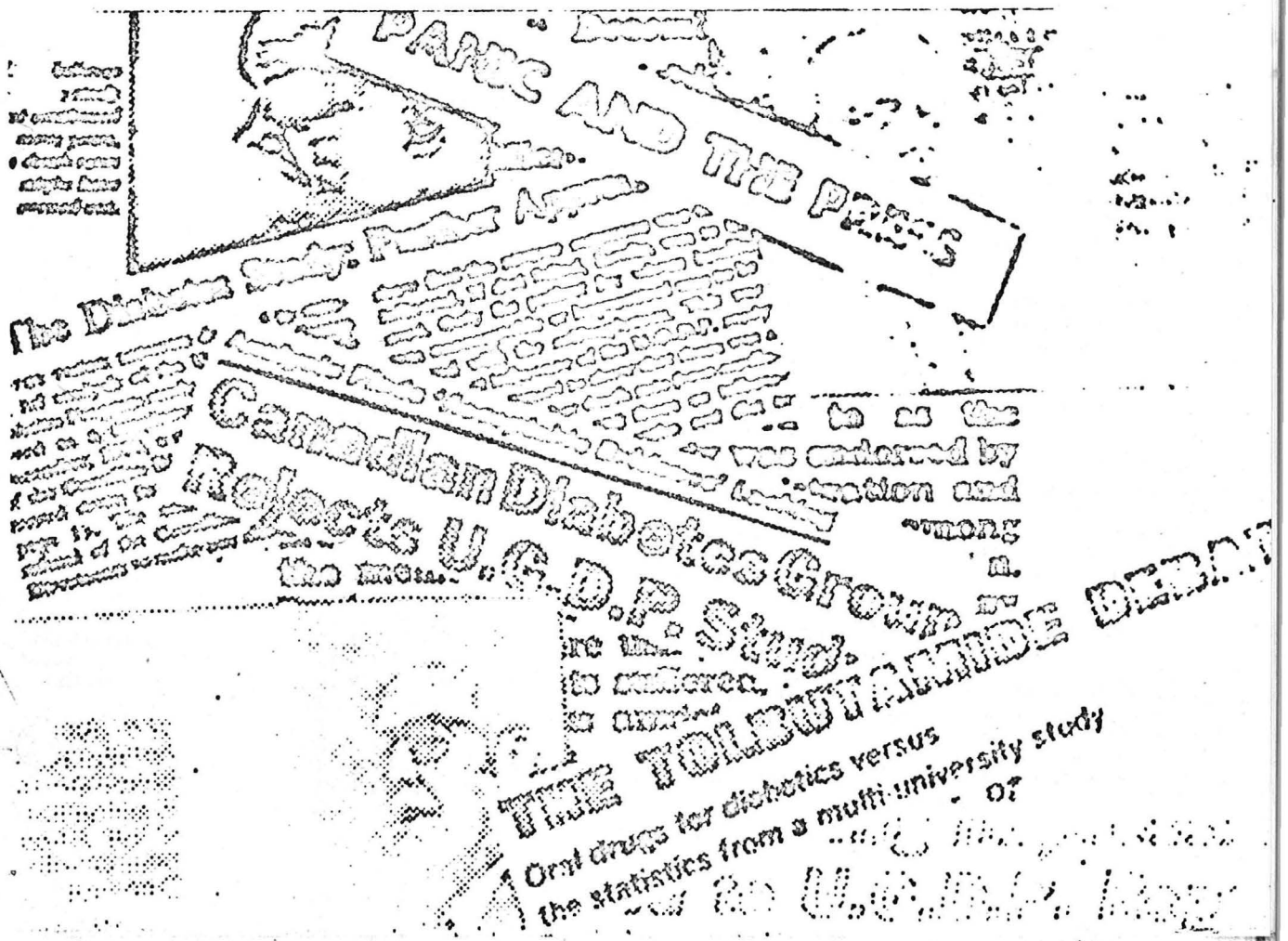
[Roger H. Unger]

R. Unger

MEDICAL GRAND ROUNDS
PARKLAND MEMORIAL HOSPITAL
MAY 20, 1971

THE UGDP AND THE PRESENT STATUS OF ANTIHYPERGLYCEMIC THERAPY IN DIABETES



I. STUDY PERSONNEL AS OF JANUARY 1970 FOR EACH PARTICIPATING INSTITUTION IN THE UNIVERSITY GROUP DIABETES PROGRAM

Clinical Centers

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Principal Investigator:	Charles A. Jones, M.D.
Co-Principal Investigator:	William H. Jacobs, M.D.
Secretary:	Janet Tackett
Dietician:	Mary Louise Kessinger
Nurse:	Roberta Schwartz
Laboratory Technicians:	Jack Bevins
	Von Ada Justice

THE JEWISH HOSPITAL AND MEDICAL CENTER OF BROOKLYN
Brooklyn, New York

Principal Investigator:	Martin G. Goldner, M.D.
Co-Principal Investigator:	Shirley Weisenfeld, M.D.
Physicians:	M. K. Husain, M.D.
	Stanley Newhouse, M.D.
Secretary:	Naomi Trauber
Nurse:	Elaine Farber
Laboratory Technicians:	Hilda Waters
	Ignatius E. Emeghebo

THE JOHNS HOPKINS SCHOOL OF MEDICINE
Baltimore, Maryland

Principal Investigator:	Thaddeus E. Prout, M.D.
Physicians:	Edwin Berstock, M.D.
	Paul J. Edgar, M.D.
	David I. Miller, M.D.
Secretary:	Marie E. Classon
Dietician:	Millicent T. Kelly
Laboratory Technicians:	Mahala Alford
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MASSACHUSETTS GENERAL HOSPITAL
Boston, Massachusetts

Principal Investigator:	Robert K. Osborne, M.D.
Co-Principal Investigator:	Donald Martin, M.D.
Secretary:	Mary Jane Heros
Nurse:	Mary T. Ryan
Consultant:	Richard A. Field, M.D.

PRESBYTERIAN-ST. LUKE'S HOSPITAL
Chicago, Illinois

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Co-Principal Investigator:	Frank O. Becker, M.D.
Dietician:	Ana Boller Beach
Nurse-Secretary:	Julie Madler
Nurse:	Eloise Fernell
Consultants:	D. V. L. Brown, M.D.
	R. E. Buenger, M.D.
	Thomas Coogan, M.D.
	Geza De Takats, M.D.
	Robert M. Kark, M.D.
	Will G. Ryan, M.D.

UNIVERSITY OF ALABAMA MEDICAL CENTER
Birmingham, Alabama

Principal Investigator:	Boris R. Boshell, M.D.
Co-Principal Investigator:	James C. Barrett, M.D.
Physicians:	Arthur L. Ennis, M.D.
	Leon S. Smelo, M.D.
Nurse-Secretary:	Edith H. McCulloch
Technician:	Kaye N. Carlisle
Ophthalmologist:	Elmar Lawaczeck, M.D.
Radiologist:	Alvaro Ronderos, M.D.

UNIVERSITY OF CINCINNATI MEDICAL CENTER
Cincinnati, Ohio

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Co-Principal Investigator:	Kenneth Kreines, M.D.
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	Paul Sweeney, M.D.
Secretary:	Vivian J. Martin
Dietician:	Ann Maher
Technicians:	Lou Ardinghaus
	Elizabeth Zalme
Consultants:	Tayler Asbury, M.D.
	Kenneth Rowe, M.D.
	Harold Schneider, M.D.

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Cleveland, Ohio

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Co-Principal Investigator:	William B. Newberry, Jr., M.D.
Physician:	Helen Cash, M.D.
Secretary:	June Snyder
Dietician:	Ruth Laidig
Nurse:	Elizabeth Davis
Statistician:	Lucille Goldsmith
Technicians:	Susan Csegezi
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STUDY PERSONNEL AS OF JANUARY 1970 FOR EACH
PARTICIPATING INSTITUTION IN THE
UNIVERSITY GROUP DIABETES PROGRAM (CONTINUED)

Clinical Centers (Continued)

THE VIRGINIA MASON RESEARCH CENTER
Seattle, Washington

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Co-Principal Investigator:	Angela J. Bowen, M.D.
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Secretary:	Patricia Swanson
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Co-Principal Investigator:	Marvin E. Levin, M.D.
	Charles Kilo, M.D.
Secretary-Technician:	Betty Passman
Dietician:	Rose Lee Summers
Ophthalmologist:	Allan Kolker, M.D.

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UNIVERSITY OF MARYLAND
Baltimore, Maryland

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Co-Principal Investigator:	Curtis L. Meinert, Ph.D.
	Genell L. Knatterud, Ph.D.
Administrative Assistant:	Phillip A. Crouch
Programming Personnel:	George Bowden
	Margaret Breitenstein
	Patricia Collins
	Kendra Thomas
Secretaries:	Marian Bell
	Angelia Blankenship
	Nancy Garner
	Charlene Johnson
Key Punch Supervisor:	Doris A. Lewis
Key Punch Operators:	Mary Mugavero
	Patricia Patton
	Betty Schleigh

Lipid Laboratories

UNIVERSITY OF MINNESOTA
(Laboratory of Physiological Hygiene)
Minneapolis, Minnesota

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WEST VIRGINIA UNIVERSITY MEDICAL CENTER
Morgantown, West Virginia

Principal Investigator:	Margaret Albrink, M.D.

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(As of January 1970)

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Christian R. Klimt, M.D. (study coordinator)
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Henry Blackburn, M.D., Electrocardiography, University of Minnesota Minneapolis, Minnesota

Byron W. Brown, Jr., Ph.D., Statistics, Stanford University, Palo Alto, California

Jerome Cornfield, Statistics, University of Pittsburgh, Pittsburgh, Pennsylvania

Alan Freemond, M.D., Ophthalmology, University of Cincinnati, Cincinnati, Ohio (Until 1966)

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Wallace McNeel, M.D., Ophthalmology, Retina Associates, Boston, Massachusetts

Frederick Rose, M.D., Radiology, University Hospitals of Cleveland, Cleveland, Ohio

LIAISON OFFICERS FROM THE
NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES
FOR THE UNIVERSITY GROUP DIABETES PROGRAM

John F. Sherman, Ph.D.	1959 - 1960
James W. Pratt,* Ph.D.	1960 - 1964
Edward T. Offutt, Ph.D.	1964 - 1965
Rose Marie Petrucelli, Ph.D.	1965 - 1968
LeMar F. Kemmert, Ph.D.	1968 - Present

*Deceased

II. OBJECTIVES

The University Group Diabetes Program had three major objectives:

(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 diabetics.

(3) Development of methods applicable to cooperative clinical trials.

III DESIGN AND METHODS

A Therapeutic Regimens Selected

The investigators agreed to study five treatment groups "Insulin Variable" in which maintenance of normal" blood glucose was stressed; "Insulin Standard" in which small doses of insulin were given in a constant dose; "Tolbutamide". which represented the oral hypoglycemic drugs of the sulfonylurea group; "Phenformin", which represented the biguanide group of oral hypoglycemic drugs, and lactose "Placebo" All patients received the same diet prescription. These treatment groups are described in greater detail in Table 2

TABLE 1

STUDY TREATMENTS*

TREATMENT	ABBREVIATION	DOSAGE
Insulin Variable (U-80 Lente Iletin or other insulins)	IVAR	Insulin as much as is required to maintain "normal"* blood glucose The minimum dose is 5 U per day. **
nsulin Standard (U-80 Lente Iletin insulin)	ISTD	10, 12, 14, or 16 units per day depending on body surface (injected before breakfast)
Tolbutamide (Orinase)	TOLB	1.5 grams per day (1 gram before breakfast and 0.5 grams before the evening meal)
Phenformin (DBI-TD)	PHEN	100 mg per day 50 mg before breakfast and 50 mg before the evening meal. First week of study only 50 mg before breakfast.
Lactose Placebo	PLBO	Dosage schedule corresponding to that used for oral hypoglycemic agents

*"Normal" = FBS <110 mg% and BS <210 mg% 1 hour after 50 g of glucose p.o and 1-1/2 hours after morning insulin injection

** In the event that both of these levels were exceeded at a scheduled test, the insulin dose was to be raised by at least two units. Investigators were to decrease the insulin dosage when it appeared necessary in order to prevent hypoglycemic episodes. A minimum dose of five U per day was stipulated at the low end of the dosage scale in order that all patients in this group would receive insulin. It was permissible, at the discretion of the study physicians, to supplement lente forms of insulin with semi-lente and regular types of insulin.

B. Diet for all Study Patients

The prescribed diet consisted of 45% carbohydrate, 20 % protein, and 35% fat calories for all patients irrespective of the assigned treatment. The number of calories prescribed at each follow-up examination was designed to achieve and to maintain normal body weight within plus or minus 15%. The table for desirable body weights is given in Appendix B.

C. Patient Selection Criteria

Patients were eligible for participation in the UGDP only if the diagnosis of diabetes had been established no more than one year prior to entry into the study. The time of diagnosis was determined by the date of the first positive glucose tolerance test or by the time at which hypoglycemic treatment was first initiated. The clinic physicians used their judgment to screen all patients for absence of life-endangering diseases so as to obtain patients with a minimum life expectancy of at least five years. No age limitation for study patients was specified.

Patients were given a diagnostic glucose tolerance test The sum of the four blood glucose values had to be equal to or greater than 500 mg per 100 ml in order for a patient to be eligible for the study

Patients who met all of the diagnostic criteria were observed during four weeks while on diet alone.

No attempt was made to exclude patients who already had signs of vascular disease since they could be observed for progression or regression of that abnormality. Moreover, presence of vascular disease in one organ system did not preclude the evaluation of the onset of disease in other organs.

D. Patient Recruitment

A total of 1,027 patients were enrolled in the study during this 5-year period.

E. Assignment to Study Treatment

Patients enrolled in the UGDP were randomly assigned to one of the five treatment groups listed in Table 2.

F. Diagnosis of "Diabetes"

In the UGDP the summed value of the four blood glucose levels had to be 500 mg per 100 ml in order for a patient to be eligible for the study. Patients were challenged with 30 grams of glucose for each square meter of estimated body surface (Appendix A).

Venous antecubital blood samples were taken immediately prior to glucose ingestion and one, two, and three hours thereafter. Whole blood glucose determinations were performed with the use of the Hoffman ferricyanide method on the Autoanalyzer®.

All patients were seen by their study physician at three-month intervals after initiation of the study treatment.

G. The Heart Examination

The heart examination included obtaining a clinical history fromthe patient which consisted of information on hospitalizations for heart disease, digitalis prescription, attacks of angina pectoris and whether or not serum transaminase determinations had been performed. The results of SGOT determinations and the date of a suspected myocardial infarction were recorded.

The patient's physical examination for the heart included the measurement of systolic and the fourth and fifth phase diastolic blood pressure, a standard twelve-lead electrocardiogram, chest x-rays from which cardiothoracic diameters were determined (chest x-rays were obtained at baseline and at annual intervals thereafter) and examination for presence of congestive heart failure.

H. The Peripheral Vascular Examination

The peripheral vascular examination included a search for a history of intermittent claudication and amputation and clinical examimation of pulses, oscillometry and soft tissue x-rays of the lower extremities.

I. Other Determinations

Serum specimens were collected upon the patient's entry into the study and at annual intervals thereafter for cholesterol determinations and serum triglyceride levels.

Biothesiometry measurements were made at entry and at annual intervals thereafter.

J. Demographic Characteristics

The youngest patient enrolled was 20 years of age and the oldest patient 79 years of age. A large proportion of the study population was female (71%). The mean ages at entry for males and for females were 54 and 52, respectively. Nearly 60% of all patients were in the age range 45 through 64. Fifty-five percent of the patient population was white.

IV. DIAGNOSTIC CRITERIA FOR DIABETES

69 Patients < 500 sum (~ 7%)

339 Patients FBS < 110 mg/100 ml (33%)

V. PERCENT OF PATIENTS WITH SELECTED BASELINE CHARACTERISTICS

(Denominators given in parenthesis)

Demographic Characteristics

Age ≥ 55	45.4 (823)
Male	27.8 (823)
Non-White	47.1 (823)

Baseline Cardiovascular Risk Factors

Hypertension		31.5 (806)
Blood Pressure:		
Systolic:	<140 - 51.5	
	>139 - 48.6	
	>160 - 23.1	
Diastolic	< 90 - 67.8	
	> 89 - 32.2	
History of Digitalis Use		5.7 (808)
History of Angina Pectoris		5.8 (812)
Significant ECG Abnormality		4.1 (810)
Originally 19.2%		
Now 4.3%		
Cholesterol ≥ 300 mg/100 ml		13.4 (805)
	<250 mg% - 70.2	
	>250 - 29.8	
	>290 - 15.7	
One or More Cardiovascular Risk Factors Listed Above		46.8 (772)

Other Selected Baseline Characteristics

Fasting Blood Glucose ≥ 110 mg/100 ml	66.8 (819)
Relative Body Weight 1.25	55.7 (823)
Visual Acuity (either eye 20/200)	5.4 (766)
Serum Creatinine 1.5 mg/100 ml	2.3 (799)
Arterial Calcification*	16.8 (799)

* Evidence of calcification noted by two independent readings of soft tissue x-rays of right lower limb.

VI. RESULTS

A. Fatal Events

1. Deaths by Rx

2. Deaths by Baseline Characteristics

   a. Demographic
   b. C-V Risk Factors
   c. Other

3. Deaths by Adherence (see table on page 14)

4. Deaths by Blood Glucose Control (see table on page 15).

B. Non-Fatal Events

(See table on page 16).

NUMBER AND PERCENT DEAD BY CAUSE OF DEATH

	PLBO	TOLB	ISTD	IVAR
Number at Risk at Death	205	204	210	204
Cardiovascular Causes				
1. Myocardial Infarction	0	10	3	2
2. Sudden Death	4	4	4	5
3. Other Heart Disease	1	5	1	2
4. Extracardiac Vascular Disease	5	7	5	3
All C.V. CAUSES	10	26	13	12
Non-Cardiovascular Causes				
5. Cancer	7	2	4	2
6. Cause Othern Than 1-5	3	2	2	3
7. Unknown Cause	1	0	1	1
All CAUSES	21	30	20	18
Percent Dead From:				
C.V. Causes	4.9 (10)	12.7 (26)	6.2	5.9
All Causes	10.2	14.7	9.5	8.8

PERCENT DEAD BY SELECTED BASELINE CHARACTERISTICS

Part B. Cardiovascular Causes

	PLBO	TOLB	ISTD	IVAR
1. Demographic Characteristics				
Age				
< 55	1.7	7.5	1.8	1.8
≥ 55	9.4	18.4	11.3	10.6
Sex				
Male	11.1	17.5	8.8	4.3
Female	2.1	10.6	5.2	6.3
Race				
White	5.8	16.7	7.8	7.4
Non-white	3.9	8.3	4.7	3.6
2. Cardiovascular Risk Factors				
Definite Hypertension				
Absent	3.9	11.5	4.2	0.7
Present	6.8	13.3	10.9	19.6
History of Digitalis Use				
No	3.6	10.9	5.1	4.7
Yes	33.3	33.3	25.0	30.0
History of Angina Pectoris				
No	3.6	11.8	5.2	5.7
Yes	30.0	21.4	18.8	14.3
Significant ECG Abnormality				
Absent	3.6	10.9	5.6	4.7
Present	33.3	30.0	18.2	37.5
Cholesterol				
< 300 mg/100 ml	5.0	12.4	4.6	4.0
≥ 300 mg/100 ml	5.9	13.3	14.7	18.5
C. V. Risk Factors Listed Above				
None	2.0	9.0	2.0	0.0
One or More	8.0	15.2	10.9	15.0
3. Other Baseline Characteristics				
Fasting Blood Glucose				
< 110 mg/100 ml	5.4	8.6	2.6	3.1
≥ 110 mg/100 ml	4.7	24.3	8.3	7.2
Relative Body Weight				
< 1.25	7.2	15.5	6.7	9.6
≥ 1.25	2.8	10.8	5.8	2.7
Visual Acuity				
> 20/200	5.6	12.1	5.4	6.2
≤ 20/200	0.0	30.0	16.7	0.0
Serum Creatinine				
< 1.5 mg/100 ml	4.2	10.8	5.0	5.6
≥ 1.5 mg/100 ml	20.0	20.0	25.0	0.0
Arterial Calcification				
Absent	5.2	9.4	4.2	4.9
Present**	13.8	25.6	25.7	22.6

*Major or minor Q-waves (codes 1-1-1 through 1-2-7), S-T depression (code 4-1), T wave inversion (code 5-1), complete heart block (code 6-1), left bundle branch block (code 7-1), or ventricular tachycardia (code 8-2).

**Recorded as present only if calcification noted on two independent readings of the

PERCENT DEAD BY CLINIC

	PLBO	TOLB	ISTD	IVAR	Number of Deaths	
All Causes						
Baltimore	0.0	4.5	0.0	0.0	1	
Cincinnati	30.4	31.8	16.7	23.8	23	
Cleveland	5.3	5.6	0.0	10.0	4	
Minneapolis	13.6	33.3	20.8	8.3	18	
New York	13.6	10.0	9.5	13.6	10	
Williamson	8.7	18.2	13.0	12.5	12	
Birmingham	15.4	18.2	0.0	0.0	4	
Boston	6.7	29.4	12.5	6.7	9	
Chicago	9.1	0.0	8.3	9.1	3	
St. Louis	10.0	0.0	8.3	0.0	2	
San Juan	0.0	0.0	7.7	7.7	2	
Seattle	0.0	0.0	9.1	0.0	1	
Cardiovascular Causes						
Baltimore	0.0	4.5	0.0	0.0	1	
Cincinnati	8.7	31.8	16.7	19.0	17	
Cleveland	0.0	5.6	0.0	5.0	2	
Minneapolis	9.1	25.0	8.3	8.3	12	
New York	13.6	10.0	0.0	0.0	5	
Williamson	4.3	13.6	8.7	12.5	9	
Birmingham	0.0	18.2	0.0	0.0	2	
Boston	6.7	23.5	6.3	6.7	7	
Chicago	9.1	0.0	8.3	9.1	3	
St. Louis	0.0	0.0	8.3	0.0	1	
San Juan	0.0	0.0	7.7	0.0	1	
Seattle	0.0	0.0	9.1	0.0	1	
					Total # of Patients	Median Years of Follow-Up
Denominators						
Baltimore	24	22	21	20	87	7.2
Cincinnati	23	22	24	21	90	8.0
Cleveland	19	18	20	20	77	6.8
Minneapolis	22	24	24	24	94	6.6
New York	22	20	21	22	85	6.8
Williamson	23	22	23	24	92	7.5
Birmingham	13	11	13	12	49	7.2
Boston	15	17	16	15	63	7.0
Chicago	11	12	12	11	46	5.3
St. Louis	10	11	12	11	44	5.7
San Juan	12	14	13	13	52	5.3
Seattle	11	11	11	11	44	5.0

PERCENTAGE DISTRIBUTION OF PATIENTS BY LEVEL OF BLOOD GLUCOSE CONTROL

LEVEL OF CONTROL*	PLBO	TOLB	ISTD	IVAR
GOOD	27.0	37.4	38.5	49.0
FAIR	32.3	37.0	33.2	39.4
POOR	40.7	25.6	28.3	11.6
Number of Patients	204	203	205	198

*Based on the fasting blood glucose values obtained from the SHORT GTT for a given patient.

GOOD : 70% or more of all the patient's SHORT GTT fasting blood values <110 mg per 100 ml.

POOR : 70% or more of all the patient's SHORT GTT fasting blood glucose values 130 mg per 100 ml.

FAIR : Patient classified as having neither GOOD or POOR blood glucose control.

PERCENTAGE DISTRIBUTION OF PATIENTS
BY LEVEL OF ADHERENCE

LEVEL OF ADHERENCE*	PLBO	TOLB	ISTD	IVAR
LOW	10.2	10.3	12.8	14.8
INTERMEDIATE	20.0	15.7	29.8	39.9
HIGH	69.8	74.0	57.6	45.3
Number of Patients	205	204	210	204

*Based on percent of follow-up periods during which patient took ALL of prescribed study medication.

LOW : Patient took ALL of prescribed study medication < 25% of all follow-up periods.

INTERMEDIATE : Patient took ALL of prescribed study medication 25-74% of all follow-up periods.

HIGH : Patient took ALL of prescribed study medication > 75% of all follow-up periods.

PERCENT OF PATIENTS WITH THE FIRST OCCURRENCE OF A SPECIFIED NON-FATAL EVENT IDENTIFIED AT A FOLLOW-UP EXAMINATION

(Denominators Given in Parentheses)

NON-FATAL EVENT	PLBO	TOLB	ISTD	IVAR
Visual Acuity 20/200 in Either Eye	6.7(179)	9.4 (181)	5.6 (179)	5.7 (175)
Significant ECG Abnormality*	14.1(198) (28)	8.2 (196) (15)	8.2 (195)	7.9 (190)
Hypertension	36.8 (125)	44.4 (135)	41.3 (138)	44.3 (140)
Serum Creatinine 1.5 mg/100 ml	6.5 (184)	5.9 (188)	3.6 (192)	5.4 (186)
Urine Protein 1 gram/liter	0.5 (204)	2.5 (204)	0.0 (204)	2.0 (198)
Arterial Calcification**	11.3 (168)	14.8 (155)	16.8 (161)	17.2 (157)
Amputation of All or Part of Either Lower Limb	1.0 (202)	0.0 (202)	0.0 (209)	0.0 (204)

*Major or minor Q-waves (codes 1-1-1 through 1-2-7), S-T depression (code 4-1), T-wave inversion (code 5-1), complete heart block (code 6-1), left bundle branch block (code 7-1), ventricular tachycardia (code 8-2).

**Evidence of calcification noted by two independent readings of soft tissue x-rays of right lower limb.

VII. SUMMARY

1. Tolbutamide plus diet is no more effective than diet alone, except for antihyperglycemia.

2. The particular tolbutamide regimen used here may be less effective than diet alone or diet plus insulin with respect to C-V mortality in the type of patient studied.

3. Except for superior control of blood glucose by insulin variable, no other differences between the two insulin groups were noted.

CRITIQUE

I. BASIC DESIGN

A. Data Collection - Inadequate baseline data

1. Methods of collection not described
2. Clinical definitions not stated - individual judgements prevail

B. Choice of Therapies

1. Only two of the five regimens (diet alone and insulin variable) are used in practice.

C. Choice of Patients

1. Admission criteria included:

   a. Patients who already had vascular disease--undefined as to severity.

   b. Patients who, in the judgement of the individual clinician, would live at least 5 years--a dubious a priori prognostic exercise in a study designed to obtain prognostic data (cf death rates from 0 to 33%). Death risk factors were thus to be excluded and the study not designed for mortality analyses.

   c. Non-diabetics

2. Pooling obvious heterogeneous populations as if it were random homogenous population essential for valid statistical analysis.

3. Failure to examine risk factors: e.g. smoking, parental longevity, pulmonary disease status, "co-morbid ailments" such as infection, other medications.

4. Absence of all baseline data in 481 patients.

D. Allocation and Intrusion Problems

1. Two patient pools due to DBI intrusion

2. Treatment Change

a. Drop-outs -- 12%
b. Medication arbitrarily changed due to failure but patient classified under original therapy (6.8% of placebo).
c. Non-adherence to therapy - 25%. Patients were actually on other therapy--2"tolbutamide deaths" had been off of tolbutamide for four years.

II. STATISTICAL ANALYSIS

A. Omissions:

1. No analysis of vascular complications, i.e. all vascular events, a prime original objective.

2. No analysis of other features of diabetes.

3. No DBI data.

B. Questionable Decision to Stop Tolbutamide

1. There was no significant overall mortality difference and continuation would have been ethically justifiable in view of heterogeneity. (cf cancer mortality on placebo)

2. Paasikivi and Keen experience.

3. Narrowing of excess C-V mortality at time of decision.

C. Questionable Maneuver

1. Revision of ECG criteria to eliminate baseline discrepancies and justify conclusion that excess C-V mortality was not due to chance.

D. Mathematical Errors

III. PERSONAL CONCLUSIONS:

A. Validity of the Study

The study is obviously seriously flawed.

B. Tolbutamide's Danger

These flaws do not, on the basis of the limited raw data made public, necessarily absolve tolbutamide of contributing in some undetermined manner to the excess mortality of the Minneapolis-Cincinnati patients. (Was this excess C-V mortality just the "luck of the draw" or a consequence of tolbutamide Rx itself at least in this particular population? No way of knowing this).

C. Value of Antihyperglycemic Therapy in Preventing Vascular Complications

Since blood glucose was not controlled adequately in the tolbutamide and insulin standard patients, many of whom were nondiabetics, and since the adequately controlled insulin-variable patients, like the others, had a high percentage of established advanced vascular disease at the time of the study, and since meaningful data on the effect of therapy on progression of vascular disease from its baseline status was not published, the study does not answer the question of the effect of antihyperglycemic therapy of diabetes upon vascular and other complications of diabetes.

D. Status of Antihyperglycemic Therapy

1. Tolbutamide rx is not justified in a) chemical diabetes; b) diabetic patients who are frightened by the adverse publicity about the drug.

2. Tolbutamide Rx is probably not justified a) in patients who are readily controlled by diet alone; b) in elderly diabetics with asymptomatic and aglycosuric fasting hyperglycemia not controlled by diet alone, particularly if established vascular disease is likely, in which case such hyperglycemia may be

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TABLE 7-1

DECEASED PATIENTS IN PLACEBO TREATED GROUP

Number	Cause of Death	Death in Hosp	Autopsy Done	Quarter of Death	Baseline Characteristics: Age	Sex	Race	SUN Eff	Rel. Body Wt.	Blood Pressure: Syst.	Blood Pressure: Diast.	History of Infarction	History of Angina	Significant ECG Abnormality	Chol	No of CV Risk Factors	Adherence: % of Visits with Pill	Blood Glucose Control: % of Visits <110mg/100ml	Blood Glucose Control: % of Visits ≥130mg/100ml
PLBO-1	SUDDEN DEATH	NO	NO	7	64	M	W	372	1.23	159	88	NO	YES	NO	248	1	100	0	100
PLBO-2	SUDDEN DEATH	NO	NO	11	48	F	W	ND 556	1.07	99	52	NO	NO	NO	240	0	80	29	71
PLBO-3	SUDDEN DEATH	YES	NO	19	69	M	W	ND 527	1.21	185	99	YES	NO	YES	205	3	22	100	0
PLBO-4	SUDDEN DEATH	NO	NO	23	65	F	N-W	1035	1.30	179	98	NO	NO	NO	255	1	37	14	71
PLBO-5	RHEUMATIC HEART DISEASE	YES	YES	8	53	M	W	671	1.25	135	100	YES	NO	YES	264	3	100	33	33
PLBO-6	PULMONARY EDEMOUS	YES	NO	9	66	M	N-W	ND 674	1.21	179	87	NO	NO	NO	340	2	100	100	0
PLBO-7	CVA	YES	NO	21	61	M	W	904	1.07	139	83	NO	YES	NO	284	1	55	0	73
PLBO-8	CVA	NO	NO	10	63	M	N-W	ND 600	1.37	131	70	NO	NO	NO	236	0	100	100	0
PLBO-9	CVA	NO	YES	12	63	F	N-W	1498	1.04	190	84	NO	YES	NOT DONE	142	2	9	0	78
PLBO-10	DIABETIC GANGRENE	YES	NO	20	73	M	W	726	1.20	119	67	YES	NO	NO	248	1	37	21	79
PLBO-11	CANCER	NO	NO	7	57	F	W	ND 519	1.06	120	80	NO	NO	NO	316	1	100	100	0
PLBO-12	CANCER	YES	NO	14	61	M	W	868	1.62	165	95	NO	NO	NO	229	1	15	0	100
PLBO-13	CANCER	YES	YES	13	61	F	N-W	798	1.19	130	72	YES	NO	NO	263	1	83	0	100
PLBO-14	CANCER	YES	YES	18	59	M	N-W	NOT DONE	1.53	170	101	YES	NO	NO	160	2	94	69	8
PLBO-15	CANCER	NO	NO	8	64	F	N-W	ND 662	0.96	120	70	NO	NO	NO	168	0	57	80	0
PLBO-16	CANCER	NO	NO	6	57	M	N-W	1129	1.01	118	80	NO	NO	NO	275	0	100	0	100
PLBO-17	CANCER	YES	YES	19	43	F	W	ND 531	1.04	128	81	NO	NO	NO	136	0	22	100	0
PLBO-18	CHOLECYSTITIS	YES	NO	5	72	M	N-W	ND 568	1.22	123	85	NO	NO	NO	234	0	50	0	0
PLBO-19	DIABETIC NEPHROPATHY	YES	YES	20	45	F	N-W	1510	1.37	135	77	NO	NO	NO	204	0	90	0	100

4/30/90
773

TABLE B-1 (Continued)

					Baseline Characteristics												Adherence	Blood Glucose Control	
Number	Cause of Death	Death in Hosp.	Autopsy Done	Quarter of Death	Age	Sex	Race	SUBJ CTY	Rel. Body Wt.	Blood Pressure Syst.	Blood Pressure Diast.	History of Digitalis	History of Angina	Significant ECG Abnormality	Chol	No of CV Risk Factors	% of Visits with [illegible]	% of Visits <110 mg/100 ml	% of Visits ≥110 mg/100 ml
[illegible]	SUICIDE	NO	NO	13	(71)	M	W	326	1.11	132	80	NO	NO	NO	172	0	100	22	22
[illegible]	[illegible]	NO	NO	16	54	M	W	1221	0.91	127	62	NO	NO	NO	263	0	60	0	100

8 had heart disease = EKG A, angina, CHF
only 2 had 2 of the above.

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TABLE

DECEASED PATIENTS IN TOLBUTAMIDE TREATED GROUP

Number	Cause of Death	Death in Hosp.	Autopsy Done	Quarter of Death	Age	Sex	Race	SGOT OTT	Rel. Body Wt.	Blood Pressure Syst.	Blood Pressure Diast.	History of Digitalis	History of Angina	Significant ECG Abnormality	Chol	No of CV Risk Factors	Adherence % of Visits with All	Blood Glucose Control % of Visits <110mg/100ml	Blood Glucose Control % of Visits ≥110mg/100ml
TOLB-1	MI	YES	YES	17	62	F	W	[illegible]	1.22	114	55	NO	NO	NO	196	0	100	46	[illegible]
TOLB-2	MI	YES	NO	10	37	F	W	892	1.15	134	77	NO	NO	NO	325	1	100	0	[illegible]
TOLB-3	MI	YES	YES	10	60	F	W	912	1.35	210	96	NO	NO	NO	282	1	100	29	[illegible]
TOLB-4	MI	YES	YES	9	53	M	W	ND 517	1.23	136	80	NO	NO	NO	262	0	100	100	[illegible]
TOLB-5	MI	YES	NO	18	66	M	W	ND 507	1.24	177	78	NO	NO	NO	243	1	100	91	[illegible]
TOLB-6	MI	YES	YES	22	65	M	W	1085	0.81	135	86	NO	NO	NO	227	0	100	0	10
TOLB-7	MI	YES	NO	12	59	F	W	909	1.48	141	70	NO	NO	NO	234	0	100	100	[illegible]
TOLB-8	MI	YES	YES	15	49	M	W	1152	1.20	109	67	NO	NO	NO	232	0	100	0	[illegible]
TOLB-9	MI	YES	YES	18	67	F	N-W	727	1.39	147	90	NO	NO	NO	241	0	100	92	
TOLB-10	MI	YES	YES	14	69	F	W	824	1.26	185	90	NO	NO	NO	215	1	100	80	[illegible]
TOLB-11	SUDDEN DEATH	NO	NO	11	68	F	W	726	1.14	138	73	NO	NO	NO	281	0	90	43	[illegible]
TOLB-12	SUDDEN DEATH	NO	NO	23	76	M	N-W	723	1.18	151	90	NO	NO	YES	214	1	5	20	[illegible]
TOLB-13	SUDDEN DEATH	NO	NO	27	52	M	N-W	635	1.14	155	85	YES	YES	YES	406	4	92	27	[illegible]
TOLB-14	SUDDEN DEATH	NO	NO	26	63	F	N-W	ND 551	1.45	NOT DONE	NOT DONE	UNK	UNK	NOT DONE	208	UNK	28	25	[illegible]
TOLB-15	ASHD	YES	YES	25	51	M	W	834	1.31	165	100	YES	NO	NO	120	2	100	0	[illegible]
TOLB-16	ASHD	NO	NO	15	54	F	N-W	856	1.07	151	95	NO	NO	NO	208	1	86	0	91
TOLB-17	ASHD	NO	NO	30	61	M	N-W	723	1.07	141	82	NO	NO	NO	296	0	90	55	20
TOLB-18	ASHD	YES	NO	21	67	F	W	608	0.92	140	NOT DONE	NO	NO	NO	214	0	95	40	20

6 CV deaths in Cincinnati
6 " " Minneapolis

TABLE B-2 (Continued)

Number	Cause of Death	Death in Warn	Autopsy Done	Quarter of Death	Age	Sex	Race	SUM GTT	Rel. Body Wt.	Blood Pressure Syst.	Blood Pressure Diast.	History of Digitalis	History of Angina	Significant ECG Abnormality	Chol	No of CV Risk Factors	Adherence % of Visits with All	Blood Glucose Control % of Visits <110mg/100ml	Blood Glucose Control % of Visits ≥130mg/100ml
TOLB-19	HEART DISEASE	YES	NO	5 ✓	68	M	W	ND 500	1.05	122	80	YES	YES	YES ✓	199	3	100	100	0
TOLB-20	PULMONARY EMBOLUS	NO	YES	25	54	F	W	668	1.57	119	60	NO	NO	NO	NOT DONE	0/4	100	0	94
TOLB-21	CVA	NO	NO	24	52	M	W	901	1.35	140	95	NO	NO	NO	267	1	73	9	35
TOLB-22	CVA	YES	YES	6 ✓	60	F	W	1010	1.38	140	90	YES	YES ✓	NO	247	2	100	50	0
TOLB-23	CVA	YES	YES	12	55	F	W	ND 522	1.43	172	81	NO	NO	NO	✓307	2	64	100	0
TOLB-24	CVA	YES	YES	13	49	F	N-W	1377	1.32	110	70	YES	NO	YES ✓	✓370	3	91	33	12
TOLB-25	CVA	YES	YES	17	55	M	N-W	1218	1.51	150	101	NO	NO	NO	271	0	100	0	100
TOLB-26	CVA	YES	NO	18	64	F	W	1182	2.07	130	70	NO	NO	NO	266	0	100	0	100
TOLB-27	CANCER	YES	NO	12	61	M	W	1283	0.91	140	70	NO	NO	NO	160	0	91	22	78
TOLB-28	CANCER	YES	NO	25	(72)	F	W	ND 533	1.15	170	85	NO	NO	NO	242	1	.92	100	0
TOLB-29	DUODENAL ULCER	YES	YES	5 ✓	69	M	W	902	1.04	121	60	NO	NO	NO	177	0	100	50	0
TOLB-30	PNEUMONIA	NO	YES	6 ✓	66	F	W	659	1.03	200	70	NO	NO	NO	213	1	100	25	25

Exclude H.D., ↑ Chol ≥ 300, and age ≥ 70 and non-diabetes

Plac = 11

Tolb = 21

Tol = 15

then add < 2 years comparison

Tolb = 16

D + ↑ chol excluded

Tolb = 12

= 21 or 22

Tolb heart deaths = 24

Placebo heart deaths = 13

If one excludes each group's heart disease at baseline from Tol: 6 had heart disease = EKG A, angina, CHF

But since Tolb deaths were concentrated in 2 clinics whereas placebo deaths were not, could difference in tx been a factor?

Also 4 of 6 had 2 or more of these 3 manifestations of heart disease in Tolbut group

excluding 4 heart disease

Tolbut = 26

Plac = 19

TABLE

DECEASED PATIENTS IN INSULIN STANDARD TREATED GROUP

Number	Cause of Death	Death in Home	Autopsy Done	Quarter of Death	Baseline Characteristics: Age	Sex	Race	Sum GTT	Rel. Body Wt.	Blood Pressure Syst.	Blood Pressure Diast.	History of Digitalis	History of Angina	Significant ECG Abnormality	Chol	No of CV Risk Factors	Adherence: % of Visits With All	Blood Glucose Control: % of Visits <110mg/100ml	% of Visits ≥110mg/100ml
ISTD-1	MI	YES	NO	13	75	F	W	1461	0.92	195	65	NO	NO	NO	100	1	93	22	44
ISTD-2	MI	YES	YES	25	52	M	W	512	1.26	127	80	NO	YES	NO	256	1	92	100	0
ISTD-3	MI	YES	NO	19	63	M	W	709	1.27	149	89	NO	NO	NO	172	0	100	43	36
ISTD-4	SUDDEN DEATH	NO	NO	10	54	F	N-W	772	1.32	130	85	NO	YES	YES	192	2	100	0	67
ISTD-5	SUDDEN DEATH	NO	NO	26	52	F	N-W	1193	1.27	122	78	NO	NO	NO	364	1	76	0	94
ISTD-6	SUDDEN DEATH	NO	NO	14	53	F	N-W	651	1.60	140	97	NO	NO	NO	352	2	85	11	78
ISTD-7	SUDDEN DEATH	DOA	NO	18	53	F	N-W	1063	1.17	205	92	NO	NO	NO	336	2	94	15	35
ISTD-8	RHEUMATIC HEART DISEASE	YES	NO	6	59	F	W	747	1.07	162	82	YES	NO	YES	301	4	80	50	0
ISTD-9	PULMONARY EMBOLUS	NO	YES	21	63	F	W	838	1.00	189	95	NO	NO	NO	228	1	60	71	29
ISTD-10	CVA	NO	NO	26	72	M	W	697	1.09	120	66	NO	YES	NO	180	1	52	76	12
ISTD-11	CVA	YES	YES	14	68	M	W	868	1.20	145	70	NO	NO	NO	150	0	85	10	90
ISTD-12	CVA	NO	NO	2	68	M	W	631	1.31	175	103	YES	NO	NO	162	2	100	100	0
ISTD-13	CVA	YES	NO	33	63	F	N-W	1041	1.43	220	90	YES	NO	NO	305	3	84	25	54
ISTD-14	CANCER	NO	YES	27	66	M	W	537	1.06	187	77	NO	NO	NO	227	1	88	100	0
ISTD-15	LYMPHOSARCOMA	YES	YES	23	59	F	W	688	1.54	118	73	YES	YES	YES	212	3	59	71	12
ISTD-16	RETICULUM CELL SARCOMA	YES	NO	11	64	F	W	964	1.33	123	NOT DONE	YES	NO	YES	242	2	80	0	100
ISTD-17	CANCER	YES	YES	11	55	M	W	554	1.14	105	80	NO	NO	NO	220	0	100	57	14
ISTD-18	ACCIDENT	YES	NO	21	72	M	W	715	1.38	150	90	NO	YES	NO	223	1	100	8	62
ISTD-19	ACCIDENT	NO	YES	8	62	M	W	681	1.25	165	87	NO	YES	NO	204	2	57	100	0
ISTD-20	UNKNOWN	NO	NO	2	72	M	W	986	1.29	145	70	NO	YES	NO	197	1	100	0	100

SLIDE ✓

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TABLE

DECEASED PATIENTS IN INSULIN VARIABLE TREATED GROUP

Number	Cause of Death	Death in Hosp	Autopsy Done	Quarter of Death	Baseline Characteristics												Adherence	Blood Glucose Control	
					Age	Sex	Race	FDI GTT	Rel. Body Wt.	Blood Pressure Syst.	Blood Pressure Diast.	History of Diabetic	History of Angina	Significant Ecg Abnormality	Chol	No of CV Risk Factors	% of Visits with ATT	% of Visits <110mg/100ml	% of Visits >130mg/100ml
IVAR-1	MI	YES	NO	11	53	M	W	841	1.21	175	91	NO	NO	NO	239	1	50	43	0
IVAR-2	MI	YES	YES	4	69	F	W	1428	1.25	167	89	NO	NO	NO	252	1	67	0	67
IVAR-3	SUDDEN DEATH	NO	NO	12	66	F	W	960	0.84	190	70	NO	NO	NO	254	1	67	33	25
IVAR-4	SUDDEN DEATH	NO	NO	4	59	M	W	870	1.13	169	70	YES	YES	YES	240	4	100	67	0
IVAR-5	SUDDEN DEATH	YES	NO	3	50	F	W	1474	0.70	185	82	YES	NO	NO	420	3	50	0	100
IVAR-6	SUDDEN DEATH	NO	NO	8	73	F	N-W	1110	1.13	169	78	NO	NO	NO	440	2	100	100	0
IVAR-7	SUDDEN DEATH	NO	NO	31	40	F	W	1370	1.27	130	80	NO	NO	NO	350	1	44	0	100
IVAR-8	ASHD	YES	NO	23	79	F	W	654	1.46	181	90	NO	NO	NO	181	1	65	47	40
IVAR-9	RHEUMATIC HEART DISEASE	YES	NO	13	65	F	W	524	0.95	147	99	YES	NO	NO	264	2	0	100	0
IVAR-10	CVA	YES	NO	6	70	F	W	644	1.22	160	88	NO	NO	YES	363	3	100	0	100
IVAR-11	CVA	YES	NO	8	62	F	N-W	1223	1.27	194	88	NO	NO	YES	310	3	17	0	100
IVAR-12	PULMONARY EMBOLUS	YES	YES	1	67	F	N-W	898	1.10	198	103	NO	NO	NO	297	1	0	NA	NA
IVAR-13	CANCER	NO	NO	19	72	F	N-W	1373	1.47	127	75	NO	NO	NO	250	0	50	44	11
IVAR-14	CANCER	YES	YES	20	45	F	W	770	1.61	119	81	NO	NO	NO	222	0	7	89	11
IVAR-15	MYOCARDIAL INFARCT POST OP.	YES	NO	31	46	F	N-W	891	1.22	121	91	NO	NO	NO	214	0	74	60	4
IVAR-16	SENSOR TUMOR OF CNS	YES	NO	24	51	F	N-W	1082	2.21	129	90	NO	NO	NO	163	0	39	33	22
IVAR-17	SUICIDE	YES	YES	12	46	F	W	629	1.16	213	110	NO	NO	NO	156	1	67	100	0
IVAR-18	UNKNOWN	YES	NO	16	41	F	N-W	1424	0.99	139	86	NO	NO	NO	NOT DONE	0	0	0	0

6|57'76
Sum=1089

1) DuBois, D. and DuBois, E. F. A formula to estimate the approximate surface area if height and weight be known. The Archives of Internal Medicine 17:863-871, 1916.

2) Welsh, George W. III, Henley, Elaine D., Williams, Robert H., and Cox, Robert W. Insulin I-131 metabolism in man. American Journal of Medicine 21:324-338, 1956.

3) Williams, Robert H. Differences in the pharmacology of the sulfonylureas, pp. 719-720, Textbook of Endocrinology (4th Edition), W. B. Saunders, 1968.

4) Tolbutamide...After Ten Years. Orinase (tolbutamide), p. 328, International Congress Series 149, Excerpta Medica Foundation, New York, 1967.

5) Balodimos, M. C., Gleason, R. E., Bradley, R. F. and Marble, A. Long-term tolbutamide therapy in diabetes: A controlled study of the frequency of cardiovascular disease and other findings. In Tolbutamide... After Ten Years, p. 272, International Congress Series No. 149, Excerpta Medica Foundation, New York, 1967.

6) Lozano-Castaneda, O., Villasenor, A., Gonzalez-Millan, H., and Rull, J.A. Treatment of diabetes with a single dose of tolbutamide. In Tolbutamide...After Ten Years, p. 298, International Congress Series No. 149, Excerpta Medica Foundation, New York, 1967.

7) Mehnert, Hellmut. Clinical results after 10 years treatment with tolbutamide. In Tolbutamide...After Ten Years, pp. 281-285, International Congress Series No. 149, Excerpta Medica Foundation, New York, 1967.

8) The Rand Corporation. A Million Random Digits with 100,000 Normal Deviates. Free Press, Glencoe, Illinois, 1955.

9) University Group Diabetes Program. A study of the effects of hypoglycemic agents on vascular complications: II. Mortality Results. Diabetes 19, Supplement ___, 1970.

10) Committee on Statistics of the American Diabetes Association. Standardization of the oral glucose tolerance test. Diabetes 18:299-310, 1969.

11) Klimt, C. R., Meinert, C. L., and Prout, T. E. (Unpublished data)

12) Blackburn, H., Keys, A., Simonson, E., Rautaharju, P., and Punsar, S. The electrocardiogram in population studies. Circulation 21: 1160-1175, 1960.

13) Owens, J. A., Iggo, B., Scandrett, F. J., and Stewart, C. P. The determination of creatinine in plasma or serum, and in urine; a critical examination. Biochemical Journal 58:426-437, 1954.

14) Peters, John P. and Van Slyke, Donald D. Quantitative Clinical Chemistry, Vol. 2 (Methods), pp. 682-683, The Williams and Wilkins, Company, 1932.

15) Anderson, J. T. and Keys, A. Cholesterol in serum and lipoprotein fractions, its measurement and stability. Clinical Chemistry 2: 145-159, 1956.

16) Abell, L. L., Levy, B. B., Brodie, B. B., and Kendall, F. E. A simplified method for the estimation of total cholesterol in serum and demonstration of its specificity. Journal of Biological Chemistry 195: 357-366, 1952.

17) Lofland, H. B. Jr., A semiautomated procedure for the determination of triglycerides in serum. Analytical Biochemistry 9:393, 1964.

18) Van Handel, E., and Zilversmit, D. B. Micromethod for the direct determination of serum triglycerides. Journal of Laboratory and Clinical Medicine 50:152, 1957.

19) Gregg, E. G. Jr. Absolute measurement of the vibratory threshold. Archives of Neurology and Psychiatry 66:403, 1951.

20) Wilkerson, H. L. C. Diagnosis: Oral glucose tolerance tests. In Diabetes Mellitus: Diagnosis and Treatment, pp. 31-34, American Diabetes Association, Inc., New York, 1964.

21) Cooper, R. G. and McDaniels, V. Workshop Manual on Methods for Determination of Glucose, pp. 117-118, Annual Meeting of American Society of Clinical Pathologists, Washington, D. C., September, 1966.

22) Fajans, S. S. and Conn, J. W. Prediabetes, subclinical diabetes and latent clinical diabetes: Interpretation, diagnosis and treatment. On the Nature and Treatment of Diabetes, pp. 641-656, Excerpta Medica International Congress Series, No. 84, New York, 1965.

23) Snedecor, G. W. and Cochran, W. G. Statistical Methods (6th Edition) pp. 172-193, The Iowa State University Press, Ames, Iowa, 1967.

24) Expert Committee on Arterial Hypertension and Ischaemic Heart Disease. Arterial hypertension and ischaemic heart disease. World Health Organization Technical Report Series, No. 231, 1962.

25) Subcommittee on Nutrition, Committee on Public Health, Medical Society of the County of New York. New height-weight tables, JAMA 173:134, 1960.

26) Seltzer, Holbrooke S. A Different Interpretation of the Mortality Data of the University Group Diabetes Program (UGDP) (submitted to Diabetes)