patient managed by diet alone in one month interval
Followup: Four visits per year every three months

Data harvests
From paper forms mailed to the coordinating center

3. The UGDP

Closeout design
Common closing date; everybody followed to same date regardless of when enrolled

4. Life in the coordinating center

The UK streptomycin tuberculosis trial (published 1948) is regarded as being the first randomized multicenter trial.[43] It helped put coordinating centers on the map.

> *Dr Marc Daniels was appointed to coordinate the trial, and he, D'Arcy Hart and Bradford Hill – supported by a highly efficient trial manager, Mrs Charlene Agnew – were the team responsible for the design, coordination, analysis and reporting of the study. Daniels had had experience of coordinating multicentre investigations in tuberculosis; four years previously, D'Arcy Hart had been responsible for the first well controlled clinical trial done under the aegis of the MRC; and Bradford Hill had set out the principles of clinical trial design in a book based on a series of articles published in the Lancet.*[11]

The UGDP trial goes in the annals as being the first multicenter prevention trial.

The coordinating center was funded separate from clinics. It was headed by Chris Klimt and had a staff of one – me. By the time the tolbutamide results were published we had expanded to a couple dozen people to deal with coordinating centers for the UGDP and Coronary Drug Project.[10]

The coordinating center was located in the School of Public Health at the University of Minnesota when the trial started. It was moved to the University of Maryland in Baltimore in 1963. Administratively it was part of the Institute of International Medicine (Director Fred McCrumb) in the Department of Medicine.

Since the trial was ongoing, the move was accomplished by Chris Klimt moving to Baltimore about four months before me. I stayed behind to keep the home fires burning until things were in place at Maryland for a "seamless" transfer.

4. Life in the coordinating center

If two moves equal one fire, we had two. In addition to the move from Minneapolis to Baltimore there were three moves in Baltimore. Two to different locations on the Baltimore campus and one to an off-campus location about four miles north of the Baltimore campus. The center in Baltimore was part of the School of Medicine until 1974 when it became part of an incorporated non-profit research corporation (Maryland Medical Research Institute; ceased operations in 2010).

When the UGDP started, the science of coordinating multicenter trials was still in its infancy. We existed in a vacuum. If there were other coordinating centers with whom we could communicate, we did not know of them. That changed in the 1970s with the advent of funding for several large-scale multicenter trials with coordinating centers. We were all doing pretty much the same thing but without any interaction. It was as if we were all engaged in inventing the wheel.

It was about then that I became interested in establishing communications with sister coordinating centers to make the work of coordination less lonely. Toward that end I (not always to the liking of Chris), in conjunction with Dale Williams at the University of North Carolina in Chapel Hill, set about organizing a meeting of coordinating centers to facilitate interaction and exchange of ideas on coordination. The first meeting took place in Columbia, Maryland 7-8 June 1973. The meetings continued each May or June thereafter until they merged into the annual meetings of Society for Clinical Trials shortly after it was formed in 1978.

One of my first jobs in the UGDP was construction of the randomization schedule for the trial.

The system of assignments used in the streptomycin tuberculosis trial, as described in reference 11 was:

4. Life in the coordinating center

When a consultant physician identified a potentially eligible patient, the patient's details were sent to Marc Daniels at the national coordinating centre for the trial. If the patient was judged to meet the eligibility criteria, admission was arranged to the next available hospital bed in the nearest participating centre. Each gender in each centre was allotted a numbered series of envelopes, bearing only the name of the hospital. Each envelope contained a card indicating S(treptomycin) or C(ontrol). The numerical order of the envelopes was based on a series of random numbers. When a patient was approved for the trial the next envelope for that centre and gender was opened. Streptomycin and control patients were usually admitted to different wards but otherwise treated exactly the same.

We considered an "envelope system" akin to that described above but rejected the system because assignments could be known in advance of issue if envelopes were opened before persons were judged eligible and willing to participate.

We opted for a system of telephone assignments issued on a per patient basis after being assured by requesting clinics that patients were eligible and willing to participate. Once an assignment was issued, the patient was counted as enrolled to the treatment group to which assigned, even if they never came back for visits.

I had no idea what coordinating centers did when I came onboard and I was not so sure Chris did either. Being the lone statistician in a gaggle of clinicians was not what I had bargained for in Gradual School. (Chris Klimt was an MD with the mind set of an epidemiologist.) Biostatisticians, at least then, were an odd lot as seen by clinicians. (Early on I was tempted to come to a meeting wearing a green visor and shelve garters worn by bookkeepers to fit their stereotype, but I resisted.)

4. Life in the coordinating center

A difficulty for people in coordinating centers is being accepted as colleagues while also "policing" the trial. Doing so constitutes a delicate mix of milk and honey with a touch of vinegar. Part of my job at semi-annual meetings of the research group was to air dirty linen of the trials by noting problems in individual clinics with regard to enrollment, followup, and compliance to the study protocol.

The UGDP was in the punch card era. Punch cards were the medium for imputing and storing data. Early on, we generated frequency distributions using card sorters. Statistical analyses were done using the IBM 101 Electronic Statistical Machine. I became quite adept at wiring boards to do all manner of things. I enjoyed the challenge.

Sometime in the mid 1960s we acquired an IBM 1620 computer. You would have thought we had died and gone to heaven. It was lightning fast compared to what we had but no faster than a turtle by today’s standards. Indeed, cell phones have considerable more computing power than the 1620 – but still lightning fast compared to what we were use to.

All of a sudden we had the means to write programs for analysis. Programs were Fortran (FORmula TRANslation). To produce an executable program, you had to key the program into punch cards and then feed the cards into the 1620 in the hope of getting an "object deck". You got one if the program compiled, otherwise you got what Paddy shot. The object deck was fed into the 1620 to produce an "executable" program – in quotes because it might execute alright but produce gibberish.

The 1620 was a behemoth by today’s standards. It and associated peripherals filled a 20’ x 20’ room. It sat on elevated flooring to hide cables connecting peripherals. The room needed its own air conditioning system to keep the machine from overheating.

4. Life in the coordinating center

Even with the machine, complicated analyses could take hours. Those usually were set to run at night expecting output the next morning, but that only happened about 50% of the time. The other times you got nothing because you forgot to load paper into the printer or because it ran out of paper printing "Error F8" line after line until the paper was gone.

There was a time in the life of the coordinating center when, by movement of the constellations, Max Halperin[6] (waylaid on his way to the NIH and work with Jerry Cornfield), Olli Miettinen, and (Pillip) Dave Wilson were in the center. If there are three people, anywhere, who are given to arguing and more agnostic regarding statistical methods, I would like to meet them.

Max Halperin was a cigarette smoker and the only person I know who could smoke a cigarette without the ashes falling off. When he finished they were still on the cigarette, neatly curled in a half circle. They never fell off, even when arguing with Olli, Dave, and me.

5. Issues

Doing a trial is like backpacking. You plan the trip, layout your gear, map your course, let people know your plans, double check your gear, and head off. The first night out you discover you forgot to pack a camp stove so you have to make do heating food over a campfire. The next day it starts to rain so you go for your rain gear only to remember that you left it on the kitchen table. The third day you discover your maps are outdated and now you are left guessing as to your route out. On the 6th day you get back to where your car is parked, though not quite sure how you made it back.

Trials are not "paint by the numbers" affairs. Protocols underlying them are not blueprints but rather like maps used by backpackers as guides to where they should be heading. Protocols like maps get revised. The longer the trial, the more revisions.

One can think of trials proceeding in stages.

1st stage: Design (culminating in a study protocol)
2nd stage: Execution (characterized by enrollment and followup of study participants and data collection)

5. Issues

3rd stage: Data analysis on completion of data collection
4th stage: Publication of the results

The characterization is alright as an approximation to reality, but misleading to the extent that it suggests the stages are distinct, nonoverlapping. In the UGDP, issues of design overlapped the 2nd and 3rd stages. Issues of analysis in the form of data monitoring arose soon after the start of data collection and were ongoing over most of the trial.

Likewise for paper writing. The first primary results publication appeared in 1970. The last one appeared 12 years later – a year after the end of funding.

The following sections detail some of the major design and operational issues confronted by investigators over the 22 year course of the trial.

1. Sample size

Sample sizes for trials are calculated based on the size difference to be detected and allowable type I and II errors or are fixed by pragmatic considerations. The target sample size in the UGDP was set at 200 per treatment group, based on what investigators considered possible and fundable by the NIH.

2. Timetable

The amount of time needed to do a trial is the sum of that needed to get started, to enroll, for followup after completion of enrollment, and for analysis and paper writing. The time needed when the trial was planned was guesstimated to be at least 10 years, probably more because followup was to be a minimum of five years after the last person was enrolled with everybody followed to a common closing date. Since NIH grant funding comes in five year increments, the original five year request was for what was needed to get started and complete enrollment.

5. Issues

But UGDP investigators, like those coming after them, were notorious for overestimating their recruitment potentials and for underestimating the time it would take for enrollment. They realized by the end of the second year of funding that they would have to round up additional clinics if there was to be any hope of reaching their enrollment goal in the time specified.

3. Adding clinics

The study was funded in 1960 with five clinics located in Baltimore, Boston, Cincinnati, Minneapolis, and New York. Two additional clinics in Cleveland and Williamson (W Va) were added in 1961. Three more in Birmingham, Chicago, and Saint Louis were added in 1962 and two more in San Juan and Seattle in 1963 to bring the total to twelve.

4. Adding another treatment

As is often the case with treatments, newest is best. That was the expectation with phenformin (DBI-TD®; TD for timed disintegration). The approval for marketing came too late for inclusion in the UGDP, but that did not stop people in the study from wanting to add phenformin to the trial. Ted Schwartz (Chicago center), in particular, wanted the treatment added. He believed the drug was likely to be best and that failure to include it would render the UGDP irrelevant.

The principal resistance came from the coordinating center because of the obvious difficulties involved in modifying the design to accommodate a fifth treatment group. People in the center argued that the better course would be to design a separate trial with just phenformin and a matching placebo.

The argument against that position was the time and cost involved in mounting a separate trial and the inability to compare phenformin and tolbutamide assessed in the same trial.

5. Issues

The approach ultimately taken was to modify the existing design to incorporate phenformin as a fifth treatment group. The solution was practical but not pretty.

With the support of the funding agency, investigators moved to add five additional clinics to bring the total to twelve. The randomization design for the five clinics was permuted blocks of size 14 with three times as many assignments to phenformin as to the other four treatment groups (i.e., 6:2:2:2:2 for Phen:Tolb:IStd:IVar:Plbo). In addition, the assignment ratio in the lowest recruiting clinic among the original seven was changed to that for the new clinics after enrollment of the 16th patient. The finished sample sizes for the five treatment groups were 204:204:210:204:205 (Phen:Tolb:IStd:IVar:Plbo).

The parity of sample sizes across treatment groups is aesthetically appealing but deceptive in that treatment comparisons are confounded by clinic. The two hundred and five patients assigned to placebo came from all twelve clinics, but results for phenformin were from six clinics. The proper phenformin-placebo comparison, independent of clinic, involved the 204 patients assigned to phenformin and the 64 patients assigned to placebo in the six "phenformin" clinics. Likewise the proper comparison for phenformin versus tolbutamide free of clinic effect, was the 204 patients assigned to phenformin and the 66 patients assigned to tolbutamide in the six "phenformin" clinics.

Another compromise was in masking. The administration schedule and pill forms were different for the two oral agents (tablets for tolbutamide and capsules for phenformin). This would have meant use of two placebo pills in "phenformin" clinics to mask the two treatments but that design was impractical. As it was with just a matching placebo for phenformin, there were only six or seven patients assigned to receive that placebo per clinic. The degree to which this reality unmasked tolbutamide assignments

in "phenformin clinics" is only a matter of conjecture because clinic investigators were not informed that the placebo in "phenformin clinics" was only for phenformin.

Ironically, after all the effort, phenformin turned out to be a bust. Phenformin has the distinction of being the only drug removed from the market (1977) by the “imminent hazards provisions” of power vested in the then Secretary of Health, Education, and Welfare.

5. Outcome measures

The primary aim of the UGDP was:

evaluation of the efficacy of hypoglycemic treatments in prevention of vascular complications in a long-term, prospective, and cooperative clinical trial.[87]

The outcomes were "vascular complications". Death was not mentioned but tolbutamide was stopped because of a difference in deaths against tolbutamide.

Mortality was not mentioned in design documents of the trial because the sample size of the trial was considered to be too small to detect treatment differences in mortality. That absence of mention caused critics to suggest that investigators had no basis for stopping tolbutamide because of mortality.

The criticism suggests that stops can be only for outcomes specified when the trial was planned. On its face we would have been obliged to ignore differences in deaths because death was not mentioned as an outcome when the trial was designed. That approach does not meet requirements of the Mother Test (see reference 46, pages 473-476 for the test).

6. Matching placebos

The design called for double masked administration of tolbutamide (and of phenformin when it was added later). The insulin treatments were not masked because placebo injections were considered unethical and, in any case, there would not have been any viable means of masking the IVar treatment since dosage was based on level of blood sugar control achieved.

Masking is for bias control. Double masking is done to keep patients and clinic personnel in the dark as to the treatment being administered. The masking for drugs administered as pills requires placebos that look, feel, and taste the same as the drug being masked. Accomplishing this is a virtual impossibility. Invariably, even under the best of circumstances, there will be subtle differences in shape, sheen, texture, or taste detectable if the drug and placebo are compared side by side.

The only chance for any reasonable match is to acquire placebo from the manufacturer of the study drug. (It is illegal to distribute tablets designed to match marketed drugs except as produced by the manufacturer for use in research.) That was the case in the UGDP. Orinase® and its matching placebo was supplied by Upjohn. DBI-TD® and its matching placebo was supplied by USV Pharmaceutical Corporation.

7. Informed consent

Institutional Review Boards (IRBs) did not exist when the UGDP started. There were no consent forms for patients to read and sign. Whatever persons were told about what they were being approached for was up to clinic personnel.

In reality, the requirement for informed consents as a condition for researching on human beings existed long before the start of the UGDP. The requirement is the first item in a ten point manifesto growing out of

the Nüremberg war crimes trials and known as the Nüremberg War Code, promulgated in 1947.

> *The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.*

Though the requirement existed, it was largely ignored. The prevailing view in a then paternalistic medical profession was that discussions regarding such arcane issues as randomization to select treatments patients were to receive would be anxiety inducing and, hence, to be avoided or down played.

The climate changed in the mid 1960s with accounts of a few "celebrated" studies involving people without their consents. Among them, one involving infecting "mentally defective" children in the Willowbrook State Hospital in New York with hepatitis and another involving injection of live cancer cells into patients in the Jewish Chronic Disease Hospital in New York City.[41] A publication by Beecher in the *New England Journal of Medicine* in 1966[1] focused attention on the issue of ethics in clinical research.

5. Issues

The outrage led to the Surgeon General of the USPHS to announce, 8 February 1966, that henceforth NIH grantees would have to provide evidence of procedures and practices designed to ensure documented informed consents in order to receive funding. The order and implementation of it eventually led to the creation of institutional review boards.

The problem for UGDP investigators was that the order came about when enrollment was finished. Memory no longer serves as to what investigators did to comply with the order, but whatever they did there is no evidence of widespread departures from the study based on consenting.

8. Local versus central laboratories

A design issue was whether to use local labs or a central lab for laboratory tests required in the trial. The decision was to rely on local labs, a mistake in retrospect, given the mix up with blood versus plasma for glucose determinations (Chapter 15, Part 5.2).

Part of the reason for local labs was that costs for central labs had not been built into the original funding proposal. That being so, the only viable option was local. Investigators, wisely, opted for central lipid labs and ECG readings when those measures where added after the trial started.

9. Data entry

Data collection was via paper forms designed for entry without intermediate coding or transcription. Data forms were mailed to the coordinating center for entry using punch cards. The option of entry at the clinics was not viable in view of the cost of equipping clinics with punch card machines and training personnel in their use.

5. Issues

10. Cutoff dates

If you stop a treatment midcourse what is the cutoff date for the dataset used for the presentation or publication? When the decision was made or downstream, and if downstream from the decision how far downstream?

Datasets are never final, even after a trial is finished. That fact raises vexing operational questions. For example, if a publication has to do with deaths what do you do if you learn of another death within the cutoff limit after publication? Usually, such discoveries do not change conclusions, but prudence suggests that the editors of publications be notified so they can decide what, if anything, should be done to update the publications.

Datasets during the trial were in constant flux as data flowed from study clinics to the coordinating center. There was a time lag of weeks between when data were collected and harvested into datasets at the coordinating center.

The dataset used for reports seen by investigators when they voted on whether to stop tolbutamide was different from the one used for publication. The cutoff date for the publication was 7 October 1969, several months after the vote. That date was chosen to allow study patients to transit through clinic visits at which treatment was stopped and to allow sufficient time thereafter for data to be received and processed in the coordinating center.

11. Safety monitoring

Uncharted ground in the UGDP had to do with safety monitoring (aka treatment effects monitoring also aka data and safety monitoring) – monitoring performed at periodic time points over the course of the trial to determine if it should continue unaltered. Note that safety from the point of view of persons enrolled is a two edged sword. A treatment may be

unsafe because of the ill-effects it causes or because there is a better treatment available to them.

The issue with interim looks to see if the trial should continue unaltered has to do with the effect such looks have on p-values. The problem has been picturesquely described by Cornfield[8]:

> *Just as the Sphinx winks if you look at it too long, so if you perform enough significance tests you are sure to find significance, even when none exists*.

Cornfield was a likelihoodist. He believed the information needed for inference was in the data, not in p-values.

Another issue was who should do the monitoring. It was given that the coordinating center would play a pivotal role, but who else should see interim results? The decision was that it would be the entire Steering Committee.

One might have preferred a subset of investigators in order to have a smaller, more compact, group. The duty could have been vested in the Executive Committee consisting of eight people (see Chapter 3; Part 9), but that would have required a two stage process involving recommendations for stops from the EC being passed to the full SC for up or down votes.

The involvement of the full SC avoided that two stage process and the logistical issues of having to organize separate meetings for safety monitoring.

Having been involved in monitoring various trials since the UGDP, I can say, without hesitation, that the quality of deliberation and discussion was second to none. The SC was better informed regarding nuances of

data and how it was collected than monitoring bodies comprised of members with no connection to the trial.

But even with that said, monitoring by clinician investigators has given way to monitoring by bodies largely independent of clinician investigators, at least as required for NIH funded trials (NIH Policy for Data and Safety Monitoring; 10 June 1998).

12. Publish first, present later?

I am of the "publish first, present later" school even though that rule was violated in my first experience in trials with the tolbutamide results.

The danger of presenting first and publishing later is that the publication may never come and because of differences in the dataset for the presentation versus that for publication. Fortunately we avoided those two mistakes with publication coming a few months after presentation and with use of the same dataset for the presentation as for the publication.

But even somebody like me knows that there are times to avert the rule. Whether the UGDP results rose to that level is questionable. They got presented before publication because of a failed effort at orchestration (Chapter 6; Part 9).

However, it is apparent that there are occasions where results need to be communicated stat. A reasonable middle ground when that is the case, at least for NIH-funded trials, is via issue of "clinical alerts" by the NIH. A catalog of alerts is maintained by the National Library of Medicine (NLM) (http://www.nlm.nih.gov/databases/alerts/clinical_alerts.html#alerts). Of the 38 alerts issued since inception in January 1991, 16 were about negative treatment effects and 22 were about positive effects.

5. Issues

13. Leaks

A leak in trials is disclosure of treatment results before presentation or publication. Leaks can be accidental or purposeful.

They can be discrediting to the trial and lead to legal action if the leaked information is used for financial gain (e.g., as seen with Martha Stewart's conviction and jail sentence for trading ImClone Systems stock based on insider information). The risk of leaks is proportional to the number of people who know results. In the case of the UGDP, that was the Steering Committee and people associated with them.

Obviously, people in the FDA were in the know by virtue of reporting required under investigational new drug applications (INDs). Dr Klimit held the INDs for tolbutamide and phenformin; see item 6 in Memorabilia listing for letter to FDA reporting decision to stop use of tolbutamide). What we had not bargained for was the assertive role of the FDA in wanting to use results from the trial to relabel the sulfonylureas. The agency's tacit endorsement of the results was reassuring, but we got tarred with the same brush used on the FDA by critics who distrusted the FDA and our results.

Upjohn, USV Pharmaceutical Corporation, and Elli Lilly, suppliers of durg to the UGDP, received advance information concerning the decision to stop use of tolbutamide and results of the study.

That some flows were illicit by today's standard goes without saying. But that said, it must also be recognized that the preoccupation with and prosecutions for insider trading now was barely on the radar screen in 1970.

5. Issues

It is a fact that people from the UGDP, unhappy with the decision, were retained by Upjohn after the results were published to speak about shortcomings of the trial.

One of the advantages of investigator blackouts of results by removing them from the monitoring process has to do with reducing the chance of leaks but that protection is time limited if the monitoring body makes a recommendation to stop a treatment. At that point the blackout has to be lifted to allow investigators to see results so they can decide whether to accept or reject the recommendation.

As indicated in elsewhere in this account, investigators agreed to a "publish first and present later" policy but that policy went by the wayside after the group decided to stop use of tolbutamide in the trial. There was general consensus when the decision was made that investigators would refrain from presentations until results were presented at the ADA or published, but it is obvious that even that policy was violated as evidenced by a complaint from Upjohn voiced in a letter of 15 December from Alan Varley to Max Miller (see item 14 in Memorabilia listing).

> *Last August we discussed by telephone my concern over the public and medical confusion resulting from public disclosure of UGDP "conclusions" without presentation of supporting study data which would allow detailed analysis and discussion. ... It is therefore particularly disconcerting to hear that some of the UGDP members are delivering formal presentations and summaries of your study around the country without publication of supporting data for analysis and critique. This is clearly different than your plans for detailed publication expressed to me last August, and again recently in the December 12, 1969 issue of Medical World News. More important, I sincerely believe*

that this piecemeal presentation based upon data to be contained in a future publication is not in the best interest of either the diabetic population or the medical profession to which we both have deep commitments.

6. Memories and reflections

1. I'd put you up at the hotel but it burned down the other day

Chris and I made the rounds to clinics early on. Most of the clinics were located in easy to reach cities except the one located in Williamson, West (By God) Virginia. Williamson is on the Kentucky-West Virginia border, in the heart of coal mining country. It had a population of about 6,500 in 1960 and now about half that number.

The clinic was in the Appalachian Regional Hospital. The hospital was one of a number established by and operated by the United Mine Workers Association. The hospital stood as a beacon in an otherwise depressed and impoverished community.

Our first trip was by train via a sleeper. Sometime in the middle of night there was a layover to switch engines from diesel to steam because diesels were not allowed in coal country!

The next morning Charlie Jones, head of the Williamson clinic, picked us up and promptly announced that he would have put us up at the hotel but it burned down the other day, so we would have to stay with him. And so we did for what Charlie called "recreational eating". (Alas, he paid the price with an early demise in 1974 from a heart attack).

6. Memories and reflections

A few years later, we made another visit. This time by car. When we arrived Charlie greeted us and announced that the hotel burned down the other day so we would have to stay at his house for more recreational eating.

To a midwesterner the other day is the other day. Either the "other day" meant something different in West Virginia or the town had the misfortune of having its only hotel burn down twice in a few years. Being suspicious that the town could not be that unlucky, I asked Charlie to drive me past where the hotel sat. It was then I learned the "other day" did not mean what it did in Minnesota. There were trees, two feet in diameter, where the hotel sat.

2. Riding with Klimt

Riding with Klimt was an experience. For years he had a VW bug. Later on, he had a Ford station wagon and after that a Mercedes. I hated when he suggested driving because, for my taste, he drove too fast and spent too much time looking at pretty women he passed. Not many cars passed him because he trained on the Autobahn in Germany. Most of the trips were white knuckle affairs made worse by the fact that they were before seat belts.

Our second trip to Williamson was with Chris behind the wheel in his Ford station wagon. Thad Prout was in the suicide seat. I was in the back. It could not have been a mile from having been picked up when I ended up on the floor. There would be several more such incidents before we got back home. So many that on the way back I was tempted to sit on the floor simply to avoid the wear and tear of getting off the floor.

6. Memories and reflections

3. The shootout in St Louis

Have you noticed how baseball players have graphic memories for a celebrated feat years back? The inning, the pitch count, runners on base, the weather, the temperature, who was pitching, and who was catching.

This is the case with me concerning Sunday, June 14th, 1970. It was around 8am when Thad Prout and I boarded a plane for St Louis. Thad was our front man. He drew the short straw making him the person to present the tolbutamide results at the American Diabetes Association meetings in St Louis. I was tagging along for moral support.

We landed at Lambert field around 10am. Hot and humid. Neither one of us relished cooling our heels at meetings, so the JIT arrival suited us fine.

When we walked into Stouffer's Riverfront Inn (now the Millennium Hotel) around 11am you could feel the tension. We made ourselves scarce until "show time" (after the lunch break). The ballroom was packed.

The first presentation was by Klimt detailing the design of the UGDP. Then it was Prout's turn. When he finished there was perfunctory clapping. No boos but, most assuredly, no standing ovation either.

There were press conferences following the presentations. Polite enough, but pointed questions. After the press conference and appropriate milling around, we hightailed it for the airport; happy to leave the Riverfront Inn behind. It was a little after 6pm, but dark with the threat of rain. About half way to the airport I gave Thad a poke and said "What do you make of that?" motioning to the right to draw his attention to a tornado funnel cloud keeping pace with us as if to underscore the events of the day.

6. Memories and reflections

4. My God there really is a Sleepy Eye

In 1970 Thad Prout and I had the job of writing the tolbutamide results paper. Two or three nights a week, for six months running, we would gather in his office. He would be seated in his MD papal chair and me in a dinky squeaky chair outside his office.

Some nights we made great progress with little bantering or bickering and then there were others when we were lucky if we got a sentence written – hopelessly bogged down in arguments and impasses of monumental import. Often he would characterize the issue I was pushing as "two cents worth" (if only he had given me two cents every time he said that, I would not have to worry now about making ends meet in retirement). Usually, when he said that, I would lean back in my squeaky chair, prop my feet on the desk, and proceed to explain how farmers, back in Nodhardt's Saloon in Sleepy Eye, would resolve the argument. Over the months there was a parade of people, all real (save for a little embroidery here and there).

It was, perhaps, the embroidery that made Thad suspicious. By the time we finished writing, he was certain Sleepy Eye was my mythical hometown.

It was about a year later when he ran into me and proclaimed, "My God! There really is a Sleepy Eye" (having just discovered it "map browsing").

5. The Goldner affair

Martin Goldner was in charge of the study clinic at the Jewish Hospital and Medical Center of Brooklyn. It was fairly early in the course of the UGDP, at an investigators meeting in Cincinnati. We had just broke for lunch and were in the milling around phase. I was talking with Harvey Knowles and a couple of others when distracted by loud voices behind me.

6. Memories and reflections

I turned to discover that Martin Goldner and Chris Klimt were toe-to-toe over some authorship dispute for a UGDP paper in the works. The argument was because Chris had changed the order of authors in a way I can no longer recall, but to me of no real consequence. For a time it looked as if they might come to blows, but eventually tempers settled and the incident faded.

At the time Goldner was not one of my favorites because he seemed aloft and arrogant. I sided with Klimt, but the incident puzzled me. It seemed too trivial to have precipitated such an outrage.

I learned back on the farm from my Mother that when 2 + 2 does not equal 4 that I am missing something, but what?

I found out about a year later. By that time, I had warmed to Martin Goldner with a touch of fondness. It was at an investigators meeting, during a private moment at cocktails, when I asked Dr Goldner what the brouhaha was about in Cincinnati. He said it created a flashback to his days in Germany in the late 1930s. He was working with his professor on a textbook (in chemistry, I believe). When the book was published his name was gone.

Finally, I understood his outrage in Cincinnati. Dr Goldner regarded the change, even if seemingly trivial, a violation of trust.

Eventually, Martin Goldner became one of my most cherished colleagues from the UGDP.

6. Memories and reflections

6. The cherry tree incident

It is, I should guess, the late 70s. I am still at the University of Maryland, still working on the UGDP and by then also on the Coronary Drug Project.

By then we had expanded from when it was just Klimt and me to many, one of the many being Olli Miettinen.

Olli was from Finland. He was an MD, PhD with a medical degree from the University of Helsinki and a PhD from the University of Minnesota.

Surprisingly, Olli and Chris got along – until Olli decided to leave for Harvard and take a study we had with him. Once that happened, Chris regarded him as a wayward son. His fall from grace was rapid and irretrievable.

I got along OK with Olli and I knew stuff he did not so he asked me to help him in the transition. I said I would.

Klimt got wind of that and festered until a Saturday afternoon in July. Here he comes up the driveway. (I never liked it when he showed up because almost always there was something bad that had happened or that was about to happen.)

I was busy working in the yard and did not want to invite him in (because I had a notion that he wanted to bitch about me and Olli), so I dragged up lawn chairs under the cherry tree. We talked for a time and then he got to why he was there. He wanted me to cut my tie to Olli. I said I did not want to do that because I had already said "yes".

So we bantered. The longer we did the more Chris dug in. Finally, he puffed himself up and said "I am the boss and I am telling you to cut the

tie!" I took a deep breath and said quietly and deliberately, "Chris, I recognize your right to give such an order, but if you do I will resign." Klimt said "I so order" and I said "I resign". With that I got up and walked in the house and told my wife that I just quit my job. "Oh my! What are we going to do?" I said "I have not the foggiest".

The next morning, around 10, here comes Klimt. I say to myself, "For certain he can’t be coming to fire me again".

I sensed a change of heart. Sure enough. He offered that if I wanted to maintain my tie with Olli it was alright. "OK, then I withdraw my resignation." And with that, I unquit.

Ironically, a couple of years later, Olli fired me. Oh well!

7. Controlled burns

Chris was fond of extolling "controlled burns" as a strategy for dealing with difficult issues. I had witnessed a few. To me they were more like what happened to Challenger after liftoff.

A memorable burn was on checking into the Fairmont Hotel in San Francisco. Our plane had been delayed. It was about midnight when we arrived. We had guaranteed reservations, but the hotel was full.

We were to be shunted to another hotel. On hearing that, Chris puffed himself up like a grouse and started snorting at the hotel clerk. Before long he was shouting and I retreated behind a big flower pot in the middle of lobby.

The clerk summons his supervisor. Chris shouts at him. The supervisor tells him the same thing – no rooms. Chris keeps shouting. I slink further behind the flower pot.

This goes on until the supervisor announces that the bridal suite is available.

We had great accommodations that night.

8. The telephone cord issue

There we were on the 11th floor of the Mayo Building on the University of Minnesota campus. Chris in the front office and me in the back office.

When Chris moved into his office he rearranged it with the result being that the phone cord no longer reached his desk. As a result, whenever he used the phone he had to lean to his right to reach it. Eventually, the cord being a growing irritation, he went to the department administrator to request a longer one.

The administrator took the order.

Nothing a week later so Chris asks again. He waits a week. Still no cord. Now he does a "controlled burn" with the administrator but that was like talking to the hand so he gets in his VW bug, heads to Radio Shack, buys a cord, and installs it himself that afternoon.

The next day he and the chairman of the Department, Len Schuman, are in a toe-to-toe argument, like Earl Weaver, the Orioles manger, with an umpire. Three days later, Chris shows up at our house about 7:30pm and says he is going to the University of Maryland Medical School and wants me to come along. The rest is history.

6. Memories and reflections

9. The grand orchestration

Investigators, early on, agreed to a "publish first, present later" policy in regard to primary results. The first test of that policy came with the decision to stop the tolbutamide treatment.

But, as often happens with such policies, there is backsliding. Ultimately, investigators decided in favor of presentation with the expectation of having the results published by the time they were presented.

Abstracts[84,85,86] were submitted for the 1970 American Diabetes Association meeting early in 1970. The pair of papers ultimately comprising a separate supplemental issue of Diabetes were submitted about the same time. 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 paper appeared in print in November, about five months after the presentation in St. Louis. The intervening time meant that investigators stood helpless in answering the deluge of criticism until the papers were published. 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 their questions without benefit of a publication made them hostile to the study. By the time the publication appeared, they had decided that the study was “no good” and that, therefore, there was no point in reading it.

One can argue that presentation prior to publication was a major mistake. There is no doubt that the lack of credible information contained in a peer-reviewed publication until months after the presentation and scary headlines about a "killer drug" was debilitating. Further, the black eye it

gave the study probably detracted from the importance of the insulin results from the trial.

But one can also argue that the controversy created was good for the diabetes field to the extent that it helped stimulate development of other trials to "disprove" the UGDP. Indeed, the DCCT (Diabetes Control and Complications Trial),[15] an NIH-funded trial, arose, in part, out of a desire to disprove the UGDP results.

Also, the likelihood is that without the controversy, the paper would have appeared and been quickly forgotten. In that regard we can say what movie stars say about reviews "I don't care what you say about me. Just spell my name correctly".

10. Marriages

I know of two marriages directly credited to the UGDP. Dave Wilson's and Marv Levin's. Dave Wilson worked with us in the coordinating center in Baltimore. Marv Levin was an investigator in the St Louis clinic.

They both became taken with nurses. With Dave it was Marilyn Halverson working with Fred Goetz in the Minnesota UGDP clinic. With Marv it was with Barbara Symes working in the Department of Preventative Medicine for Dr Lillian Recant and the St Louis UGDP study clinic.

Dave's romance was long distance with him being in Baltimore and Marilyn in Minneapolis. Marv's was just across the hall in St Louis. Interestingly, Dave met Marilyn in St Louis at a UGDP investigators meeting there. Dave needed coaching from me to get up the nerve to call Marilyn after the St Louis meeting. Marv needed none, at least not from me. Dave and Marilyn got married in 1965 in Minnesota. They remained

together until Dave's death in 2011. Marilyn died in 2014. Marv Levin and Barbara Symes married in 1976 and are still married.

11. Chris Klimt

Chris Klimt[38] (1918-1994): born in Austria; medical degree from the University of Vienna (1944); DrPH from Johns Hopkins (1959). He and his wife, Helga, had four children, Claudius, Ronald, Andrea, and Sandra.

Chris's most famous relative was Gustav Klimt (1862-1918). An artist with "The Kiss" being his most famous work.

After the war, Chris joined the World Health Organization. He and his family came to the U.S. to Baltimore in 1958 and then a little later to Minneapolis to start the UGDP.

I joined Chris at the University of Minnesota in 1960 and stayed joined until his death in 1994.

His first job in Minnesota was to find a niche for himself in the study being started and in the center he was about to head. For the center he wanted a name to set it apart from the clinical centers in the study. A name like "Service Center" was too pedestrian and demeaning in that it did not connote leadership. Service, to be sure, would be part of what was to be provided but in the larger context of leadership.

Names like "Data Center" or "Statistical Center" were too confining in that the work envisioned was broader than implied by those names. He wanted a name with standing, panache.

What he came up with was "Coordinating Center". I thought it presumptuous, but he did not seek my counsel.

6. Memories and reflections

Where it came from, I do not know. Today, the name is in common usage, but back when the UGDP was established the name was not used.

Chris did not lack for an ego. Well he did not because his ego helped define what coordinating centers do.

At work Chris was boss. At home Helga was boss. It was interesting to know both sides of Chris. The demanding boss at work and subservient Chris at home. It did not take many visits to his house to know that Helga was the glue that held the family together. When she died Chris was lost. He died soon after her.

In the Center, if you wanted something you had to clear it with Chris. If you wanted your way, you had to convince Chris. Eventually, I learned that the shortest distance between A and B was to make Chris think that whatever I wanted to do was his idea. Then it was smooth sailing.

He thrived on controversy. Thad Prout characterized his attraction to controversy like that of a moth drawn to a flame. He was at his best when the going got tough. In many ways he relished the tolbutamide controversy. I wanted to pull the covers over my head. He wanted more.

We each had our hot button issues. His was being left out of the loop. Mine was getting orders (as chronicled in "The cherry tree incident").

In many regards we were opposites. Our work styles were different. His was linear, mine was chaotic. His was Germanic; mine "midwestern". His sentences long. Mine curt.

Our work hours were different; mine 9 to 5; his 9 to 7 with a four hour break from noon to 4. I tried to avoid Chris when he got back from his "break" so not to be drawn into some lengthy discussion, but only with

moderate success. There were many nights when I came home to an angry wife and left overs.

Chris was about 5’8" and slightly round. I was 6’6" and skinny (then). We looked like Mutt and Jeff.

Chris could lose his temper. When he did we ran for cover.

We had different sensors. His appraisal of meetings was often different than mine. He could come away thinking it was a good meeting and me thinking it was terrible. We reacted to different things. He to what was said and me to what was not said.

We travelled together for business and sometimes for pleasure. I have fond memories of a sojourn to Kössen, his ancestral home in Austria in the 1980s.

Chris was organized. I acquired some of my fetishes for organization from him. He never went to a meeting without a tabbed loose-leaf notebook with meeting materials. I came to appreciate that and expanded on it. Just ask people who have worked with me.

7. The Biometrics Society Committee

The decision to stop use of tolbutamide created a firestorm of criticisms. As soon as the results were published there were calls for audits of the results by critics, convinced that something was wrong and that an audit would reveal what they suspected. About a year after publication of the results, the NIH commissioned an audit committee via the International Biometrics Society. The sections that follow are reproduced from the report of the audit committee, as published in JAMA in 1975.[30]

Basically, the audit failed to find anything of note for study critics. The concluding sentence in the report was:

In conclusion, we consider that in the light of the UGDP findings, it remains with the proponents of the oral hyperglycemics[sic] to conduct scientifically adequate studies to justify the continued use of such agents.

Committee Charge (reproduced from reference 30)

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

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

The interest of NIH in this matter arises from the fact that approximately four million Americans have diabetes, as defined by an

7. The Biometrics Committee

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

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

1. *to make an in-depth assessment of the scientific quality of the UGDP study and in particular of the biometric aspects of the design, conduct, and analysis of the trial;*
2. *to make a similar assessment of other controlled trials of oral hypoglycemic agents.*

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

The committee was appointed by the President of the Biometric Society with membership as follows:

Members

Colin White, MB, BS (Chair)

Department of Epidemiology and Public Health, Yale University, New Haven, Conn

7. The Biometrics Committee

John P. Gilbert, PhD
Office of Information Technology, Harvard University, Cambridge, Mass
Paul Meier, PhD
Department of Statistics, University of Chicago, Chicago
Christian L. Rümke, MD
Afdeling Medische Statistiek, Vrije Universiteit, Amsterdam
Rodolfo Saracci, MD
Sezione di Biostatistica e, Epidemiologia Clinica Laboratorio-di Fisiologia Clinica del CNR, Pisa, Italy
Marvin Zelen, PhD
Statistical Science Division, State University of New York at Buffalo, Buffalo

Observers from the Biometrics Society

Peter Armitage, PhD
Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine, London
Berthold Schneider, DPhil
Department für Biometrie und Medizinische Informatik Medizinische Hochschule, Hannover, West Germany

Research Associate

Theodore Holford, PhD
Department of Epidemiology and Public Health, Yale University, New Haven, Conn

Consultant Diabetologist

Henry T Ricketts, MD
Department of Medicine, University of Chicago, Chicago

7. The Biometrics Committee

Committee meetings and work (reproduced from reference 30)

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

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

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

Committee conclusions (reproduced from reference 30)

Protocol

Was the target population for this study an appropriate one?

Critics have pointed out that certain patients were required to accept treatment that would not normally conform to clinical practice, and they argue, therefore, that the target population was unsuitable. Such a claim, however, overlooks the important but ill-understood prophylactic aspect of the trial, in which certain treatments were given to patients who, initially at least, could safely go without drugs, in order to test whether the

7. The Biometrics Committee

common vascular complications of diabetes could be prevented. The issue was the testing of certain possibly preventive treatments rather than the implementation of certain standard therapeutic regimens.

Was the decision to include phenformin in the study justified?

In the event it proved to be, since valuable information was obtained about the limitations of that drug. Its use, however, greatly complicated an already difficult study. It is clear that one of the problems of a long-term clinical trial is that potentially interesting therapies may develop while the trial is in progress, and the natural desire to include them may divert resources.

The omission of a history of smoking was a blunder.

Conduct of the Study

This was necessarily a lengthy and complex trial, and a substantial pioneering effort was needed to mount it successfully. We have raised a question of whether the randomization was properly carried out. The only evidence that it might not have been is the data on the allocation of treatments according to the sex of the patient. Against this possibility are two considerations – the quality of the work at the Coordinating Center, as illustrated by their records and procedures, and the lack of purpose that anyone could see in assigning men or women to a particular treatment.

Methods of Analysis

The UGDP investigators sought to examine their data from a number of different points of view, and in so doing they made use of some relatively unfamiliar and exploratory statistical techniques. In some cases these methods would not necessarily have been chosen by other groups of statisticians faced with the same situation, but since the results of all the analyses tended to point in the same direction, there would be little

advantage in discussing at length the weight to be attached to the different analyses.

The likelihood calculations seem to us to add very little to the other analyses. The results are rather difficult to grasp and require rather arbitrary weighting to be given to the likelihood of different hypotheses. The method does not take concomitant variables into account.

The Monte Carlo monitoring procedure was a major attempt to overcome the selective effect of a sequential analysis of the mortality data. The investigators were concerned lest they had paid undue attention to contrasts between treatments at a particular moment when extreme fluctuations might have occurred. Their method was ingenious, and although minor points of criticism may be raised, we do not think that these materially affect the issue. (Some of these points might be (1) the use of national mortality data, with death rates higher than those in the study population; (2) the use of an "average" survival curve for all patients in the simulation; (3) the adding of life table death rates at different ages to obtain the death rates during intervals; and (4) the arbitrariness of the linear boundaries. For an alternative approach to the sequential analysis of survival data, using internal comparisons only, see Breslow and Haug.) The detailed outcome of such a monitoring procedure is of no great importance. The decision to stop the use of tolbutamide must have depended on considerations of various sorts, among which the monitoring procedure provided a contribution – no more than that.

The UGDP did not try to determine whether interactions were present in their data. This criticism was raised by Feinstein and is valid.

Findings

Although we have concerned ourselves almost entirely with issues related to the possible toxicity of tolbutamide, we wish to point out that

one of the valuable aspects of the completed UGDP trial will be the provision of data on the long-term treatment of adult-onset diabetes with insulin. It is already clear that the benefits from this treatment are not dramatic, and the only worthwhile information about them will have to come from the relatively precise methods of a controlled clinical trial. In this sphere, the UGDP trial has no competitor. Indeed, we would generalize from this and point out the necessity of the continued use and development of randomized clinical trials of the treatment of chronic diseases.

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 reservation about the conclusion that the oral hyperglycemics are toxic must remain. Nonetheless, we consider the evidence of harmfulness moderately strong. The risk is clearly seen in the group of older women as shown in Table A.4. 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.

There remains the question of generalization of these findings. As has been frequently pointed out, the conditions of drug use in this study were, to some extent, abnormal. Tolbutamide dosage is varied in practice, and the patient unable to maintain adequate control with tolbutamide could be shifted to insulin. A good deal rests, then, on the matter of whether tolbutamide is actually toxic. If this should be admitted, it is hard to see

7. The Biometrics Committee

how it could be regarded as a reasonable therapy, even when given in variable rather than fixed dosage.

There is also the question of the extent to which the UGDP subjects reasonably represent the population of maturity-onset diabetics who are candidates for oral therapy. Little of the commentary available to us raises questions on this point, and we assume that the UGDP population is representative of a large fraction of the maturity-onset, non-insulin-dependent diabetic population.

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

8. The FDA audit

The FDA telegraphed its intention to revise the label for sulfonylurea drugs to warn against cardiovascular risks associated with use when results of the trial became known. The proposed relabeling riled many in the diabetic community because it was seen as heavy-handed and precipitous in view of reservations in the community regarding the validity of the results.[4] (See Chapter 11 for details on the labeling effort.)

Since the labeling focused on risks of cardiovascular deaths with sulfonylurea drugs, critics raised questions as to the accuracy of cause of death classifications. The text below details processes used in the study for classification of deaths.[88]

> *A preliminary death report identifying the study patient, the date of his death, and the clinic responsible for follow-up of that patient was forwarded to the Coordinating Center within one week of the time personnel at that clinic first became aware of the fact that a death had occurred in their study population. A detailed death report was forwarded to the Coordinating Center as soon as all the necessary information had been collected. Each detailed death report was to include a copy of the death certificate, a copy of the autopsy report, if available, and a clinical summary of the patient's terminal course of illness. The clinical summary was prepared by the study physician most familiar with the medical history of the deceased patient. This summary included an abstract of all pertinent medical records and the study physician's opinion regarding the principal cause of death. If the patient died suddenly and unexpectedly, the study physician was instructed to contact those individuals most familiar with the patient's condition at the time of death in order to obtain a description of the events leading to death.*
>
> *The final judgment concerning the principal cause of death for each deceased patient was made by a special review team without knowledge of the treatment group to which the patient had been assigned. This team consisted of the chairman of the UGDP Mortality Committee and*

8. FDA audit

a consultant pathologist. Their decision regarding principal cause of death was based on information provided in the detailed death report prepared at the study clinic. In those instances in which the decision of the review team was in disagreement with that reached by the patient's study physician, the decision of the review team was the one used in the analyses summarized in this report. Most of these disagreements were minor and occurred within the category of Cardiovascular (C.V.) Deaths or within the category of Noncardiovascular Deaths. Only two disagreements resulted in a change of classification of cause of death from the category Cardiovascular to the category Noncardiovascular or vice versa. Both of these disagreements occurred with patients in the insulin standard treated group.

Eventually, the FDA succumbed to pressures to audit records in the coordinating center. The audit took place in the summer of 1977. The summary of the audit, dated 20 September 1977, is reproduced below. The entire audit report is posted to trialsmeinertsway.com under "Historical Archive".

Summary of FDA auditors (verbatim from the audit report)

The objective of this review was to compare causes of death submitted by the participating clinical centers to the UGDP Coordinating Center with the causes of death assigned by the UGDP mortality review team and those published by the UGDP. The cause of death assigned by the review team was a judgment made on the basis of the information available, which in addition to the UGDP death forms filled out by the clinic physicians, included death certificates, autopsy reports when available, and case summaries or other information provided by the clinic physicians in correspondence.

There were 11 deaths in which the cause of death published by the UGDP differed from that listed by the clinic physicians on the UGDP

death form and the cardiovascular/non-cardiovascular classification was different. In 24 additional deaths the listed causes of death were different but there was no change in the cardiovascular/non-cardiovascular classification.

In many cases changes in the cause of death by the UGDP review team were based on the decision to assign what was interpreted as the underlying or principal cause of death rather than the immediate cause of death. Although not resulting in a change in the cardiovascular/non-cardiovascular classification, a frequent change made by the review team was from myocardial infarction not supported by electrocardiogram or other laboratory data to sudden death.

It was not the intention in this review to make a judgment on the cause of death in each case based on a detailed review of all the information available, but rather to determine if there were obvious discrepancies or errors in listing the cause of death. There appeared to be no such major discrepancies between the information available on these deaths and the cause of death assigned by the UGDP review team, although it is recognized that assignment of cause of death is a judgment and differences of opinion could arise when the information is reviewed by different individuals.

In comparing the causes of death coded by the UGDP review team with those published by the UGDP, differences were found in 3 patients. The cause of death in one case was listed by the review team as myocardial infarction, but was published as sudden death, which did not change the cardiovascular classification. In two additional cases that involved a change in the cardiovascular/non-cardiovascular classification, the causes of death initially assigned by the review team were later changed by the review team, but the initial assignments and not the corrected assignments were published. If published and analyzed as the review team apparently

intended, one death in the placebo groups would have been classified as non-cardiovascular rather than cardiovascular and one death in the insulin variable group would have been classified as cardiovascular rather than non-cardiovascular.

A retabulation of deaths by treatment and cardiovascular or non-cardiovascular categories is given, which includes the 2 cases discussed above that apparently were not published as the mortality review team intended, and also the 9 deaths that were not included in the published analyses because the records were not received prior to the cut-off dates for analysis, although the deaths had occurred prior to these cut-off dates.

Tolbutamide Analysis

	No. at risk	CV deaths		Non-CV deaths	
		Published	Retabulation	Published	Retabulation
Plbo*	205	10	10	11	13
Tolb	204	26	26	4	4
IStd	210	13	13	7	7
IVar	204	12	15	6	6

8. FDA audit

Phenformin Analysis

	No. at risk	*CV deaths*		*Non-CV deaths*	
		Published	*Retabulation*	*Published*	*Retabulation*
Plbo[*]	*64*	*3*	*4*	*4*	*4*
Phen	*204*	*27*	*29*	*7*	*8*
Plbo[*]*+IStd+IVar*	*197*	*12*	*13*	*5*	*5*
IStd+IVar	*133*	*9*	*9*	*1*	*1*

[*] *Of the 3 placebo patients in the group of 9 deaths not included in the original analyses, 2 patients (nos. 158 and 159) were in the placebo group for tolbutamide and died prior to the 1969 cut-off date, and one patient (no. 156) was in the placebo group for phenformin and died in August 1971.*

9. The Committee on the Care of the Diabetic

The Committee on the Care of the Diabetic (CCD) was formed as a counter force to the efforts of the FDA to relabel tolbutamide and other members of the sulfonylurea class of drugs. It was organized in the fall of 1970; several months after results were presented and about when results were published.[88] Its 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). See reference 4 for an account of the CCD's concerns regarding the UGDP and of the role of the FDA in the controversy.

The coordinating committee for the CCD, as comprised when the CCD was formed, was:

Robert F Bradley, MD (chair of CCD), Medical Director, Joslin Clinic, Boston

Henry Dolger, MD, Professor of Clinical Medicine, Mount Sinai School of Medicine, City University of New York, New York

Peter H Forsham, MD, Chief of Endocrinology, Professor, Department of Medicine, University of California Medical Center, San Francisco

Holbrooke S Seltzer, MD, Chief of Endocrinology, Professor of Internal Medicine, Veterans Administration Hospital, University of Texas Southwestern Medical School, Dallas

Neil L Chayet, Esq., Attorney for the Committee, 15 Court Square, Boston

The dates and events below are relevant to actions taken by the committee pursuant to the three above mentioned areas of focus.

1969 June 6	UGDP investigators vote to discontinue tolbutamide treatment[84]
1970 May 20	Tolbutamide results on Dow Jones ticker tape[49]

9. The CCD

1970 May 21, 22	*Wall Street Journal*, *Washington Post*, and *New York Times* articles on tolbutamide results[40,50,55]
1970 June 14	Tolbutamide results presented at American Diabetes Association meeting, St Louis[84,85,86]
1970 October 30	Food and Drug Administration (FDA) publishes bulletin supporting findings[29]
1970 November	Tolbutamide results published[88]
1970 November	Committee on the Care of Diabetic (CCD) formed[26]
1971 April	Feinstein criticism of UGDP published[18]
1971 May 16	UGDP investigators vote to discontinue phenformin treatment in UGDP[82,80]
1971 June	FDA outlines labeling changes for sulfonylureas[28]
1971 August 9	UGDP preliminary report on phenformin published[82]
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[7]
1971 September 20	Schor criticism of UGDP published[56]
1971 September 20	Cornfield defense of UGDP published[9]
1971 October 7	CCD petitions FDA commissioner to rescind proposed label change[26]
1972 May	FDA reaffirms position on proposed labeling change[27]
1972 June 5	FDA commissioner denies CCD 7 October 1971 request to rescind proposed label change[26]
1972 July 13	CCD requests evidentiary hearing before FDA commissioner on proposed labeling changes[26]
1972 August 3	Commissioner of FDA denies 13 July 1972 CCD request for evidentiary hearing[65]

9. The CCD

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[65]
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[26,65]
1972 August	Biometrics Society Committee starts review of UGDP and other related studies[7]
1972 September	Seltzer criticism of UGDP published[59]
1972 October 17	Second motion for injunction against label change filed by CCD in the United States District Court for the District of Massachusetts[65]
1972 October	Response to Seltzer critique published[81]
1972 November 3	Temporary injunction order granted by Judge Murray of the United States District Court for the District of Massachusetts[65]
1972 November 7	Preliminary injunction against proposed label change granted by United States District Court for the District of Massachusetts[26]
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[26,65]
1973 October	FDA hearing on labeling of oral agents[26]
1974 February	FDA circulates proposed labeling revision[26]
1974 March-April	FDA holds meeting on proposed label change, then postpones action on change until report of Biometrics Committee[26]

9. The CCD

1974	Sept 18-20	Testimony taken concerning use of oral hypoglycemic agents before the United States Senate Select Committee on Small Business, Monopoly Subcommittee[70]
1975	January 31	Additional testimony concerning use of oral hypoglycemic agents before the United States Senate Select Committee on Small Business, Monopoly Subcommittee[71]
1975	February 10	Report of the Biometrics Committee published[7]
1975	February	UGDP final report on phenformin published[80]
1975	July 9, 10	Additional testimony concerning use of oral hypoglycemic agents before the United States Senate Select Committee on Small Business, Monopoly Subcommittee[71]
1975	August	End of patient followup in UGDP[76]
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[67]
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[69]
1975	December	FDA announces intent to audit UGDP results[73]
1976	February 5	United States District Court for the District of Columbia rules UGDP raw data not subject to FOIA[66]
1976	February 25	CCD files appeal of February 5 decision in United States Court of Appeals for the District of Columbia Circuit[73]

9. The CCD

1976 October	FDA Endocrinology and Metabolism Advisory Committee recommends removal of phenformin from market[23]
1977 March 8	United States District Court for the Southern District of New York rejects Ciba-Geigy request for UGDP raw data[68]
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[24]
1977 May 6	FDA begins formal proceedings to remove phenformin from market[24]
1977 May 13	FDA holds public hearing on petition of HRG[24]
1977 July 25	Secretary of HEW announces decision to suspend New Drug Applications (NDAs) for phenformin in 90 days[24]
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[25]
1977 December	UGDP announces release of data listings for individual patients[78]
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[77]

9. The CCD

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[64,73]
1978 July 25	CCD petitions United States Court of Appeals for the District of Columbia Circuit for rehearing on July 11 ruling[73]
1978 October 17	Petition for rehearing at the United States Court of Appeals for the District of Columbia Circuit denied[73]
1978 November 14	Results of FDA audit of UGDP announced[22]
1978 November 15	FDA Commissioner orders phenformin withdrawn from market[72]
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[73]
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[72]
1980 March 3	United States Supreme Court holds that HEW need not produce UGDP raw data; 7 to 2 decision[72]
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[74,75]

9. The CCD

1984 March 16	Revised label for sulfonylurea class of drugs released[19,20,21]

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

10. The UGDP and Henry Kissinger

Members of the CCD regarded the UGDP as badly flawed* and reasoned that if they were to gain access to raw data# of the trial they would be able to reanalyze and show where investigators went wrong.

Raw data has various meanings:[45]

1. Measurements and observations as recorded on a data record or data form.
2. Data before any editing.
3. Data prior to adjustment.
4. Data contained in an electronic data file or listing prior to manipulation for reduction or analysis.

Data transform from "raw" to "processed"& as soon as they are edited or transformed for repose in a dataset for processing.

The CCD request was for "forms transmitted to the Coordinating Center and the computer tapes and/or programs on the basis of which the data were analyzed".[64] Data on "forms transmitted to the coordinating center" would be "raw", but "computer tapes and/or programs" are not "raw" by any definition of the term.

The CCD filed suit against David Mathews, Secretary of Health, Education, and Welfare in the United States District Court for the District of Columbia[67] on 30 September 1975 for access to the raw data of the UGDP under the Freedom of Information Act (FOIA). (A similar request was filed in the United States District Court for the Southern District of New York[69] by Ciba-Geigy two weeks later.) The court ruled against the CCD 5 February 1976.[66]

The CCD appealed the decision to the United States Court of Appeals for the District of Columbia Circuit 25 February 1976.[73] That appeal was denied 11 July 1978. The ruling was that the public does not have right to UGDP data under the FOIA.[64,73]

10. The UGDP and Henry Kissinger

The CCD petitioned for a rehearing 25 July 1978. That petition was denied 17 October 1978.[73]

That denial was followed on 15 January 1979 by a petition to the United States Supreme Court for a writ of certiorari to the United States Court of Appeals for the District of Columbia Circuit.[73] The writ was granted 14 May 1979.

At about the same time as the CCD's initial request, William Safire of the New York Times filed a request for Henry Kissinger's telephone notes from 21 January 1969 through 12 February 1971.

That request was followed by one from the Military Audit Project (28 December 1976) and one from the Reporters Committee for Freedom of the Press (13 January 1977). Those two requests were for all telephone notes while Kissinger was Secretary of State.

Safire's request was denied on grounds that Kissinger was National Security Adviser during the time period covered in his request and that advisers to the President are not considered to be governmental agencies under the FOIA. The court of appeals ordered the State Department to produce Kissinger's telephone notes for the other two requests. That order was appealed.
(https://www.quimbee.com/cases/kissinger-v-reporters-committee-for-freedom-of-the-press)

The CCD's request and the two for Kissinger's telephone notes were heard at the same time by the Supreme Court; argued 31 October 1979 and decided 3 March 1980.

The ruling in the Kissinger case was 4 to 2 against the requestors. The majority opinion was written by Rehnquist with Burger, White, and Powell joining. Brennan and Stevens filed opinions concurring in part and

10. The UGDP and Henry Kissinger

dissenting in part with Rehnquist. Justices Marshall and Blackmun did not take part in the consideration or decision of the cases.

The ruling in the UGDP was 7 to 2 that

> *Written data generated, owned, and possessed by privately controlled organization as grantee of funds from HEW, held not accessible as 'agency records' under Freedom of Information Act when HEW never obtained data.*

The majority opinion was written by Justice Rehnquist and joined by Burger, Stewart, White, Blackmun, Powell, and Stevens. Brennan and Marshall dissented. The opinion in its entirety is posted to trialsmeinertsway.com; tab "Historical Archive".

The opinion in the UGDP hinged primarily on the fact that the NIH did not ask for data when the trial was ongoing. It is apparent that the ruling might well have been different if the trial was done under contract with the NIH and subjected to closer monitoring by the agency.

A decision granting the CCD's request would have created problems in the coordinating center identifying the "computer tapes and/or programs" to be provided. Which analysis and what dataset? The programs and dataset used to prepare the report presented to investigators when they voted to stop tolbutamide or the programs and dataset used to produce the published report?

The request would have involved copying thousands of data forms. The request was before the Health Insurance Portability and Accountability Act of 1996.[14] Certainly any transmission of data forms on research subjects today would constitute a violation of the act without permission of the persons on whom forms were completed.

10. The UGDP and Henry Kissinger

What the CCD intended to do with data forms is unclear. The supposition is that they would have rekeyed forms to compare keyings with ours. Such comparisons would have been tedious because of editing that went on at the coordinating center during entry processes.

---

* One of the universal criticisms[47] of trials is that "the trial is flawed". Just fill in the name. But nature abhors perfection. In regard to trials, that means every trial is flawed. Hence, the issue is not whether the trial is flawed, but rather whether the flawing is sufficient to make one doubt the findings. If the "flawing" is uniform across treatment groups (as is usually the case in randomized trials), all the flawing does is add "noise" to the treatment comparisons.

It was never clear what the CCD was after. The 1970 UGDP publication[88] contained a listing of data for deceased patients included in the publication. Announcement of availability of a paper listing of baseline and followup data for all 1,027 people was contained in the December 1977 issue of Diabetes.[78] In 1983 that listing and a magnetic tape containing the same information was deposited at the National Technical Information Service.[74,75]

& The term "cooked" is used in some circles to distinguish raw from processed data but "cooked" in reference to data in trials means made up or fudged. Referring to data as "cooked" to a trialist would probably produce the same result as with the woman in the Polaner All Fruit ad when her dinner guest asks her to pass the jelly. (http://youtu.be/hawQ5wobi1Y).

11. The saga of the label change

The tolbutamide-placebo difference in CV mortality was striking. The conventional p-value for the difference was 0.005 when tolbutamide was stopped. But even with that, it is likely the results would have faded into obscurity had it not been for the efforts of the FDA to relabel the drug warning of CV risks associated with use.

The opening salvo from the FDA was telegraphed in a Bulletin issued from the FDA by the Commissioner, Charles Edwards, and included as front matter in the Diabetes supplement containing the tolbutamide results.

The proposed relabeling had medical-legal implications in that it opened the door to legal action if persons on the drug experienced heart attacks. The concern regarding relabeling was a driving force behind creation of the Committee on the Care of the Diabetic (CCD) (Chapter 9).

Efforts of the CCD focused on forestalling the relabeling. The CCD began its efforts via a request to the Commissioner of the FDA (7 October 1971) to stay the relabeling. A stay was granted 7 November 1972.[26] The label had been printed and supplied to manufacturers when the stay was granted.

Chronology of events relevant to relabeling effort

1970 October	Food and Drug Administration (FDA) publishes statement indicating concerns regarding the place of oral antidiabetic agents in the treatment of diabetes mellitus; published as front matter in the Diabetes supplement containing UGDP results[88]
1971 June	FDA outlines labeling changes for sulfonylureas[28]
1971 October 7	CCD petitions FDA commissioner to rescind proposed label change[26]
1972 May	FDA reaffirms position on proposed labeling change[27]

11. The saga of the label change

1972 June 5	FDA commissioner denies 7 October 1971 CCD request[26]
1972 July 13	CCD requests evidentiary hearing before FDA commissioner on proposed labeling changes[26]
1972 August 3	Commissioner of FDA denies CCD request for evidentiary hearing[65]
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[65]
1972 August 30	Request to have the FDA enjoined from making labeling change denied by United States District Court for the District of Massachusetts[26,65]
1972 October 17	Second motion for injunction against label change filed by CCD in the United States District Court for the District of Massachusetts[65]
1972 November 3	Temporary injunction order granted by United States District Court for the District of Massachusetts[65]
1972 November 7	Preliminary injunction against proposed label change granted by United States District Court for the District of Massachusetts[26]
1973 July 31	Preliminary injunction vacated by United States Court of Appeals for the First Circuit; case sent back to FDA for further deliberations[26,65]
1973 October	FDA hearing on labeling of oral agents[26]
1974 February	FDA circulates proposed relabeling[26]
1974 March-April	FDA holds meeting on proposed label change, then postpones action on change until report of Biometrics Committee[26]
1975 December	FDA announces intent to audit UGDP results[73]
1976 September	FDA audit of UGDP

11. The saga of the label change

1978	November 14	Results of FDA audit of UGDP announced[22]
1984	March 16	Revised label for sulfonylurea class of drugs released[19,20,21]

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

It was 13 years after relabeling was proposed before it was accomplished. The warning is reproduced below.

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 1/2 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

11. The saga of the label change

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 for proponents of the change. By the time it was incorporated in the label, the diabetes world had moved onto other drugs not of the sulfonylurea class.

The battle also serves as a warning to those who rely on labels for timely information on side effects of drugs.

12. The media and scientific journals

The investigators plan was "mum's the word" in regard to tolbutamide results until they were published. But the plan fell apart when investigators decided to present the results at the ADA meeting in June 1970 in anticipation of the results being published by then. They misjudged.

The publication came months after the presentation. But even if they had managed to time the publication to come when results were presented, they still would have had a time gap created by release of results prior to the meeting.

1. Mainstream press

The first report ran at 2:17 pm Wednesday 20 May 1970 on the Dow Jones ticker. It was a report from a Kidder Peabody analyst warning investors of results adverse to Upjohn. That the first report was on a financial service wire was no surprise in retrospect in view of the volume of sales due to uses of Orinase®. The drug accounted for nearly half of all prescriptions for oral hypoglycemic agents at the time.[48]

That report was followed in the next few days by articles in major newspapers, including the *Wall Street Journal*, *Washington Post*, and *New York Times*,[40,50,55,49] featuring headlines such as:

Safety of Upjohn's oral antidiabetic drug doubted in study: Firm disputes findings (21 May 1970, Wall Street Journal)

Antidiabetes pill held causing early death (22 May 1970, Washington Post)

Scientists wary of diabetic pill: FDA study indicates oral drug may be ineffective (22 May 1970, New York Times)

Discovery of diabetes drug's perils stirs doubts over short-term tests (8 June 1970, Washington Post)

12. The media and scientific journals

By the time of the meeting it seemed that everyone knew of the results, including patients calling their doctors to find out if they were on that "killer diabetes drug".

The presentation in St Louis did nothing to quell the criticisms.

2. Throwaway medical journals

We were crucified in the throwaway medical journals. We were accused of grandstanding, data dredging, malfeasance, and fraud. We were to the Medical Tribune and Hospital Tribune what Jackie Kennedy Onassis was to magazines at check out counters in supermarkets, always on the front page. Sample headlines follow.

Medical Tribune

Investigators question study group's findings (Monday, June 29, 1970)
Experts challenge data, design of investigation (Monday, July 6, 1970)
Irish study of antidiabetics contradicts findings in US (Wednesday, December 15, 1971)
Why the conclusions of the UGDP are incorrect (Wednesday, June 4, 1975)
Biometric Report on UGDP study stirs skepticism (Wednesday, June 11, 1975)
A UGDP “Miracle”?...Some UGDP questions (Wednesday, August 27, 1975)
Doctors' debate. UGDP computer vs. clinical data (Wednesday, June 23, 1976)

Hospital Tribune

2 Diabetes researchers quit over demand for “unanimity” (Monday, December 14, 1970)
Tolbutamide fiasco (Monday, December 14, 1970)

12. The media and scientific journals

"Misleading impression" laid to UGDP report (Monday, February 22, 1971)
Danger is seen in hasty action on antidiabetics (Monday, March 22, 1971)
Canadian diabetes group rejects UGDP study (Monday, April 19, 1971)
3 Nonpartisan experts doubt worth of UGDP findings (Monday, July 25, 1971)
Why the conclusions of the UGDP are incorrect (Monday, June 16, 1975)
Europe skeptical of Biometric Study of UGDP (Monday, July 14, 1975)

The inclination was to respond to criticisms in the throwaway press, but it became clear that doing so would sap our energy, so we opted to sit on our hands in regard to the throwaway press.

3. Medical journals

A more difficult question was what to do about criticisms published in peer reviewed journals. There were several over the years, starting with Schor's,[56] and Feinstein's[18] in 1971, then Selzer's[59] in 1972, Feinstein's again in 1976[16,17], Kilo's et al[37] in 1980 and others since. Most of these we answered. Responses are contained in references 81 and 57, and in an article by Cornfield[9] and summarized in the next chapter.

Other pro and con publications concerning the UGDP published through 1980 in indexed medical journals are listed below.

1. Status of problem of usage of tolbutamide. Preliminary statements. FDA statement. Friday, May 22, 1970. Diabetes 1970 19:467.

2. Status of problem of usage of tolbutamide. Preliminary statements. Statement of chairman of UGDP. Thursday, May 21, 1970. Diabetes **1970** 19:467.

12. The media and scientific journals

3. Hazards of Leaks. Nature **1970** Jul 18;227:224-225.

4. **Ricketts** HT (for the American Diabetes Association): Editorial statement on the University Group Diabetes Program Research Group. October 7, 1970. Diabetes **1970** 19(Suppl 2):iii-v.

5. Statement regarding the University Group Diabetes Program (UGDP) Study. AMA Council on Drugs. Nov 2, 1970. Diabetes **1970** 19(Suppl 2):vi-vii.

6. Oral hypoglycemic agents. Report of the Food and Drug Administration. Oct 30, 1970. Diabetes **1970** 19(Suppl 2):viii-ix.

7. Drug fears dismissed. Nature **1970** Nov 14;228:599.

8. Are antidiabetic drugs dangerous? Br Med J **1970** Nov 21;4(5733):444-445.

9. Tolbutamide study raises blood pressures. Nature **1970** Dec 26;228:1251-1251.

10. **Barclay** WR: Tolbutamide: More questions than answers (editorial). JAMA **1971** Jan 4;215(1):108-109.

11. **Spodick** DH: Ethics and clinical trials (letter). JAMA **1971** Feb 15;215(7):1156

12. The tolbutamide evidence. Lancet **1971** Jan 23(1);171-172.

13. **Palmer** RF, Lasseter KC, McCarthy J: Tolbutamide: An inotropic effect on rabbit atria (letter). Lancet **1971** Mar 20;1(7699):604.

12. The media and scientific journals

14. **Smelo** LS: University Group Diabetes Program (letter). JAMA **1971** Mar 29;215(13):2115.

15. Canadian Diabetic Association Statement concerning tolbutamide. Bulletin. Published by the Food and Drug Directorate. **1971** May:65-66.

16. **Leibel** B: An analysis of the University Group Diabetes Study Program: Data results and conclusions. Can Med Assoc J **1971** August 7;105:292-294

17. Year-end report: Still no agreement about the UGDP study (Medical News). JAMA **1971** Aug 9;217(6):760762.

18. **Ballin** JC: Phenformin treatment of diabetes (editorial). JAMA **1971** Aug 9 Vol 217(6):817.

19. **Winegrad** AI, Davidson JK, Ricketts HT, Sprague RG: The University Group Diabetes Program Study pertaining to phenformin (editorial). JAMA **1971** Aug 9 Vol 217(6):817.

20. **Leibel** B: An analysis of the University Group Diabetes Study Program: Data results and conclusions. Can Med Assoc J **1971** Aug 7;105(3):292-294.

21. **Feinstein** AR: Clinical biostatistics: VIII. An analytic appraisal of the University Group Diabetes Program (UGDP) study. Clin Pharmacol Ther **1971** 12:167-191.

22. **Roth** J, Prout TE, Goldfine IRD, Wolfe SM, Muenzer J, Grauer L, Marcus ML: Sulfonylureas: Effects in vivo and in vitro (NIH conference). Ann Intern Med **1971** Oct;75(4):607-621.

12. The media and scientific journals

23. **Seltzer** HS: Tolbutamide mortality in the six “phenformin clinics” (letter). JAMA **1971** Oct 25;218(4):594.

24. **Salsburg** DS: The UGDP study (letter). JAMA **1971** 218(11):1704-1705.

25. **Cornfield** J: The UGDP study (letter). JAMA **1971** 218(11):1705.

26. **Seltzer** HS: Avoiding the pitfalls for long-term therapeutic trials: Lessons learned from the UGDP study. J Clin Pharmacol New Drugs **1972** Oct;12(10):393-398.

27. **Prout** TE, Knatterud GL, Meinert CL, et al: The UGDP controversy: Clinical trials versus clinical impressions. Diabetes **1972** 21:1035-1040.

28. Tolbutamide and the heart (editorial). JAMA **1972** 222(9):1179-1180.

29. **Moser** RH: Let's stop the donnybrook. A perspective on the UGDP-Biometric Society study. JAMA **1975** Mar 24;231(12):1274-1276.

30. **Moss** JM: The UGDP scandal and cover-up (letter). JAMA **1975** May 26;232(8):806-808.

31. **Marble** A: The UGDP scandal and cover-up (letter). JAMA **1975** May 26;232(8):808.

32. **Haunz** EA: The UGDP scandal and cover-up (letter). JAMA **1975** May 26;232(8):808-809

12. The media and scientific journals

33. **O'Sullivan** JB, D'Agostino RB: Decisive factors in the tolbutamide controversy. JAMA **1975** May 26;232(8):825-829.

34. **Davidson** JK: The FDA and hypoglycemic drugs. JAMA **1975** May 26;232(8):853-855.

35. **Williams** RH, Palmer JP: Farewell to phenformin for treating diabetes mellitus. Ann Intern Med **1975** Oct;83(4):567-568.

36. **Cahill** GF, Etzwiler DD, Freinkel N: Blood glucose control in diabetes. Diabetes **1976** March;25(3):237-239

37. **Knowles**, Jr HC: An historical view of the medical-social aspects of the UGDP. Trans Am Clin Climatol Assoc **1977** 88:150-156.

38. FDA upholds findings of UGDP study (Medical News). JAMA **1979** 241(1):17-18.

39. **Kilo** C, Williamson JR, Sung CC, Miller JP: Insulin treatment and diabetic vascular complications (letter). JAMA **1979** Jan 5;241(1)26-27.

40. **American Diabetes Association Policy Statement**: The UGDP Controversy. Diabetes Care **1979** Jan-Feb 2(1):1-3.

41. **Whitehouse** FW, Arky RA, Bell DI, Lawrence PA, Freinkel N: Policy statement. The UGDP controversy. Diabetes **1979** Feb 28:168-170.

42. **Goldner** MG: Diabetes drugs: Clinical trial (letter). Science **1979** 204:363-365.

43. **Meier** P: Diabetes drugs: Clinical trial (letter). Science **1979** 204:365.

44. **Scott** J, Poffenbarger PL: Tolbutamide pharmacogenetics and the UGDP controversy. JAMA **1979** 242(1):45-48.

45. **Kilo** C, Williamson JR, Choi SC, Miller JP: Refuting the UGDP conclusion that insulin treatment does not prevent vascular complications in diabetes. Adv Exp Med Biol **1979** 119:307-311. Camerini-Davalos RA and Hanover B (eds). *Treatment of Early Diabetes*, Plenum Press, New York

46. **Kilo** C, Miller JP, Williamson JR: The Crux of the UGDP. Spurious results and biologically inappropriate data analysis. Diabetologia **1980** Mar 18(3):179-185.

47. **Sackler** AM: The unsettling UGDP controversy. JAMA **1980** Apr 11;243(14):1435-1436.

48. **Council on Scientific Affairs**: Hypoglycemic treatment. Guidelines for the non-insulin-dependent diabetic. JAMA **1980** May;243(20):2078-2079.

49. **Melander** A, Wahlin-Boll E: Clinical pharmacology of glipizide. Am J Med **1983** Nov 30;75(5B):41-45.

50. **Kaplan** RM, Ganiats TG: Trade-offs in treatment alternatives for non-insulin-dependent diabetes mellitus. J Gen Intern Med **1989** Mar-Apr;4(2):167-171.

13. Criticisms

Show me a trial, and I will produce a list of criticisms of the trial. Some perhaps legitimate and others not, but all designed to play well in Peoria. My own list of universal criticisms is contained in a table in Chapter 49 of the 2nd edition of my text on clinical trials.[46] The list below is of criticisms of the UGDP. Some legitimate and some not.

Criticism*	**Comment**
The study was not designed to detect differences in mortality (Schor, 1971)[56]	The aim of the trial was to detect differences in nonfatal vascular complications of diabetes (UGDP Research Group, 1970d).[87] However, this focus in no way precludes comparisons for mortality differences. In fact, it is not possible to interpret results for nonfatal events in the absence of data on fatal events.
The observed mortality difference was small and not statistically significant (Feinstein, 1971; Kilo et al, 1980)[18,37]	It is unethical to continue a trial, especially one involving an elective treatment, to produce unequivocal evidence of harm.
The baseline differences in the composition of the study groups are large enough to account for the excess mortality in the tolbutamide treatment group (Feinstein, 1971; Kilo et al, 1980; Schor, 1971; Seltzer, 1972)[18,37,56,59]	The tolbutamide-placebo mortality difference remains after adjustment for important baseline characteristics.[9]

13. Criticisms

Criticism	Comment
The tolbutamide-assigned group had a higher concentration of baseline cardiovascular risk factors than any of the other treatment groups (Feinstein, 1971; Kilo et al, 1980; Schor, 1971; Seltzer, 1972)[18,37,56,59]	Differences in the distribution of baseline characteristics, including CV risk factors, is within the range of chance. Further, the mortality excess is as great for the subgroup of patients who were free of CV risk factors as those who were not. Simultaneous adjustment for major CV baseline risk factors did not account for the excess (UGDP Research Group, 1970e; Cornfield, 1971).[88,9]
The treatment groups included patients who did not meet study eligibility criteria (Feinstein, 1971; Schor, 1971)[18,56]	Correct. However, the number of such cases was small and not differential by treatment group. Further, analyses in which ineligible patients were removed did not effect the tolbutamide-placebo mortality difference (UGDP Research Group, 1970d).[87]
Data from patients who received little or none of the assigned study medication should have been removed from analysis (Kilo et al, 1980; Seltzer, 1972)[37,59]	The initial analysis included all patients to avoid the introduction of selection biases. This analysis approach tends to underestimate the true effect. Analyses in which noncompliant patients were not counted enhanced the mortality difference (UGDP Research Group, 1970d)[87].

13. Criticisms

Criticism	Comment
The data analysis should have been restricted to patients with good blood glucose control (Kilo et al, 1980)[37].	The analysis philosophy for this variable was the same as for drug compliance. The removal of patients using a variable influenced by treatment has a good chance of rendering the treatment groups noncomparable with regard to important baseline characteristics. In any case, analyses by level of blood glucose control did not account for the mortality difference (UGDP Research Group, 1971a)[83].
The study failed to collect relevant clinical data (Feinstein, 1971; Seltzer, 1972)[18,59]	The criticism is not justified. The study collected data on a number of variables needed for assessing the occurrence of various kinds of peripheral vascular events. It is always possible to identify some variable that should have been observed with the perspective of hindsight. The criticism lacks credibility, in general and especially in this case, because of the nature of the result observed. It is hard to envision other clinical observations that would offset mortality, an outcome difficult to reverse!

13. Criticisms

Criticism	Comment
There were changes in the ECG coding procedures midway in the course of the study (Schor, 1971; Seltzer, 1972)[56,59]	Correct. However, the changes were made before investigators had noted any real difference in mortality and were made without regard to observed treatment results (Cornfield, 1971).[9]
The patients did not receive enough medication for effective control of blood glucose levels (Seltzer, 1972)[59]	A higher percentage of tolbutamide-assigned patients had blood glucose values in the range indicative of good control than the placebo-assigned patients. The percentage of patients judged to have fair or good control, based on blood glucose determinations done over the course of the study, was 74 in the tolbutamide-assigned group versus 59 in the placebo-assigned group (UGDP Research Group, 1971a, 1976).[83,79]

13. Criticisms

Criticism	Comment
The excess mortality can be accounted for by differences in the smoking behavior of the treatment group (source unknown)	The argument is not plausible. While it is true that the study did not collect baseline smoking histories, there is no reason to believe that the distribution of this characteristic would be so skewed so as to account for the excess (Cornfield, 1971).[9] The study did in fact make an effort to rectify this oversight around 1972 with the collection of retrospective smoking histories. There were no major differences among the treatment groups with regard to smoking histories. However, the results were never published because of obvious questions involved in constructing baseline smoking histories long after patients were enrolled and then with the use of surrogate respondents for deceased patients. The oversight is understandable given the time the trial was designed. Cigarette smoking, while recognized at that time as a risk factor for cancer, was not widely recognized as a risk factor for coronary heart disease.

13. Criticisms

Criticism	Comment
The observed mortality difference can be accounted for by differences in the composition of the treatment group for unobserved baseline characteristics (Feinstein, 1971; Schor, 1971)[18,56]	This criticism can be raised for any trial. However, it lacks validity since there is no reason to assume treatment groups in a randomized trial are any less comparable for unobserved characteristics than for observed characteristics. And even if differences do exist, they will not have any effect on observed treatment differences unless the variables in question are important predictors of outcome.
The majority of deaths were concentrated in a few clinics (Feinstein, 1971; Seltzer, 1972)[18,59]	Differences in the number of deaths by clinic are to be expected. However, the differences are irrelevant to comparisons by treatment groups, since the number of patients assigned to treatment groups was balanced by clinic (UGDP Research Group, 1970d, 1970e).[87,88]
The study included patients who did not meet the "usual" criteria for diabetes (Seltzer, 1972)[59]	There are a variety of criteria used for diagnosing diabetes, all of which are based, in part or totally, on the glucose tolerance test. The sum of the fasting one, two, and three hour glucose tolerance test values used in the UGDP represented an attempt to make efficient use of all the information provided by the test (UGDP Research Group, 1970d).[87]

13. Criticisms

Criticism	Comment
The patients received a fixed dose of tolbutamide. The usual practice is to vary dosage, depending on need (Feinstein, 1971; Schor, 1971; Seltzer, 1972)[18,56,59]	Most patients in the real world receive the dosage used in the study (UGDP Research Group, 1972).[81]
The randomization schedules were not followed (Schor, 1971)[56]	The Biometrics Committee reviewed the randomization procedure and found no evidence of any breakdown in the assignment process (Committee for the Assessment of Biometric Aspects of Controlled Trials of Hypoglycemic Agents, 1975).[7]
There were "numerous" coding errors made at the coordinating center in transcription of data into computer readable formats (Feinstein, 1971)[18]	There is no evidence of any problem in this regard. The few errors noted in audits performed by the Biometrics Committee and FDA audit team were of no consequence in the findings of the trial (Committee for Assessment of Biometric Aspects of Controlled Trials of Hypoglycemic Agents, 1975; Food and Drug Administration, 1978).[7,22]

13. Criticisms

Criticism	Comment
There were coding and classification discrepancies in the assembled data (Kolata, 1979)[39]	The coding and classification error rate was in fact low and the errors that did occur were not differential by treatment group. There were no errors in the classification of patients by treatment assignment or by vital status. Hence, the argument does not provide a valid explanation of the mortality differences observed (Committee for Assessment of Biometric Aspects of Controlled Trials of Hypoglycemic Agents, 1975; Food and Drug Administration, 1978; Prout et al, 1979).[7,22,53]
The cause of death information was not accurate (Feinstein, 1971; Schor, 1971; Seltzer, 1972)[18,56,59]	Independent review of individual death records by the FDA audit team revealed only three classification discrepancies, only one of which affected the tolbutamide-placebo comparison (Food and Drug Administration, 1978).[22] However, in any case, the main analyses in the study and the conclusions drawn from them relate to overall mortality.

13. Criticisms

Criticism	Comment
The study does not prove tolbutamide is harmful (Feinstein, 1971; Schor, 1971; Seltzer, 1972)[18,56,59]	Correct. It would be unethical to continue a trial to establish the toxicity of an elective treatment. Toxicity is not needed to terminate an elective treatment (UGDP Research Group, 1970d).[87]

* The criticisms and comments are as taken from Chapter 49 of reference 46.

14. Results

1. The tolbutamide mortality results

Conclusion (verbatim from reference 88): *All UGDP investigators are agreed that 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.*

Tolbutamide, as a member of the family of sulfonylurea drugs, came into common use for treatment of non-ketosis prone diabetics in the mid 1950s.[35] The drug was heralded as an advance in the treatment of adult-onset diabetes (type 2 diabetes) and, although the hypothesis on which use rested (namely that blood sugar control translates into benefit in reduced morbidity and mortality) was untested, the drug was widely embraced as "safe and effective".

The first test of the hypothesis came with the UGDP. Its results raised doubts as to the benefit of tolbutamide. However, for the most part, diabetologists, rather than questioning the underlying hypothesis, spent their energy attacking the trial.

The mortality results leading to the decision to discontinue tolbutamide are presented in Table 1 and Figures 1 and 2; see also "The UGDP controversy: Thirty-four years of contentious ambiguity laid to rest" by Schwartz and Meinert.[58]

14. Results

1. Tolbutamide results

The tolbutamide-placebo mortality difference in the UGDP started to trend against tolbutamide around year 6 of the trial (1967), with the difference for all cause mortality ultimately approaching the upper 95% monitoring bound (Figure 2) and crossing the 95% upper monitoring bound for CV mortality in year 8 (Figure 2).

Investigators voted to stop use of tolbutamide in the summer of 1969, but not without considerable debate, prompted, in large measure, by a vocal minority who objected to stopping because they did not believe the results were sufficient to show tolbutamide to be harmful.

The tolbutamide-placebo difference in CV mortality was striking. The conventional p-value for the difference was 0.005 by the time tolbutamide was stopped. The concern regarding CV mortality was sufficient to cause the FDA to propose a labeling change for tolbutamide to include a special warning regarding potential CV risks associated with use of the drug. However, the CCD was successful in staying the change via prolonged court battles. Ultimately, the revised label, complete with the special CV warning was issued after court challenges were exhausted – 1984, 13 years after having been proposed by the FDA (see Chapter 11 for warning).

14. Results

2. The phenformin mortality results

Conclusion (verbatim from reference 82): *This study provided no evidence that phenformin was more efficacious than diet alone or than diet and insulin in prolonging life for the patients studied. In fact, the observed mortality from all causes and from cardiovascular causes for patients in the phenformin treatment group was higher than that observed in any of the other treatment groups. In addition, there was no evidence that phenformin was more effective than any of the other treatments in preventing the occurrence of nonfatal vascular complications associated with diabetes. For these reasons, the use of phenformin has been terminated in the UGDP.*

The mortality results leading to the decision are presented in Table 2 and Figure 3 as contained in the above referenced publication.

3. The insulin results

Summary (verbatim from reference 80): *Mortality rates among the treatment groups were comparable. The differences in the occurrence of nonfatal vascular complications among the patients in these three treatment groups were small and only one of the drug-placebo differences was considered significant by the study criterion, and that was the insulin-standard versus placebo comparison for the occurrence of elevated serum creatine levels (8.3% versus 18.5%, p value = 0.005). The occurrence of serious microvascular complications was surprisingly low. The latter finding as well as the slow progression of microvascular complications underscores the differences in the course and the nature of the two principal types of diabetes mellitus, the rather stable and non-ketosis-prone maturity-onset type (type II) and the relatively unstable insulin-dependent juvenile-onset type (type I).*

The insulin results are presented in Tables 3 and 4 and Figure 4 as contained in the above referenced publication.

14. Results

4. Discussion and conclusion

Neither of the two oral agents tested showed evidence of benefit in prolonging life or in reducing the risk of morbidity associated with adult-onset diabetes. Indeed, phenformin disappeared from use on the U.S. market before the trial was finished when it was forcibly removed by action of the Secretary of Health, Education, and Welfare in 1977 because of deaths from lactic acidosis linked to the drug.[24]

Use of Orinase® declined following publication of the tolbutamide results, but the decline was short-lived and soon offset by increased use of other oral agents.[48] Marketing of Orinase® (in pill form) was discontinued in 1999.

An obvious shortcoming of trials is that testing is usually done in ways that depart from everyday usage. Hence, an issue is whether results obtained under "idealized" circumstances generalize to everyday settings. In regard to blood sugar control, the usual everyday practice is to change the dosage, albeit generally within fairly narrow limits, to achieve the desired level of blood sugar control. That option did not exist in the UGDP because investigators opted for a "fixed dose design" in regard to administration of the oral agents tested. The decision was prompted by the desire to evaluate the treatments in a double-masked/blind, placebo-controlled, setting. Hence, the issue of whether the results are generalizable to settings involving individualized dosage schedules is a matter of conjecture.

An even bigger shortcoming, however, is the reality that only a few drugs can be tested in any given trial. Phenformin and tolbutamide are members of the biguanide and sulfonylurea respective class of drugs.

Technically, a trial like the UGDP reveals nothing about the safety and efficacy of other members of the classes. Although scientifically, it is

reasonable to expect that side effects associated with one member of a class will likely be present in other members of the class. That some judgment is needed regarding the similarity of drugs within a class is obvious from the reality that new members of a class appear faster than they can be tested. For example, around the time the tolbutamide results were published, marketing shifted from Orinase® (tolbutamide) to Tolinase® (tolazamide; approved by the FDA July 1966), both members of the sulfonylurea class of drugs – no doubt a shift prompted, in part, by the expiration of patent protection for Orinase®.

One of the problems is the way antidiabetic drugs are approved by the FDA. For approval, an antihyperglycemic drug has to be shown to be safe and effective in lowering blood sugar. However, blood sugar control in non-insulin-dependent adult-onset diabetes is merely a means to an end (see reference 52 for necessary conditions). The supposition is that blood sugar control confers benefits in reducing the risk of death and morbidities associated with diabetes – an intuitively appealing supposition even if largely untested. But drugs, even if shown effective in controlling blood sugar, have other effects: A fact brought to the fore just recently by evidence that rosiglitazone maleate (Avandia®) for blood sugar control carries risks of myocardial infarction and death from CV causes.[51]

There have been various diabetes trials since the UGDP, most notably the Diabetes Control and Complications Trial (DCCT), conducted 1983-1993,[15] and the UK Prospective Diabetes Study (UKPDS).[63] The DCCT grew out of the controversy caused by the UGDP and the equivocal insulin findings, though it concentrated on type 1 diabetes. The DCCT was instrumental in demonstrating that tight control of blood sugar levels in people with type 1 diabetes was useful in reducing the morbidity associated with diabetes.

14. Results

4. Discussion and conclusion

The prevalence of diabetes in the U.S. has increased steadily since the 1950s. The percent of people with diabetes was around 1% when the UGDP started and was estimated to be around 8% in 1993.[36] The number of people living with diabetes in the U.S. was estimated to be 23.6 million (7.8%) in 2007 (http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm#allages; accessed 17 August 2009).

Not surprisingly, there has been a veritable explosion in the prescriptions of oral antidiabetic agents. In 1980, prescriptions in the U.S. were around 13 million.[48] In 1990 there were 23 million such prescriptions and 92 million in 2001.[91] Glipizide and glyburide (sulfonylurea compounds) accounted for 77% of all prescriptions in 1990 and 33.5% in 2001.

The issue of safety of the oral antidiabetic agents remains an open question because the vast majority of diabetes trials are relatively small and short-term in nature. Even under the best of circumstances, clinical trials are weak instruments for detecting rare adverse effects and, hence, the shorter the period of followup, the less the likelihood of detection.

Most trials involving oral antidiabetic[2,34,51] agents are of short-term. For example, of the 29 reports of randomized, placebo-controlled, monotherapy trials captured in Inzucchi's meta-analysis,[34] only one had more than one year of followup. Likewise, of the 42 trials included in the meta-analysis of Nissen and Wolski,[51] only five had more than a year duration of followup.

To be sure, trials are not done to establish harm, but also the absence of evidence of harm, especially in small, short-term trials, cannot be taken as evidence that drugs are safe.

14. Results

5. Tables and figures

Table 1 UGDP tolbutamide-placebo mortality results*

	Number dead		% dead	
	Tolb	Plbo	Tolb	Plbo
Cardiovascular deaths				
1 MI	10	0	4.9	-
2 Sudden death	4	4	2.0	2.0
3 Other heart disease	5	1	2.5	0.5
4 Extracardiac vascular	7	5	3.4	2.4
All CV causes	**26**	**10**	**12.7**	**4.9**
Noncardiovascular causes				
5 Cancer	2	7	1.0	3.4
6 Other than 1-5	2	3	1.0	1.5
7 Unknown cause	0	1	-	0.5
All non-CV causes	**4**	**11**	**2.0**	**5.4**
All causes	**30**	**21**	**14.7**	**10.2**
No. enrolled	**204**	**205**		

* Table reference 88; results as of cutoff date of 7 Oct 1969

14. Results

5. Tables and figures

Table 2 UGDP phenformin-placebo mortality results*

	Number dead					% dead	
	Phen	Plbo	IStd	IVar	Plbo +IStd +IVar	Phen	Plbo +IStd +IVar
Cardiovascular deaths							
1 MI	5	1	1	0	2	2.5	1.0
2 Sudden death	6	1	2	1	4	2.9	2.0
3 Other heart disease	8	0	1	0	1	3.9	0.5
4 Extracardiac vascular	7	0	2	2	4	3.4	2.0
All CV causes	**26**	**2**	**6**	**3**	**11**	**12.7**	**5.6**
Non-cardiovascular causes							
5 Lactic acidosis	1	0	0	0	0	0.5	0.0
6 Cancer	2	3	0	0	3	1.0	1.5
7 Causes other than 1 - 6	2	1	0	0	1	1.0	0.5
8 Unknown cause	0	0	0	1	1	0.0	0.5
All non-CV causes	**5**	**4**	**0**	**1**	**5**	**2.5**	**2.5**
All causes	**31**	**6**	**6**	**4**	**16**	**15.2**	**8.1**
No. enrolled	204	64	68	65	197		

* Table reproduced from reference 82; results as of cutoff date of 6 Jan 1971

14. Results

5. Tables and figures

Table 3 UGDP insulin-placebo mortality results*

	Number dead			% dead		
	IStd	IVar	Plbo	IStd	IVar	Plbo
Cardiovascular deaths						
1 MI	6	4	1	2.9	2.0	0.5
2 Sudden death	8	11	11	3.8	5.4	5.4
3 Other heart disease	4	5	4	1.9	2.5	2.0
4 Extracardiac vascular	9	9	13	4.3	4.4	6.3
All CV causes	**27**	**29**	**29**	**12.9**	**14.2**	**14.1**
Non-cardiovascular causes						
5 Cancer	10	7	16	4.8	3.4	7.8
6 Causes other 1 - 5	9	11	8	4.3	5.4	3.9
8 Unknown cause	2	2	1	1.0	1.0	0.5
All non-CV causes	**21**	**20**	**25**	**10.0**	**9.8**	**12.2**
All causes	**48**	**49**	**54**	**22.9**	**24.0**	**26.3**
No. enrolled	210	204	205			

* Table reproduced from reference 77; results as of cutoff date of 31 Dec 1974

14. Results

5. Tables and figures

Table 4 UGDP insulin-placebo morbidity results (as of 31 Dec 1974)*

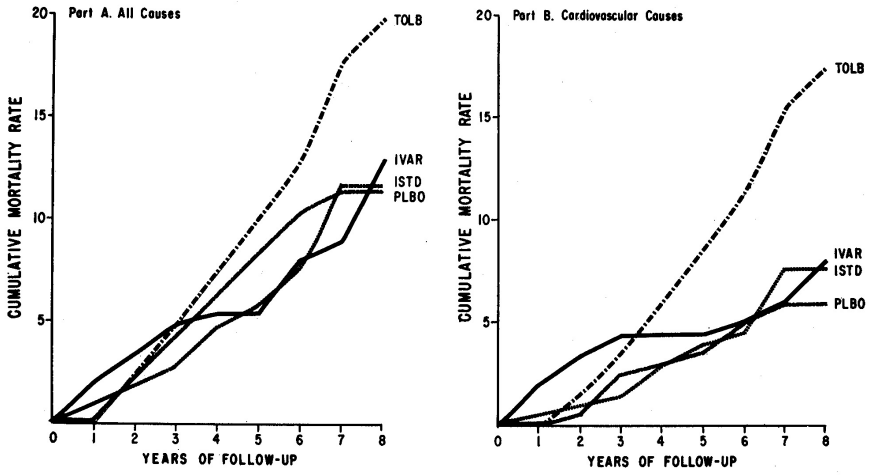
	Number with condition			% dead		
	IStd	IVar	Plbo	IStd	IVar	Plbo
ECG abnormality	192	188	190	16.7	17.6	20.0
Use of digitalis	190	184	190	12.6	12.5	12.1
Hospitalized for heart disease	190	187	194	6.8	7.0	11.9
Hypertension	139	142	128	54.7	55.6	50.0
Angina pectoris	187	187	189	15.5	16.6	19.6
Visual acuity ≤20/200 (either eye)	179	175	179	11.7	11.4	11.2
Opacity§	179	173	173	10.6	11.6	9.2
Fundus abnormalities	117	118	127	45.3	43.2	43.3
Urine protein ≥ 1.5mg/dl	195	190	189	2.1	5.8	4.2
Serum creatine ≥1.5mg/dl	193	186	184	8.3	9.1	16.3
Amputation (all or part; either limb)	198	190	194	0.5	1.6	1.5
Arterial calcification	163	155	169	28.8	28.4	29.6
Intermittent claudication	191	181	182	19.4	16.0	17.6
No. enrolled	210	204	205			

* Table reproduced from reference 77; results as of cutoff date of 31 Dec 1974
§ Vitreous, lenticular, or corneal; either eye

14. Results

5. Tables and figures

Figure 1 UGDP tolbutamide-placebo cumulative mortality*

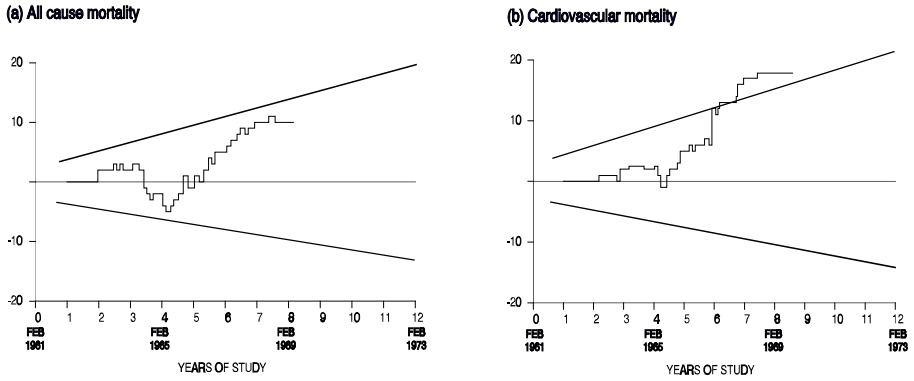


* Reproduced from reference 88

14. Results

5. Tables and figures

Figure 2 UGDP tolbutamide-placebo 95% Monte Carlo monitoring bounds*

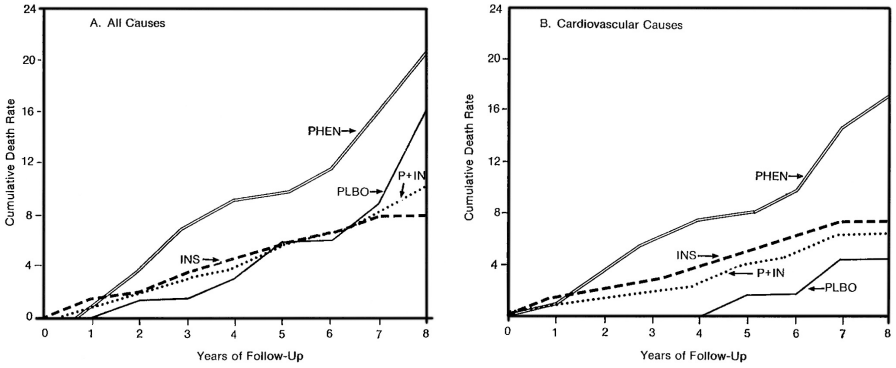


* Reproduced from reference 88

14. Results

5. Tables and figures

Figure 3 UGDP phenformin-placebo cumulative mortality*



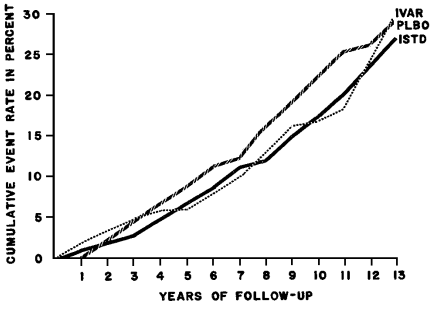
* Reproduced from reference 82

14. Results

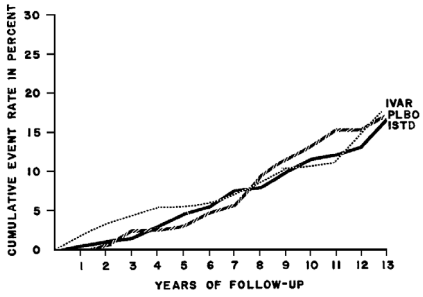
5. Tables and figures

Figure 4 UGDP insulin-placebo cumulative mortality*

a) All cause mortality



b) Cardiovascular motality



* Reproduced from reference 76

15. Lessons learned

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 in trials. The only thing I knew about trials when signing on with Chris Klimt was what I read in textbooks.

1. The order of groups

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 gradual school, but none having to do with group dynamics. Whatever I knew about that when coming to the UGDP, I learned on the farm.

As a boy, I had the job in the summer of rounding up our 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. Get her going and the others followed. 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 (that is how I got stamped out) 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 stranger 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 coffee breaks and where people sit. Who they look at when they talk, their body postures and facial expressions.

Lesson: Pay attention!

2. Trust but verify

Persons had to have a sum glucose tolerance test of ≥ 500 mg/100 ml to be eligible for enrollment.[87] The test consisted of an overnight fasting value plus 1, 2, and 3 hour post-glucose challenge values.

Glucose determinations were to be done locally. There had been discussion of sending specimens to a central laboratory, but that approach was rejected because of logistics and cost.

15. Lessons learned

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 after the start of enrollment, 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.” “You do? The protocol specifies whole blood.” “It does?” And so unfolded the “glucose story” with 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 having corrected sum GTTs below the diagnostic cutpoint of ≥ 500 mg/100 ml.[87]

Lesson: It is not sufficient to specify requirements in the study protocol. One must also check that the requirements are satisfied.

3. On the meaning of "final"

Early on I labored producing forms for data collection. It was not my favorite activity, but I endured because I reasoned that it would be time limited.

I was wrong!

I soon learned form changes and revisions are never ending. Often, before the ink was dry on one version there would be calls for revisions

and additions. I smiled politely, playing deaf to the call, but ultimately got out numbered and overrun. The changes could range from being as trivial as correcting spelling errors to as major as changing the order of items on a form or adding new sections to a form.

Lesson: Delete the word "final" from your vocabulary when it comes to data collection forms and protocols. Use version numbers instead and key the numbers as data into the data system so the different versions can be identified and sorted at analysis time.

4. We can correct that

When results are published and the world does not like them, people can always come up with some baseline variable that investigators failed to collect and attribute the difference to that variable. That was the case with critics of the UGDP with regard to smoking history.

Data were collected on current smoking habits but not on smoking history prior to enrollment. The Biometrics Committee characterized failure to include smoking history on enrollment as a blunder. (To my ear an unfortunate characterization because blunder means doing something stupid or careless.) The landscape with regard to smoking as a risk factor changed during the course of the UGDP. The foundation for data collection was laid in 1959, several years before the first report of the Surgeon General's Advisory Committee on Smoking and Health (11 January 1964) and a year after that before warnings of health risks from smoking were required on cigarette packages.

Investigators did, in fact, make an effort to rectify the oversight around 1972 with the collection of retrospective smoking histories. There were no major differences among the treatment groups with regard to smoking history. However, the results were never published because of questions

involved in constructing baseline smoking histories long after patients were enrolled and use of surrogate respondents for deceased patients.

Lesson: Retrospective data collection is not the same as prospective data collection.

5. Organized chaos

The UGDP investigative body 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 rooms and have the hotel telephone operator arrange for a conference call.

Lesson: Conference phone calls have their place, if only to restore order.

6. Seek and ye shall find?

Many of the lessons one learns in trials are “lessons” only because of shortsightedness. It should be apparent to anyone involved in long-term trials that one keeps track of everyone, even if they dropout, so that one can classify persons as to whether alive or dead at analysis time. Anyone in charge of such efforts knows that clinic personnel have to keep up-to-date “locator” information if there is to be any hope of tracing people. Even Inspector Clouseau knows that the chance of locating persons lost to followup diminishes as a direct function of the time since last contact.

15. Lessons learned

The protocol specified that clinics were to maintain “up-to-date” locator information for dropouts, but no one paid attention to that requirement. Hence, when it came time to produce the publication describing the tolbutamide mortality results, nine years after the start of enrollment, investigators had 23 dropouts in the tolbutamide-assigned group of patients and 24 in the placebo-assigned group with unknown vital status. Clearly, a differential mortality rate among those people could be large enough to explain the observed tolbutamide-placebo mortality difference. Hence, it was obvious that investigators would have to delay publication in order to locate dropouts to determine if they were alive or dead.

Ultimately, via those efforts, investigators were able to determine the vital status of everyone enrolled, except for five; one person assigned to the tolbutamide treatment group, two persons assigned to the placebo treatment group, and the other two persons assigned to the insulin-variable treatment group.

The hard core unlocatables included a person by the name of Wong who moved to Chinatown in San Francisco. He was lost among 100s of Wongs.

Lesson: Keep the “locator information” current and engage in efforts to locate people lost to followup at yearly intervals to be ready for mortality analyses whenever necessary.

7. Who said you can vote?

There came that fateful day in June 1969 when the Steering Committee was faced with an up or down vote on whether to stop use of tolbutamide. The voting policy (established early on) was two votes per center – two for each of the twelve clinics and two for the coordinating center (one vote for the center director and 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 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 vote was close: 13 to stop and 12 to continue. After the 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.

Lesson: The time to figure out who has a vote is before there are issues to vote. Consensus is wonderful, but it is certain only in groups of size one.

8. What do you mean “The visit is missed”?

The patient visit schedule after enrollment was at three month intervals over the course of followup. Each visit consisted of a general examination and, depending on the quarter, an eye, heart, kidney, or peripheral vascular examination. Visits were numbered by quarter, i.e., FU 1 for the 3rd month after enrollment, FU 2 for the 6th month after enrollment, etc. Well and good, except for what clinics did when people missed a visit.

Suppose a person does not show up for the 6 month visit, but does for the 9 month visit, i.e., the second followup visit for the patient, but the 3rd required visit according to the protocol. Does the clinic do the kidney exam or the heart exam? Some clinics did the kidney exam and labeled the exam as an FU 3 and others did the heart exam and labeled it as an FU 2 visit. Needless to say, counting visits to produce performance statistics by clinic was impossible without hard and fast rules as to when a visit was counted as missed.

15. Lessons learned

Lesson: Construct contiguous time windows that specify the limits within which a visit is to be done. Visits not done in the specified time interval are missed; no ifs, ands, or buts. Require clinics to file “missed visit” forms to enable the coordinating center to “count”.

9. The “miracle” treatment

As often happens, new treatments come along while a trial is ongoing. Indeed, usually the last treatment on the scene is seen as “best”. So it was when phenformin came into use in the late 1950s.[35] 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 study 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 well 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. 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 by the “imminent hazard provisions” power vested in the Secretary of Health, Education, and Welfare; removed in 1977.

Lesson: Be wary of “miracle” treatments!

15. Lessons learned

10. Mortality: The unspecified outcome

The trial was designed to assess the value of different forms of antihyperglycemic treatments for prevention or amelioration of the late complications of type 2 diabetes. The sample size was derived by pragmatic considerations of money and numbers that could be reasonably recruited. There was only passing mention of mortality in the protocol because investigators did not believe the trial was adequately sized to find differences in mortality, if indeed the drugs produced benefit in reduced mortality. This, however, is not to say that mortality was not tracked or that investigators did not look for differences in mortality. Indeed, it is the mortality differential in the tolbutamide-assigned group in contrast to the placebo-assigned group that ultimately led investigators to stop use of tolbutamide and to publish the mortality results.

Interestingly and surprisingly, critics suggested investigators had no basis for acting on the mortality differential, since mortality was not specified as an outcome of interest in the study protocol.

Lesson: Mortality is a “primary” outcome whether or not used to power the trial and whether or not specified in the study protocol. To ignore an important outcome, merely because it was not designated "primary", is to court danger for persons enrolled in trials.

11. The randomization recipe

Soon after the start of the firestorm of criticisms, the International Biometrics Society was asked to appoint a committee to review the UGDP and its results. The Committee came calling on the Coordinating Center in August of 1972. The first thing its members wanted to see was the “recipe” for randomization and the methods for administering the schedule. No matter that the recipe was fashioned twelve years back, they were

interested in the written details regarding construction of the schedule and "rules" for administration.

Having produced the schedule, I recalled having written documentation regarding procedures for creating the schedule. Accordingly, people in the Center were sent scrambling to locate said documentation. Sure enough, about 30 minutes later in comes a person with the desired documentation – presented with obvious pride with a filing system capable of yielding a document as obscure as the one desired.

I then proceeded to read the document aloud for the Committee, but after a sentence or two, to my great surprise (and embarrassment) I realized the document was no longer written in English. Sentences, obviously crystal clear when I put pen to paper, were now strangely incomprehensible. Clearly, something had happened to the words during those many years in a dark filing cabinet!

Lesson: Though there is no guarantee that what one writes today will make sense tomorrow, the probability of that being so is increased if what one writes is reviewed and read by someone else before "filing". Obviously, that was a step missed in the "recipe" documentation.

12. The best two out of three votes

The tolbutamide mortality difference emerged over time. At first, it was a matter of indifferent curiosity to investigators, but eventually the indifference turned to concern (data were seen about every six months). The difference became an increased focus of concern by 1967. By 1968 there were a few investigators suggesting that the prudent course was to stop use of tolbutamide.

15. Lessons learned

The trend was evident in the 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 vote carried, but just barely, too close to make the group comfortable with taking any action.

They agreed to reconvene after some additional analyses in about a month.

Again they voted with a slightly larger fraction for stopping than with the first vote.

Still the group felt uneasy in stopping so they opted to meet again a month later.

They voted again, this time only 2 against stopping. They stopped the treatment.

Lesson: Major protocol changes, such as stopping or adding a treatment, should require a 2/3rds majority. After the first vote there were those who argued a simple majority was sufficient and others for something larger. Specify the size of the vote required before there is anything major to vote on.

13. Stopping a treatment

The decision to stop tolbutamide raised a series of questions.

How do you unmask a treatment without unmasking other treatments?

Tolbutamide was administered double-masked. When tolbutamide was stopped all patients receiving tolbutamide or the matching placebo were given new bottles of medication all having the same bottle number

(number 88) to be taken on the same schedule as before. Investigators knew the bottles contained placebo.

It is possible that some of patients deduced they were on placebo, but there is no evidence of that in adherence or dropout rates. At the close of followup and data collection in 1975, 15% of patients assigned to placebo had dropped out, compared to 18% for the two insulin treatment groups.[76]

When should the tolbutamide treatment be stopped?

The options were to do it immediately by telephone or letter or to wait until the next scheduled visits. The former approach was rejected as being unnecessary given the equivocal nature of the findings. Patients were told at their next regular clinic visit following the decision.

What were patients told about the reason for stopping?

The truth if they asked.

What should happen to patients after the stop?

Followup and regular examinations continued.

What should the cutoff date be for the publication dataset?

The date used was 7 October 1967. That date corresponded roughly to the time required for patients to cycle through their next scheduled followup visit and providing adequate time for data harvests by the coordinating center.

What were other patients told about the decision?

Nothing, but if patients asked they were told of the decision.

Lesson: Stopping a treatment is more complicated than starting one.

15. Lessons learned

14. Document, document, document

The trouble with documentation in multicenter endeavors is that, usually, no one in those structures is charged with that responsibility. Largely in multicenter trials, whatever is done is done by coordinating centers and usually without notice of others – until, that is, documents are needed. If there are rules and policies as to what gets documented and how it should be documented, it is the coordinating center that produces those rules and policies and it is the coordinating center that is responsible for sticking to them.

The other problem with documentation is that it is not a favorite activity and easily put off because of more "urgent matters".

Lesson: The time to document is in the here and now. Memory is fallible.

15. What to keep?

Writing an account of events that happened decades ago has been a sobering experience for someone who fancies himself a "documenter"; humbled by what is no longer available, lost, or long ago discarded. A few of the things that I would have given my eyeteeth for when writing this essay include:

The study protocol and revisions
Study forms and revisions
Grant applications
Progress reports
Monitoring reports (especially those presented to the Steering Committee (SC) in relation to votes on stopping tolbutamide)
The 1970 American Diabetes Association program
The report by Kidder Peabody run on the Dow Jones ticker 20 May 1970

15. Lessons learned

Accurate cost figures for the study
Draft timetable for the 1970 publication
Readable electronic datasets
The randomization "recipe" memo (to see if it makes sense now)

The UGDP was before the internet and study websites. It is easy and cheap today to store things electronically. Perhaps those writing accounts of events that happen now, decades later will have a better cache of documents, but do not bet on it. That cache will not exist unless there are people in coordinating centers today who think like "historians" for tomorrow.

Lesson: Think and act like historians.

References

1. **Beecher** HK: Ethics and clinical research. N Engl J Med **1966**;274:1354-1360.
   (Beecher, 1966) **39**

2. **Bolen** S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, Wiley C, Selvin E, Wilson R, Bass EB, Brancati FL: Systematic review: Comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med **2007**;147:386-399.
   (Bolen et al, 2007) **114**

3. **Boussageon** R, Bejan-Angoulvant T, Saadatian-Elahi M, Lafont S, Bergeonneau C, Kassai B, Erpeldinger S, Wright JM, Gueyffier F, Cornu C: Effect of Intensive Glucose Lowering Treatment on All Cause Mortality, Cardiovascular death, and microvascular events in Type 2 Diabetes: Meta-analysis of Randomised Controlled Trials. BMJ **2011**;343:d4169 *doi:10.1136/bmj.d4169*.
   (Boussageon et al, 2011) **8**

4. **Bradley** RF, Dolger H, Forsham P, Seltzer H: "Settling the UGDP Controversy"?. JAMA **1975**;232(8):813-817.
   (Bradley et al, 1975) **137**

5. **Chalmers** TC: Settling the UGDP Controversy (editorial). JAMA **1975**;231(6):624-625.
   (Chalmers, 1975) **137**

6. **Colton** T (editor): Remembrances of Max Halperin. Stat Med **1990**;9:863-870.
   (Colton, 1990) **31**

References

7. **Committee for the Assessment of Biometric Aspects of Controlled Trials of Hypoglycemic Agents**: Report of the Committee for the Assessment of Biometric Aspects of Controlled Trials of Hypoglycemic Agents. JAMA **1975**;231:583-608.
(Comm Assess Biometric, 1975) **76, 77, 78, 105, 106**

8. **Cornfield** J: Recent methodological contributions to clinical trials. Am J Epidemiol **1976**;104:408-421.
(Cornfield, 1976) **42**

9. **Cornfield** J: The University Group Diabetes Program: A further statistical analysis of the mortality findings. JAMA **1971**;217:1676-1687.
(Cornfield, 1971) **76, 93, 99, 100, 102, 103**

10. **Coronary Drug Project Research Group**: The Coronary Drug Project: Design, methods, and baseline results. Circulation **1973**;47(suppl I):I-1-I-50.
(CDP Research Group, 1973a) **27**

11. **Crofton** J: The MRC randomized trial of streptomycin and its legacy: A view from the clinical front line. J R Soc Med **2006**;99:531-534.
(Crofton, 2006) **27, 28**

12. **Davidson JK** (editor): *Clinical Diabetes Mellitus: A Problem-Oriented Approach* (Third Edition). Thieme, New York, **2000**.
(Davidson JK, 2000) **3**

References

13. **Davidson JK and DiGirolamo M**: Non-Insulin-Dependent (Type 2) Diabetes Mellitus and Obesity. In Davidson JK (Editor): *Clinical Diabetes Mellitus: A Problem-Oriented Approach* (13-36 pgs). Thieme, New York, **2000**.
(Davidson and DiG, 2000) **3**

14. **Department of Health and Human Services**: HIPAA Administrative Simplification: Standard Unique Health Identifier for Health Care Providers (final rule). Federal Register **23 January 2004**;69:3434-3469.
(DHHS, January 23, 2004) **85**

15. **Diabetes Control and Complications Trial Research Group**: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med **1993**;329:977-986.
(DCCT Research Group, 1993) **8, 56, 113**

16. **Feinstein** AR: Clinical biostatistics: XXXVI. The persistent biometric problems of the UGDP study. Clin Pharmacol Ther **1976**; 19:742-85.
(Feinstein, 1976A) **93**

17. **Feinstein** AR: Clinical biostatistics: XXXV. The persistent clinical failures and fallacies of the UGDP study. Clin Pharmacol Ther **1976**; 19:78-93.
(Feinstein, 1976) **93**

18. **Feinstein** AR: Clinical biostatistics: VII. An analytic appraisal of the University Group Diabetes Program (UGDP) study. Clin Pharmacol Ther **1971**;12:167-191.
(Feinstein, 1971) **76, 93, 99, 100, 101, 104, 105, 106, 107**

References

19. **Food and Drug Administration**: *Guideline Labeling for Oral Hypoglycemic Drugs of the Sulfonylurea Class*. Docket no 83D-0304, Rockville, MD, March 16, **1984**.
(Food and Drug Admin, 1984a) **81, 89**

20. **Food and Drug Administration**: Labeling of oral hypoglycemic drugs of the sulfonylurea class. Federal Register **1984** (April 11);49:14303-14331.
(Food and Drug Admin, 1984b) **81, 89**

21. **Food and Drug Administration**: Oral hypoglycemic drug products: Availability of guideline labeling. Federal Register **1984** (April 11);49:14441-14442.
(Food and Drug Admin, 1984c) **81, 89**

22. **Food and Drug Administration**: Oral hypoglycemic drugs: Availability of agency analysis and reopening of comment period on proposed labeling requirements. Federal Register **1978** (Nov 14);43:52732-52734.
(Food and Drug Admin, 1978) **80, 89, 105, 106**

23. **Food and Drug Administration**: Phenformin: New labeling and possible removal from the market. FDA Drug Bull **1977** (May-July);7:6-7.
(Food and Drug Admin, 1977a) **79**

24. **Food and Drug Administration**: HEW Secretary suspends general marketing of phenformin. FDA Drug Bull **1977** (Aug);7:14-16.
(Food and Drug Admin, 1977b) **79, 112**

References

25. **Food and Drug Administration**: Status of withdrawal of phenformin. FDA Drug Bull **1977** (Sep-Oct);7:19-20.
(Food and Drug Admin, 1977d) **79**

26. **Food and Drug Administration**: Drug labeling: Failure to reveal material facts; labeling of oral hypoglycemic drugs. Federal Register **1975** (July 7);40:28582-28595.
(Food and Drug Admin, 1975) **76, 77, 87, 88**

27. **Food and Drug Administration**: Oral hypoglycemic drug labeling. FDA Drug Bull, May, **1972**.
(Food and Drug Admin, 1972a) **76, 87**

28. **Food and Drug Administration**: Oral hypoglycemic agents. FDA Drug Bull, June 23, **1971**.
(Food and Drug Admin, 1971) **76, 87**

29. **Food and Drug Administration**: Oral hypoglycemic agents: Diabetes prescribing information. FDA Current Drug Information, Oct **1970**.
(Food and Drug Admin, 1970c) **76**

30. **Gilbert** JP, Meier P, Rümke CL, Saracci R, Zelen M, White C: Report of the Committee for the Assessment of Biometric Aspects of Controlled Trials of Hypoglycemic Agents. JAMA **1975**;231(6):583-608.
(Gilbert et al, 1975) **14, 61, 64**

31. **Gele** EAM, DeMeyts P, Sharpey-Schafer E (1850-1935): [internet]. 2014 Aug 13; *Diapedia 1104098115 rev. no. 16*. Available from: http://dx.doi.org/10.14496/dia.1104098115.16.
(Gele et al, 2014) **1**

References

32. **Hazlett** BE: Historical Perspective: The Discovery of Insulin. In Davidson JK (Editor): *Clinical Diabetes Mellitus: A Problem-Oriented Approach* (3-11 pgs). Thieme, New York, **2000**.
(Hazlett BE, 2000) **1**

33. **Hypertension Detection and Follow-Up Program Cooperative Group**: Five-year findings of the Hypertension Detection and Follow-Up Program: I. Reduction in mortality of persons with high blood pressure, including mild hypertension. JAMA **1979**;242:2562-2571.
(HDFP Cooperative Group, 1979a) **7**

34. **Inzucchi** SE: Oral antihyperglycemic therapy for type 2 diabetes. JAMA **2002**;287:360-372.
(Inzucchi, 2002) **114**

35. **Karam** JH, Matin SB, Forsham PH: Antidiabetic drugs after the University Group Diabetes Program (UGDP). Annu Rev Pharmacol **1975**;15:351-366.
(Karam et al, 1975) **109, 130**

36. **Kenny** SJ, Aubert RE, Geiss LS: *Prevalence and incidence of non-insulin-dependent diabetes*, pgs 47-67; Ch 4 in **National Diabetes Data Group**: *Diabetes in America, 2nd ed* (782 pgs). National Institute of Diabetes and Digestive and Kidney Disease, Bethesda, Md, NIH publ no. 95-1468, **1995**.
(Kenny et al, 1995) **114**

37. **Kilo** C, Miller JP, Williamson JR: The achilles heel of the University Group Diabetes Program. JAMA **1980**;243:450-457.
(Kilo et al, 1980) **93, 99, 100, 101**

References

38. **Knatterud** GL, Meinert C: A Tribute to Christian Robert Klimt (1918-1994). Controlled Clin Trials **1995**;16:139-142.
(Knatterud and Meinert, 1995) **57**

39. **Kolata** GB: Controversy over study of diabetes drugs continues for nearly a decade. Science **1979**;203:986-990.
(Kolata, 1979) **106**

40. **Ledger** RR: *Safety of Upjohn's oral antidiabetic drug doubted in study: Firm disputes findings. Wall Street Journal,* May 21, **1970**.
(Ledger, 1970) **76, 91**

41. **Levine** RJ: *Ethics and Regulation of Clinical Research (2nd ed).* Yale University Press, New Haven, **1988**.
(Levine, 1986) **39**

42. **Marks** HM: *The Progress of Experiment: Science and therapeutic reform in the United States, 1900-1990* (258 pgs). Cambridge University Press, Cambridge, UK, **1997**.
(Marks, 1997) . . . . . **xvi**

43. **Medical Research Council**: Streptomycin treatment of tuberculous meningitis. Lancet **1948**;1:582-596.
(Medical Research Council, 1948) **27**

44. **Meinert** CL: *Clinical Trials Handbook: Design and Conduct*. John Wiley & Sons, Inc, New York, (573 pgs) **2013**.
(Meinert, 2013) **143**

References

45. **Meinert** CL: *Clinical Trials Dictionary: Terminology and Usage Recommendations* 2nd ed (356 pgs). John Wiley & Sons, Hoboken, NJ, **2012**.
(Meinert, 2012A) **83**

46. **Meinert** CL: *Clinical Trials: Design, Conduct, and Analysis* (665 pgs). 2nd edition, Oxford University Press, New York, **2012**.
(Meinert, 2012) . . . . . **xvi, 37, 99, 107**

47. **Meinert** CL: *An Insider's Guide to Clinical Trials* (279 pgs). Oxford University Press, New York, **2011**.
(Meinert, 2011) **86**

48. **Meinert** CL, Tonascia S: *Clinical Trials: Design, Conduct, and Analysis* (469 pgs). Oxford University Press, New York, **1986**.
(Meinert and Tonascia, 1986) . . . . . **xvi, 3, 91, 107, 112, 114**

49. **Mintz** M: *Discovery of diabetes drug's perils stirs doubts over short-term tests. The Washington Post*, June 8, **1970**.
(Mintz, 1970b) **75, 91**

50. **Mintz** M: *Antidiabetes pill held causing early death. The Washington Post*, May 22, **1970**.
(Mintz, 1970a) **76, 91**

51. **Nissen** SE, Wolski K: Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med **2007**;356:2457-2471.
(Nissen and Wolski, 2007) **113, 114**

References

52. **Prentice** RL: Surrogate endpoints in clinical trials: Definition and operational criteria. Stat Med **1989**;8:431-440.
(Prentice, 1989) **113**

53. **Prout** TE, Knatterud GL, Meinert CL: Diabetes drugs: Clinical trial (letter). Science **1979**;204:362-363.
(Prout et al, 1979) **106**

54. **Ray** KK, Seshasai SRK, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, Erqou S, Sattar N: Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: A meta-analysis of randomised controlled trials. Lancet **2009**;373:1765-1772.
(Ray et al, 2009) **8**

55. **Schmeck** HM Jr: *Scientists wary of diabetic pill: FDA study indicates oral drug may be ineffective*. New York Times, May 22, **1970**.
(Schmeck, 1970) **76, 91**

56. **Schor** S: The University Group Diabetes Program: A statistician looks at the mortality results. JAMA **1971**;217:1671-1675.
(Schor, 1971) **76, 93, 99, 100, 102, 104, 105, 106, 107**

57. **Schwartz** TB: The tolbutamide controversy: A personal perspective. Ann Intern Med **1971**; 76:303-306.
(Schwartz, 1971) **93**

58. **Schwartz** TB, Meinert CL: The UGDP controversy: Thirty-four years of contentious ambiguity laid to rest. Perspect Biol Med **2004**;47:564-574.
(Schwartz and Meinert, 2004) **109**

References

59. **Seltzer** HS: A summary of criticisms of the findings and conclusions of the University Group Diabetes Program (UGDP). Diabetes **1972**;21:976-979.
(Seltzer, 1972) **77, 93, 99, 100, 101, 102, 104, 105, 106, 107**

60. **Silverman** M: Good News for Diabetics. *The Saturday Evening Post* (39-50 pgs). Published 24 Aug, **1957**.
(Silverman, 1957) **146**

61. **Sharpey-Schafer** EA: *The Endocrine Organs: An Introduction to the Study of Internal Secretion*. Longmans, Green, and Co, London, **1916**.
(Sharpey-Schafer, 1916) **1**

62. **Stewart** WH: Clinical Research Investigations Using Human Subjects. In *Final Report*, Supplemental Volume 1 (473-474 pgs). US Government Printing Office, Washington, DC, **1966**.
(Stewart, 1966) **146**

63. **UK Prospective Diabetes Study Group**: Intensive blood-glucose control with sulphonylureas or insulin compared to conventional treatment and risk of complications in patients with type 2 diabetes. Lancet **1998**;52:837-853.
(UKDS Group, 1998) **8, 113**

64. **United States Court of Appeals for the District of Columbia Circuit**: Peter H Forsham et al, versus Joseph A Califano, Jr, et al. No 76-1308, July 11, **1978**.
(US Court of Appeals, 1978) **80, 83**

References

65. **United States Court of Appeals for the First Circuit**: Robert F Bradley, et al, versus Caspar W Weinberger, Secretary of Health, Education, and Welfare, et al. No 73-1014, July 31, **1973**.
(US Court of Appeals, 1973) **76, 77, 88**

66. **United States District Court for the District of Columbia**: Peter H Forsham et al, versus David Matthews, et al. No 75-1608, Feb 5, **1976**.
(US District Court, 1976) **78, 83**

67. **United States District Court for the District of Columbia**: Forsham et al, versus Matthews, et al. No 75-1608, Sept 30, **1975**.
(US District Court, 1975) **78, 83**

68. **United States District Court for the Southern District of New York**: Ciba-Geigy Corporation versus David Matthews, et al. No 75 Civ 5049 (CHT), March 8, **1977**.
(US District Court NY, 1977) **11**

69. **United States District Court for the Southern District of New York**: Ciba-Geigy Corporation versus David Matthews, et al. No 75 Civ 5049, Oct 14, **1975**.
(US District Court NY, 1975) **78, 83**

70. **United States Senate Select Committee on Small Business**: *Oral Hypoglycemic Drugs: Hearing before the Subcommittee on Monopoly*, Sept 18, 19, and 20, 1974. Part 25, US Government Printing Office, Washington, DC, **1974**.
(US Senate Select Comm, 1974) **78**

References

71. **United States Senate Select Committee on Small Business**: *Oral Hypoglycemic Drugs: Hearing before the Subcommittee on Monopoly*, Jan 31, July 9-10, 1975. Part 28, US Government Printing Office, Washington, DC, **1975**.
(US Senate Select Comm, 1975) **78**

72. **United States Supreme Court**: Forsham, et al, versus Harris, Secretary of Health, Education and Welfare, et al. Certiorari to the United States Court of Appeals for the District of Columbia Circuit. No 78-1118, argued Oct 31, 1979, decided March 3, **1980**.
(US Supreme Court, 1980) **80**

73. **United States Supreme Court**: Peter H Forsham, et al, versus Joseph A Califano, et al. Petition for a writ of certiorari to the United States Court of Appeals for the District of Columbia Circuit. Oct term, **1978**.
(US Supreme Court, 1978) **78, 80, 83, 84, 88**

74. **University Group Diabetes Program Research Group**: Paper listing of baseline and follow-up data on UGDP patients (one volume per treatment group). No PB 83-136-325, *National Technical Information Service (NTIS)*, Springfield, VA, **1983**.
(UGDP Research Group, 1983a) **80, 86**

75. **University Group Diabetes Program Research Group**: Magnetic tape of baseline and follow-up data on UGDP patients. No PB 83-129-122, *National Technical Information Service (NTIS)*, Springfield, VA, **1983**.
(UGDP Research Group, 1983b) **80, 86**

References

76. **University Group Diabetes Program Research Group**: 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.
(UGDP Research Group, 1982) **78, 122, 134, 156**

77. **University Group Diabetes Program Research Group**: 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.
(UGDP Research Group, 1978) **79, 117, 118**

78. **University Group Diabetes Program Research Group**: University Group Diabetes Program releases data on 1,027 patients. Diabetes **1977**;26:1195.
(UGDP Research Group, 1977) **79, 86**

79. **University Group Diabetes Program Research Group**: 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.
(UGDP Research Group, 1976) **102**

80. **University Group Diabetes Program Research Group**: 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.
(UGDP Research Group, 1975) **76, 78, 111**

References

81. **University Group Diabetes Program Research Group**: The UGDP controversy: Clinical trials versus clinical impressions. Diabetes **1972**;21:1035-1040.
(UGDP Research Group, 1972) **77, 105**

82. **University Group Diabetes Program Research Group**: 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.
(UGDP Research Group, 1971b) **76, 111, 116, 121**

83. **University Group Diabetes Program Research Group**: Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes: III. Clinical implications of UGDP results. JAMA **1971**;218:1400-1410.
(UGDP Research Group, 1971a) **101, 102**

84. **University Group Diabetes Program Research Group**: The effects of hypoglycemic agents in vascular complications in patients with adult-onset diabetes: 1. Design and methods (abstract). Diabetes **1970**;19 (suppl 1):387.
(UGDP Research Group, 1970a) **55, 75, 76**

85. **University Group Diabetes Program Research Group**: The effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes: 2. Findings at baseline (abstract). Diabetes **1970**;19 (suppl 1):374.
(UGDP Research Group, 1970b) **55, 76**

References

86. **University Group Diabetes Program Research Group**: The effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes: 3. Course and mortality (abstract). Diabetes **1970**;19 (suppl 1):375.
(UGDP Research Group, 1970c) **55, 76**

87. **University Group Diabetes Program Research Group**: 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.
(UGDP Research Group, 1970d) **12, 37, 99, 100, 104, 107, 124, 125**

88. **University Group Diabetes Program Research Group**: 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.
(UGDP Research Group, 1970e) **69, 75, 76, 86, 87, 100, 104, 109, 115, 119, 120**

89. **Veterans Administration Cooperative Study Group on Antihypertensive Agents**: Effects of Treatment on Morbidity in Hypertension: Results in Patients with Diastolic Blood Pressures Averaging 115 through 120 mm Hg. JAMA **1967**;202(11):1028-1034.
(VA Coop Group, 1967) **6**

90. **von Mehring** J, Minkowski O: Diabetes mellitus nach pankreasexstirpation. Arch Exp Pathol Pharmakol **1890**;26:371-387; doi:10.1007/BF01831214.
(von Mehring & Minkowski, 1890) **1**

References

91. **Wysowski** DK, Armstrong G, Governale L: Rapid increase in the use of oral antidiabetic drugs in the United States, 1990-2001. Diabetes Care **2003**;26:1,852-1,855.
(Wysowski et al, 2003) **3, 114**

Memorabilia*

1. Coordinating Center original grant application (1 Sep 1960)
2. Minutes of UGDP Executive Committee meeting; Baltimore (28 May 1969)
3. Letter from Byron Brown to Chris Klimt supporting position arrived at during 26 May 1969 conference concerning tolbutamide (3 Jun 1969)
4. Minutes of UGDP Investigators meeting in Williamsburg, Va (5-6 Jun 1969)
5. Letter from Byron Brown to Max Miller stating reasons why he believed tolbutamide should be stopped (7 Jun 1969)
6. Letter from Chris Klimt to Director of FDA re IND 4466 informing of decision to stop tolbutamide (9 Jun 1969)
7. Letter from Jerome Cornfield to Max Miller recommending discontinuation of tolbutamide (12 Jun 1969)
8. Summary of meeting with FDA representatives (16 Jun 1969)
9. Letter from Jerome Cornfield to Chris Klimt stating rationale for his recommendation to stop tolbutamide (17 Jun 1969)
10. Preliminary evaluation of the UGDP report of May 9,1969 with covering letter from E Keith Borden of Upjohn (27 Jun 1969)
11. Summary of meeting with Upjohn; New York (29 Jun 1969)
12. Minutes of Investigators meeting; Roosevelt Hotel, New York (30 Jun 1969)
13. Letter from E Keith Borden of Upjohn to Max Miller re questions concerning tolbutamide results (8 Jul 1969)
14. Letter from Alan B Varley of Upjohn concerning premature release of results (15 Dec 1969)
15. Text of Thad Prout's presentation of tolbutamide results at the 1970 American Diabetes Association meeting in St Louis (14 Jun 1970)
16. Progress report on tolbutamide study to Director of NIH (19 Aug 1970)
17. FDA Current Drug Information bulletin supporting findings (Oct 1970)
18. Letter from Holbrooke Seltzer to Chris Klimt listing criticisms of tolbutamide results (16 Dec 1970)

17. Appendix

19. Letter to Charles C Edwards, Commissioner, FDA, from Robert Q Marston, Director NIH supporting the FDA label change (5 Apr 1971)
20. CCD petition to FDA Commissioner to rescind proposed relabeling (7 Oct 1971)
21. Statement of Max Miller in hearings before the Subcommittee on Monopoly of the Select Committee on Small Business; 93rd Congress (18 Sep 1974)
22. Statement of Christian R Klimt in hearings before the Subcommittee on Monopoly of the Select Committee on Small Business; 93rd Congress (18 Sep 1974)
23. Statement of Thaddeus E Prout in hearings before the Subcommittee on Monopoly of the Select Committee on Small Business; 93rd Congress (18 Sep 1974)
24. Statement of Jerome Cornfield in hearings before the Subcommittee on Monopoly of the Select Committee on Small Business; 93rd Congress (18 Sep 1974)
25. Statement of Thomas Chalmers in hearings before the Subcommittee on Monopoly of the Select Committee on Small Business; 93rd Congress (18 Sep 1974)
26. CCD request for access to raw data of the UGDP under the FOIA (30 Sep 1975)
27. FDA audit (20 Sep 1977)
28. Supreme court decision regarding CCD’s request for raw data under FOIA (3 Mar 1980)

---

* Available on trialsmeinertsway.com; tab "Historical Archives"

Epilogue

It has been a lifetime since September 1960 when I grabbed a chair on the 11th floor of the Mayo building on the University of Minnesota campus and started work in the coordinating center for the UGDP. It has been almost 45 years since that fateful day in June 1969 when investigators voted to stop treatment with tolbutamide and the brick baths that followed when results were presented and published. There was never a dull moment after 20 May 1970 – the day results leaked and ran on the Dow Jones ticker.

The conclusion in the paper published was bland enough:

> *All UGDP investigators are agreed that 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.*

I remember thinking when the paper was being written "What's the big deal? Just publish the results and move on." I was wrong. It was a big deal.

I am proud of the UGDP. It had its flaws, but, all in all, a good trial. Well designed. Well executed. Well reported. It has stood the test of time.

The study results put a shot across the bow of those holding the view that blood sugar control in type 2 diabetics automatically confers benefit in reduced risks of mortality and morbidity. But perhaps more importantly, the study has been invaluable in stimulating others to undertake trials to prove it wrong. There is the saying among famous people "I do not care what you say about me. Just spell my name correctly." As a trialist I say "I do not care what you say about my trial. Just do another one to prove mine wrong."

As prevention trials go, the UGDP was small. Two hundred people per treatment group is not many given the weight of the question being

addressed. In some sense, the fact that ill-effects were found for tolbutamide and phenformin with relatively small numbers of people adds credence to the validity of the findings. Generally, effects in prevention trials, whether positive or negative, require more people to find them than enrolled in the UGDP.

The preoccupation with tolbutamide has meant that the results for the insulin treatments in the trial have been largely ignored.[76] Too bad, because if the "blood sugar control people" are paying attention they would note that the insulin treatments in the trial were no better than placebo in preventing the morbidity and mortality associated with diabetes.

Back

The Trials and Tribulations of the UGDP

1	Incept.WPD	Diabetes
2	Question.WPD	The 64 dollar question
3	Crowd.WPD	The UGDP
4	CC.WPD	Life in the CC
5	Issues.WPD	Issues
6	Events.WPD	Personal recollections
7	BioComm.WPD	The Biometrics Committee
8	FDAAudit.WPD	FDA audit
9	CCD.WPD	The Committee
10	Supreme.WPD	The UGDP and Henry Kissenger
11	Label.WPD	The label change
12	Press.WPD	The brick bath
13	Critics.WPD	The criticisms
14	Results.WPD	The results
15	Lesson.WPD	Lessons
16	Refs.WPD	References
17	Append.WPD	Appendix
1	Table 1	
2	Table 2	
3	Table 3	
4	Table 4	
1	Fig 1	
2	Fig 2	
3	Fig 3	
4	Fig 4	