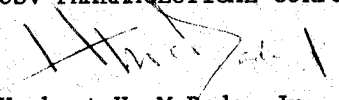
views to you, and respectfully request that they be made a part of the record in this matter.

Very truly yours,

USV PHARMACEUTICAL CORPORATION



Herbert H. McDade, Jr.
President
Chief Operating Officer

HHMcD,Jr./mem

United States Senate
SELECT COMMITTEE ON SMALL BUSINESS
(CREATED PURSUANT TO S. RES. 58, 81ST CONGRESS)
WASHINGTON, D.C. 20510

April 1, 1975

The Honorable Alexander M. Schmidt
Commissioner
Food and Drug Administration
Washington, D. C.

Dear Mr. Commissioner:

During your testimony before our Monopoly Subcommittee on January 29, 1975 Mr. Hutt stated that the Department of Justice declined to file at least seven criminal cases that the FDA forwarded to them for prosecution on false advertising issues.

In this connection, I should be extremely grateful if you would supply the Subcommittee with the names of the firms, dates, products involved, FDA's letters of transmittal and the response of the Department of Justice to FDA in each of these cases as well as for other cases which Mr. Hutt may not have been aware of.

Kindest personal regards.

Sincerely,

Gaylord Nelson
Chairman
Monopoly Subcommittee

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

APR 10 1975

Honorable Gaylord Nelson
Chairman, Monopoly Subcommittee
Select Committee on Small Business
United States Senate
Washington, D.C. 20510

Dear Senator Nelson:

Thank you for your April 1 letter to Commissioner Schmidt requesting information concerning certain criminal cases involving false advertising charges forwarded to the Department of Justice by the Food and Drug Administration which that Department has decided not to file.

We have begun a review of our files to assemble the information you requested and will supply you with an answer in the near future.

If we can be of any assistance in any other way, please let us know.

Sincerely yours,

Robert C. Wetherell, Jr.

Robert C. Wetherell, Jr., Director
Office of Legislative Services

CHAYET AND SONNENREICH, P. C.
ATTORNEYS AT LAW
6 FAYETTE STREET
BOSTON, MASSACHUSETTS 02116
(617) 357-0202

NEIL L. CHAYET
MICHAEL R. SONNENREICH

MICHAEL X. MORRELL*
HARVEY W. FREISHTAT
MARIEN E. EVANS

* NOT ADMITTED IN MASSACHUSETTS

WASHINGTON OFFICE
WATERGATE 600, SUITE 720
600 NEW HAMPSHIRE AVENUE, N. W.
WASHINGTON, D. C. 20037
(202) 965-4150

February 14, 1975

Senator Gaylord Nelson
Senate Office Building
Washington, D.C.

Dear Senator Nelson:

I am enclosing for your information a letter which I sent to Doctor Schmidt shortly after my testimony before you. It is my hope that in accordance with this letter some reasonable conclusion to this dispute will be forthcoming.

I understand that hearings will be held again before your Subcommittee at which the FDA will be present. I am requesting at this time an opportunity to testify at that session so that the proper balance can once again be provided to the Subcommittee deliberations.

Thank you for your continued attention to this matter.

Very truly yours,

Neil L. Chayet

NLC:GF
Enc.

CHAYET AND SONNENREICH, P. C.
ATTORNEYS AT LAW
6 FAYETTE STREET
BOSTON, MASSACHUSETTS 02116
(617) 357-0202

NEIL L. CHAYET
MICHAEL R. SONNENREICH

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*NOT ADMITTED IN MASSACHUSETTS

WASHINGTON OFFICE
WATERGATE 600, SUITE 720
600 NEW HAMPSHIRE AVENUE, N.W.
WASHINGTON, D.C. 20037
(202) 965-4150

February 11, 1975

Dr. Alexander Schmidt, Commissioner
Food and Drug Administration
Department of Health, Education and Welfare
5600 Fishers Lane
Rockville, Maryland 20852

Dear Dr. Schmidt:

It is my understanding that additional hearings are to be held later this month on the subject of oral hypoglycemic drugs before the Subcommittee on Monopoly, chaired by Senator Gaylord Nelson. It is my further understanding that the Food and Drug Administration will be asked to provide testimony at this hearing. I would suggest a meeting between my client and FDA officials to discuss in detail proposed labeling changes by FDA and to determine whether there now exists labeling acceptable to both sides. It is my belief that more can be accomplished at an informal meeting than in testimony before congressional committees and protracted legal proceedings.

Your testimony on September 20, 1974, indicated that there exists substantial controversy with regard to oral hypoglycemic drugs. You stated: " I have personally talked with many diabetologists around the country, and I am sure you know of the degree of controversy that yet remains about the UGDP Study. If that has not been brought up before the Committee, I think it really should be because many 'experts' do publicly attack the UGDP study."

I would also like to note the following portion of Mr. Hutt's testimony that same day: "We must then stand upon the scientific basis for our decision....That is why in part we are waiting for the Biometric Society report as well as amending our regulation Section 1.3, to which the Commissioner has already averted, to settle the legal issue that was also involved in the case."

The hope was expressed by both you and Mr. Hutt that the Biometric Society study would settle this matter. Although we have had only a brief period of time to review this study, I am authorized by my clients to inform you that, despite Dr. Chalmers' editorial entitled "Settling the UGDP Controversy," the controversy is in fact not settled. It is doubtful whether any single review of the UGDP study could settle the fundamental questions which have resulted in the controversy concerning

this study. What is needed is a new prospective study or studies to resolve the issues raised regarding oral hypoglycemics, coupled with immediate, balanced labeling reflecting the controversy.

The Committee on the Care of the Diabetic intends to pursue, through the National Institutes of Health, access to the raw data of the UGDP Study and further to continue its opposition to the proposed amendment of Regulation 1,3, as expressed in comments which we filed relative to this regulation.

I would like to call your attention to the fact that one of the most fruitful aspects of this matter which has continued these many years was the meeting held with FDA officials in October 1973. At that meeting I felt that real progress was made in achieving labeling acceptable to all parties engaged in this controversy. I am enclosing a draft of this labeling prepared by the Committee on the Care of the Diabetic and request that all parties meet once again at the FDA to further discuss this matter,

We offer our full cooperation in continuing the dialogue between the FDA and the Committee on the Care of the Diabetic which will result in new fairly balanced labeling which reflects the current scientific status which we feel, and have felt, is urgently needed.

Very truly yours,

Neil L. Chayet

NLC:GF

U.S. SENATE,
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C., May 27, 1975.

NEIL L. CHAYET, *Esq.*,
Chayet and Sonnenreich, P.C.
Boston, Mass.

DEAR MR. CHAYET: This is in response to your letter of February 14, 1975 accompanied by your correspondence with Commissioner Schmidt of the Food and Drug Administration, as well as your prior phone request to me.

It is true that our Monopoly Subcommittee plans to hold another hearing on the oral hypoglycemic drugs, at which time the FDA will testify on labeling changes. Although your request to appear once again before the Subcommittee is appreciated, this will not be necessary since your position is already part of the hearing transcript. However, should you desire to place additional material into the record following the final testimony of the FDA, you may do so.

In the meantime, I should be extremely grateful if you would send us a complete list of members (and their addresses) of the Committee on the Care of the Diabetic, the organization you represent.

Your continued interest in the work of our Subcommittee is appreciated.

Sincerely,

BENJAMIN GORDON,
Staff Economist.

CHAYET AND SONNENREICH, P. C.,
ATTORNEYS AT LAW,
Boston, Mass., July 10, 1975.

MR. BENJAMIN GORDON,
Staff Economist,
U. S. Senate,
Select Committee on Small Business,
Washington, D.C.

DEAR MR. GORDON: I am in receipt of your recent letter referring the request of the Committee on the Care of the Diabetic (CCD) to testify before the Monopoly Subcommittee in the hearings held this week relative to labeling of oral hypoglycemic drugs.

As you know, CCD has been involved in the labeling controversy for several years, appearing before administrative, legislative, and judicial bodies. From the list of witnesses who appeared before the subcommittee, it would appear that the testimony offered this week represented only one side of the controversy.

Particularly in view of very recent developments in the controversy, i.e. the FDA's proposed relabeling of the drugs (Federal Register, Vol. 40, No. 130, pp 28582–28595), CCD regrets not having been permitted to testify, as its testimony could have availed the Subcommittee of a more balanced view of the issues.

I am enclosing, per your request, a list of CCD members. Kindly include this letter on the record of the proceedings.

Very truly yours,

NEIL L. CHAYET.

Enclosure.

Frank N. Allan, Chairman Emeritus, Medical Department, Lahey Clinic, 44 Barnstable Road, West Newton, Massachusetts 02165.
Seymour Alterman, M.D., 1688 Meridan Avenue, Miami Beach, Florida 33139.
Shepard G. Aronson, M.D., 150 East 56th Street, New York, N. Y. 10022.
James B. Ashmore, M.D., Professor of Pharmacology, Indiana University School of Medicine, Indianapolis, Indiana.
Donald M. Barnard, M.D., Fargo Clinic, Fargo, N.D.
Donald Barnett, M.D., Joslin Clinic, 15 Joslin Road, Boston, Massachusetts 02215.
Samuel B. Beaser, M.D., 31 Bay State Road, Boston, Massachusetts.
Lewis H. Biben, M.D., 618 Medical Science Building, 916 Nineteenth Street, N.W., Washington, D. C. 20006.
Keith Borden, M.D., Chief, Diabetes Products, The Upjohn Company, Kalamazoo, Michigan 49001.
Angela Bowen, M.D., 1015 West 4th Street, Olympia, Washington 98501.
Robert F. Bradley, M.D., Medical Director, Joslin Clinic, 15 Joslin Road, Boston, Massachusetts 02215.

George Brown, M.D., 2021 Grand Concourse, Bronx, New York 10453.
R. A. Camerini-Davalos, M.D., Associate Professor in Medicine, New York Medical College, Flower and Fifth Avenue Hospitals, 1249 Fifth Avenue, New York, New York 10029.
John J. Canary, M.D., Director, Division of Endocrinology and Metabolic Disease, Georgetown University Hospital, 3800 Reservoir Road, N.W., Washington, D. C. 20007.
William Castelli, M.D., Department of Preventive Medicine, Harvard Medical School, Longwood Avenue, Boston, Massachusetts 02115.
David R. Challoner, M.D., Associate Professor, Assistant Chairman, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana.
Mr. Neil Chayet, 461 East 57th Street, New York, N.Y.
John W. Chriss, M.D., Medical Center, 2436 Morgan Street, Corpus Christi, Texas.
A. Richard Christlieb, M.D., Joslin Clinic, 15 Joslin Road, Boston, Massachusetts 02215.
Burton D. Cohen, M.D., Chief, Section of Metabolism, The Bronx Hospital, 1276 Fulton Avenue, Bronx, New York 10456.
Daniel T. Coughlin, Director Government Affairs, The Upjohn Company, Suite 904, 1101 Seventeenth Street, N.W., Washington, D.C., 20036.
DeWitt E. DeLawter, M.D., 500 Prospect Place, Chevy Chase, Maryland.
Harold L. Dobson, M.D., Herman Hospital, Texas Medical Center, 1203 Ross Sterling Avenue, Houston, Texas 77025.
Henry Dolger, M.D., 11 East 86th Street, New York, New York 10028.
Arthur H. Dube, M.D., Associate Professor of Clinical Medicine, Upstate Medical Center, Syracuse, New York.
Sigmund Falk, M.D., Chief, Diabetes Clinic, 15 West 11th Street, New York, New York 10014.
Alvan R. Feinstein, M.D., Professor of Medicine & Epidemiology, Yale University Medical School, New Haven, Connecticut.
Leonard Felder, M.D., 26 Fifth Avenue, New York, New York 10011.
Robert Feldman, M.D., Director of Metabolic Research, Kaiser Permanente Medical Foundation, 280 West McArthur Boulevard, Oakland, California 94611.
Philip W. Felts, M.D., Assistant Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee.
B. Dan Ferguson, M.D., Joslin Clinic, 15 Joslin Road, Boston, Massachusetts 02215.
Peter H. Forsham, M.D., Chief of Endocrinology, Professor, Department of Medicine, University of California Medical Center, San Francisco, California 94122.
Daniel Foster, M.D., Associate Professor of Internal Medicine, University of Texas, Southwestern Medical School, 5323 Harry Hines Blvd., Dallas, Texas 75235.
Adolph Friedman, M.D., 1712 Eye Street, N.W., Washington, D. C. 20006.
Gerald J. Friedman, M.D., 850 Park Avenue, New York, New York.
Richard L. Fulton, M.D., 1211 Dublin Road, Columbus, Ohio.
Edward J. Gallagher, M.D., 10090 Main Street, Fairfax, Virginia.
Edwin W. Gates, M.D., 625 Sixth Street, Niagara Falls, New York 14301.
H. Howard Goldstein, M.D., Joslin Clinic, 15 Joslin Road, Boston, Massachusetts 02215.
George Goodkin, M.D., Senior Associate Medical Director, The Equitable Life Assurance Society of the United States, 1285 Avenue of the Americas, New York, New York 10019.
Irving Graef, M.D., 791 Park Avenue, New York, New York.
Charles A. Graham, M.D., Joslin Clinic, 15 Joslin Road, Boston, Massachusetts 02215.
Robert C. Green, Jr., M.D., 230 W. Boscawen Street, Winchester, Virginia 22601.
Barnett Greenhouse, M.D., 129 Whitney Ave., New Haven, Conn.
Richard D. Grimaldi, M.D., Director of Diabetes, Bellevue Maternity Hospital, P. O. Box 1030, Stop 11 Troy Road, Schenectady, New York 12301.
William B. Hadley, M.D., Joslin Clinic, 15 Joslin Road, Boston, Massachusetts 02215.
Robert R. Hare, M.D., 2250 N. W. Flanders, Portland, Oregon 97207.
Edgar A. Haunz, M.D., Professor and Chairman, Department of Medicine, University of North Dakota, Grand Forks, North Dakota 58201.

Richard D. Hohl, M.D., Associate Physician, Division of Metabolic Diseases, Henry Ford Hospital, 2799 Grand Boulevard W., Detroit, Michigan 48202.
H. Morris Horn, M.D. FACP, Texas Diabetis Assoc., 3434 Swiss Ave., Suite 305, Dallas, Texas 75204.
Jesse D. Ibarra, Jr., M.D., Scott & White Clinic, Temple, Texas 76501.
W. P. U. Jackson, M.D., Dept. of Medicine, University of Medicine, University of Cape Town Observatory, Cape Town, SOUTH AFRICA.
Wyman E. Jacobson, M.D., Section on Endocrinology and Diabetes, St. Louis Park Medical Center, 4959 Excelsior Boulevard, Minneapolis, Minnesota 55416.
George M. Jones, M.D., Past President, Texas Diabetes Assoc., Clinical Professor of Internal Medicine, Southwestern Medical College of the University of Texas, Dallas, Texas.
William R. Jordan, M.D., 1631 Monument Avenue, Richmond, Virginia 23220.
Allen P. Joslin, M.D., Joslin Clinic, 15 Joslin Road, Boston, Massachusetts 02215.
Miles Kahan, M.D., 2405 Avenue P, Brooklyn, New York 11299.
Dorothy Kahkonen, M.D., Associate Physician, Division of Metabolic Diseases, Henry Ford Hospital, 2799 Grand Boulevard W., Detroit, Michigan 48202.
W. B. Kannel, M.D., Framingham Heart Study, 123 Lincoln Street, Framingham, Massachusetts 01701.
Norman M. Kaplan, M.D., Associate Professor of Internal Medicine, University of Texas Southwestern Medical School, 5323 Harry Hines Blvd., Dallas, Texas 73235.
George A. Kaufman, M.D., 888 Grand Concourse, Bronx, New York.
Mr. Terry G. Kelley, Public Relations Associate, The Upjohn Company, Kalamazoo, Michigan 49001.
Mavis P. Kelsey, M.D., Kelsey-Seybold Clinic, 6624 Fannin, Houston, Texas 77025.
M. H. Kolodny, M.D., 1020 Park Avenue, New York, New York.
George P. Kozak, M.D., Joslin Clinic, 15 Joslin Road, Boston, Massachusetts 02215.
Leo P. Krall, M.D., Director of Education, Joslin Diabetes Foundation, 15 Joslin Road, Boston, Massachusetts 02215.
Bernard T. Kravitz, M.D., Montefiore Hospital Medical Group, 3444 Kossuth Avenue, Bronx, New York 10467.
Arthur Krosnick, M.D., Coordinator Diabetes, Endocrine and Metabolic Disease Program, Division of Chronic Illness Control, Department of Health, P.O. Box 1540, John Fitch Plaza, Trenton, New Jersey 08625.
William Kurstin, M.D., 618 Medical Science Building, 916 Nineteenth Street, N.W., Washington, D. C. 20006.
Thomas H. Lambert, M.D., Scripps Clinic and Research Foundation, 476 Prospect Street, La Jolla, California 92037.
Richard L. Landau, M.D., Professor of Medicine, Head of Endocrinology Section, University of Chicago, Chicago, Illinois 60637.
Ira J. Laufer, M.D., 45 Gramercy Park North, New York, New York 10010.
Louis Lasagna, M.D., Department of Medicine, Strong Memorial Hospital, Crittenden Boulevard, Rochester, New York.
Ann M. Lawrence, M.D., Associate Professor of Medicine, Section on Endocrinology, University of Chicago School of Medicine, Chicago, Illinois 60637.
Sydney S. Lazarus, M.D., Chief of Pathology, Isaac Albert Research Institute of the Kingsbrook Jewish Medical Center, Rutland Road and East 49th Street, Brooklyn, New York 11203.
Paul Leifer, M.D., 1860 Grand Concourse, Bronx, New York 10457.
Rachmiel Levine, M.D., Chief, Endocrinoligy Service, City of Hope Medical Center, Duarte, California 91010.
Leon M. Levitt, M.D., 95 Buckingham Road, Brooklyn, New York 11226.
Samuel D. Loube, M.D., Washington Internal Medicine Group, 2400 H Street, N.W., Suite 7, Washington, D.C. 20037.
Glen W. McDonald, M.D., 426 Merkle Drive, Norman, Oklahoma.
Leonard L. Madison, M.D., Professor of Internal Medicine, University of Texas Southwestern Medical School, 5323 Harry Hines Boulevard, Dallas, Texas.
Alexander Marble, M.D., President, Joslin Diabetes Foundation, 15 Joslin Road, Boston, Massachusetts 02215.
Leona Miller, M.D., Associate Professor of Medicine, University of Southern California School of Medicine, Los Angeles, California.
Merton M. Minter, M.D., Minter Clinic, Nix Professiinal Building, San Antonio, Texas 78205.

James M. Moses, M.D., Fairlington Professional Building, 1707 Osage Street Alexandria, Virginia 22302.
Henry J. Oppenheimer, M.D., 141 North Meramec, Clayton, Missouri 63105.
Mr. Harold Rivkin, 510 Plymouth Avenue, Minneapolis, Minnesota.
Morris H. Rosenberg, M.D., Suite 702, University Medical Building, 2141 K Street, N.W., Washington, D.C. 20037.
A. H. Rubenstein, M.D., Associate Professor, Department of Medicine, Section of Endocrinology, University of Chicago, Chicago, Illinois 60637.
John W. Runyan, Jr., M.D., 951 Court Avenue, Memphis, Tennessee 38103.
Elliot L. Sagall, M.D., 454 Brookline Avenue, Boston, Massachusetts 02215.
Aaron G. Saidman, M.D., 5530 Wisconsin Ave., Chevy Chase, Md. 20015.
Dominick J. Savino, M.D., 27 Prospect Park West, Brooklyn, New York 11215.
George F. Schmitt, M.D., 30 Southeast 8th Street, Miami, Florida 33131.
A. Schonfeld, M.D., 50 Central Park South, New York, New York.
Stanley Schor, Ph.D., Temple University Health Services Center, Broad and Ontario, Philadelphia, Pennsylvania 19140.
O. Peter Schumacher, M.D., Cleveland Clinic, 2020 East 93rd Street, Cleveland, Ohio.
Seymour Schutzer, M.D., 67 Cedar Drive, Great Neck, New York 11021.
Zdenko Skrabalo, M.D., University of Zagreb Diabetes Center, Zagreb, Yugoslavia.
J. Stuart Soeldner, M.D., Assistant Professor of Medicine, Harvard University School of Medicine, 170 Pilgrim Street, Boston, Massachusetts 02115.
Maxwell Spring, M.D., Clinical Assistant Professor of Medicine, New York Medical College, 5th Avenue at 106th Street, New York, New York.
John W. Stephens, M.D., 2250 N.W. Flanders, Portland, Oregon 97207.
Daniel B. Stone, M.D., 530 Doctors Bldg., Omaha, Nebraska 68131.
Samuel J. N. Sugar, M.D., 4637 Eastern Avenue, Washington, D. C. 20018.
Karl E. Sussman, M.D., Associate Professor of Medicine, Acting Head, Division of Endocrinology, University of Colorado Medical School, 4200 East Ninth Avenue, Denver, Colorado 80220.
Lawrence J. Thomas, M.D., 11801 Rockville Pike, Rockville, Maryland 20852.
James Tullis, M.D., Chief of Medicine, New England Deaconess Hospital, Boston, Massachusetts.
John B. O'Sullivan, M.D., Chief, Diabetes and Arthritis, Field Research Unit, U. S. Public Health Service, 408 Atlantic Avenue, Boston, Massachusetts 02118.
Karl R. Paley, M.D., Chief, Metabolic Clinic, Lenox Hill Hospital, 77th Street & Park Avenue, New York, New York.
Arthur M. Parker, M.D., 380 East 18th Street, Brooklyn, New York 11226.
Jean O. Partamian, M.D., Associate Physician, Division of Metabolic Diseases, Henry Ford Hospital, 2799 Grand Boulvard W., Detroit, Michigan 48202.
John W. Partridge, M.D., Editor, Diabetes Bulletin, 2222 N.W. Lovejoy Street, Portland, Oregon.
Marjorie Peebles-Meyers, M.D., 3790 Woodward Avenue, Detroit, Michigan 48201.
L. Lewis Pennock, M.D., Forbes-Oakland Medical Building, 3347 Forbes Avenue, Pittsburgh, Pennsylvania 15213.
W. E. Redfern, M.D., Associate Physician, Division of Metabolic Diseases, Henry Ford Hospital, 2799 Grand Boulevard W., Detroit, Michigan 48202.
Robert L. Reeves, M.D., F.A.C.P., 1015 West 4th Street, Olympia, Washington 98501.
Harold Rifkin, M.D., Montefiore Hospital and Medical Center, 1111 East 210th Street, Bronx, New York 10467.
Howard S. Schwartz, M.D., 3201 Grand Concourse, Bronx, New York 10468.
Laurence F. Segar, M.D., 3700 Dean Dr. #1908, Ventura, Calif. 93003.
Donald W. Seldin, M.D., Professor and Chairman Department of Medicine, University of Texas, Southwestern Medical School, 5323 Harry Hines Boulevard, Dallas, Texas 75235.
Holbrooke S. Seltzer, M.D., Chief of Endocrinology, Veterans Administration Hospital, 4500 South Lancaster, Dallas, Texas 75216.
Thomas Sharkey, M.D., 60 Wyoming Street, Dayton, Ohio 45409.
L. Benjamin Sheppard, M.D., 301 Medical Arts Building, Richmond, Virginia.
Charles Shuman, M.D., Temple University Health Services Center, Broad and Ontario, Philadelphia, Pennsylvania 19140.
Abraham A. Silver, M.D., 6210 Park Heights Avenue, Baltimore, Maryland.

Marvin D. Siperstein, M.D., Professor of Internal Medicine, University of Texas, Southwestern Medical School, 5323 Harry Hines Boulevard, Dallas, Texas 75235.
Janet D. Sherman, M.D., 18181 W. 12 Mile Rd., Lathrup Village, Michigan.
Roger H. Unger, M.D., Veterans Administration Hospital, 4500 S. Lancaster Road, Dallas, Texas 75216.
Alexander G. Vongries, M.D., Asst. Director, Clinical Development, Ciba-Geigy Corp., Summit, N.J. 07901.
Robert C. Warner, M.D., Asst. Prof. of Medicine, University of N. Dakota, Fargo, N. Dakota.
Harry F. Wechsler, M.D., 737 Park Avenue, New York, New York.
Irving Weckell, M.D., 7 Pont Street, Great Neck, New York.
Charles Weller, M.D., 17 North Chatsworth Avenue, Larchmont, New York 10538.
George Welsh, M.D., III, Director of Continuing Education for Health Sciences, University of Vermont Medical School, Burlington, Vermont.
Priscilla White, M.D., Joslin Clinic, 15 Joslin Road, Boston, Massachusetts 02215.
Fred W. Whitehouse, M.D., Chief, Division of Metabolic Diseases, Henry Ford Hospital, 2799 Grand Boulevard W., Detroit, Michigan 48202.
David S. Wilcox, M.D., President, Connecticut Diabetes Association, 85 Jefferson Street, Hartford, Connecticut 06109.
T. Franklin Williams, Monroe County Hospital, East Henrietta Road, Rochester, New York.
Charles W. Wilson, M.D., Harbor and Olean Blvd., Port Charlotte, Florida 33950.
Jean D. Wilson, M.D., Professor of Internal Medicine, University of Texas, Southwestern Medical School, 5323 Harry Hines Boulevard, Dallas, Texas 75235.
Albert I. Winegrad, M.D., Director of Cox Institute, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania 19104.
Donna Younger, M.D., Joslin Clinic, 15 Joslin Road, Boston, Massachusetts 02215.
Leonard Zimmerman, Group Service Agency, 342 Madison Avenue, New York, New York 10017.
Akira Horinchi, M.D., 3-33-15 Minimimagome, Otliku, Tokyo, JAPAN.
Bernard Leibel, M.D., 200 St. Clare Street W., Toronto, Ontario, CANADA.
John A. Moorhouse, M.D., Director, Endocrine and Metabolic Laboratory, Winnipeg General Hospital, Winnipeg, CANADA.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

FOOD AND DRUG ADMINISTRATION

[21 CFR PART 310]

[DOCKET NO. 75N-0062]

ORAL HYPOGLYCEMIC DRUGS

NOTICE OF PUBLIC HEARING AND PROPOSED LABELING

The Commissioner of Food and Drugs is proposing labeling for all oral hypoglycemic drugs and announcing a legislative-type public hearing on the issues involved. Labeling for this class of drugs has been the subject of extended public controversy and legal challenge for several years. The Commissioner believes that it is now essential to resolve the outstanding issues in this matter and that it is in the interest of the public health to consider the views of all parties in achieving such resolution. Accordingly, this notice proposes class labeling for oral hypoglycemic drugs that, on the basis of all information available to the Food and Drug Administration, the Commissioner believes is consistent with the requirements of the Federal Food, Drug, and Cosmetic Act and reflects current scientific knowledge on the safety and effectiveness of these drugs.

The Commissioner invites all interested persons to submit written comments on the proposed labeling. In addition, the Commissioner's designee, the Director of the Bureau of Drugs, will conduct an oral

public hearing to afford interested persons a further opportunity for the presentation of data, information, and views. In the Commissioner's judgment, the subject matter of this notice is of sufficient importance to justify the use of this additional procedure, as provided in Part 2, Subpart E, of the regulations governing the administrative practice and procedures of the Food and Drug Administration, published in the FEDERAL REGISTER of May 27, 1975 (40 FR 23025).

Interested persons may submit comments on the labeling proposed in this notice by (insert date 60 days after date of publication in the FEDERAL REGISTER). In addition, any interested person may submit data, information, or views in writing any time within 15 days after the conclusion of the public hearing. It is the intention of the Food and Drug Administration to conduct the public hearing prior to the expiration of the time for submitting comments, and the Commissioner therefore encourages interested persons to submit their comments as soon as possible, to allow review prior to the hearing.

After consideration of all written and oral comments and all data, information, and views presented at the public hearing, the Commissioner will promulgate in the FEDERAL REGISTER a final regulation prescribing labeling for oral hypoglycemic drugs, applicable

to all drug products in this class. It is anticipated that the final labeling will conform with the guidelines for labeling of prescription drugs proposed by the Commissioner on April 7, 1975 (40 FR 15392).

I. GENERAL BACKGROUND

The following new drug applications have been approved for oral hypoglycemic drugs:

1. NDA 10,670, Orinase tablets containing tolbutamide; The Upjohn Co., 7000 Portage Rd., Kalamazoo, MI 49001.

2. NDA 15,500, Tolinase tablets containing tolazamide; The Upjohn Co.

3. NDA 11,641, Diabinese containing chlorpropamide; Pfizer Inc., 235 E. 42d St., New York, NY 10017.

4. NDA 13,378, Dymelor containing acetohexamide; Eli Lilly & Co., Indianapolis, IN 46206.

5. NDA 11,624, DBI tablets containing phenformin hydrochloride; Geigy Pharmaceuticals, Ardsley, NY 10502.

6. NDA 12,752, DBI-TD capsules containing phenformin hydrochloride; Geigy Pharmaceuticals.

7. NDA 17,126, Meltrol-50-100 capsules containing phenformin hydrochloride; USV Pharmaceutical Corp., 1 Scarsdale Rd., Tuckahoe, NY 10707.

8. NDA 17,127, Meltrol-25 tablets containing phenformin hydrochloride; USV Pharmaceutical Corp.

9. NDA 12,678, Tolbutamide tablets containing tolbutamide; Premo Pharmaceuticals Laboratories, Inc., 111 Leuning St., South Hackensack, NJ 07606.

The class of oral hypoglycemic drugs can be grouped into two categories on the basis of chemical structure: the sulfonylurea category (represented by acetohexamide, chlorpropamide, tolazamide, and tolbutamide) and the biguanide category (represented by phenformin hydrochloride). The mode of action and adverse effects are different for these two categories of oral hypoglycemic drugs. Accordingly, separate labeling is proposed for each category of drug.

Under section 505 of the Federal Food, Drug, and Cosmetic Act, the Commissioner is responsible for assuring that all new drugs have been shown to be safe and effective for their intended uses and that their labeling is not false or misleading. Exercise of this responsibility often requires reexamination of the safety, effectiveness, or labeling of drugs previously approved. The statutory scheme contemplates that new information may require the Commissioner to prescribe changes in the labeling of a drug, to reveal newly discovered limitations on use or warn of previously unanticipated hazards. And if labeling can no longer be written to assure that the benefits of use of a drug outweigh the risks of possible harm, the Commissioner is empowered, and obligated, to withdraw marketing approval.

The Commissioner believes that information about potential risks of oral hypoglycemic drugs obtained subsequent to their initial approval for marketing requires revision of their labeling.

Specifically, he believes the study of modes of treatment for adult-onset diabetes conducted by the University Group Diabetes Program requires the addition of a warning about possible cardiovascular complications associated with the use of such drugs. Because of the importance of this matter and the concerns it has generated among physicians and their patients, the Commissioner has concluded that it is appropriate to invite exploration of the issues in a public forum before reaching a final determination on the wording of the labeling, including the warning.

The scientific and legal issues relating to the labeling of oral hypoglycemic drugs have been the subject of protracted public debate. To resolve the many complex questions that have been raised, it is essential that the important issues be identified and that public comment be directed to these issues. The following discussion is presented to summarize the history of the oral hypoglycemic labeling controversy, to identify the issues that have arisen during the controversy, and to explain the position of the Food and Drug Administration on these issues.

II. ORIGIN OF THE LABELING CONTROVERSY

Although insulin and the oral hypoglycemic drugs are both effective in lowering the blood glucose level in patients with maturity-onset diabetes, it is not clear that this reduction of blood glucose has a beneficial effect on the long term vascular complications of diabetes. In an attempt to answer this question, the National Institute of Arthritis,

Metabolism, and Digestive Diseases of the National Institutes of Health sponsored a long term, prospective clinical trial. The study, begun in 1961, was conducted by the University Group Diabetes Program (UGDP) in 12 university medical centers. Patients selected for the study were maturity-onset diabetics who had been diagnosed no more than 1 year prior to entry into the study and did not require insulin to remain symptom-free.

All patients were given an appropriate diabetic diet and were randomly assigned to one of four different treatment groups: (1) Fixed dose of tolbutamide (1.5 grams/day), (2) Fixed dose of insulin (10 to 16 units based on body surface area), (3) Variable dose of insulin adjusted to control the blood glucose, or (4) Placebo. Eighteen months after the study began, a fifth group was added in which the treatment was a fixed dose of phenformin hydrochloride (100 milligrams/day). Patient recruitment was completed in 1966 with a total of 1,027 patients in the entire study and approximately 200 patients per treatment group.

By 1969 the unexpected finding of a significantly higher mortality due to cardiovascular causes was present in the tolbutamide group (12.7 percent or 26 out of 204) compared to the placebo group (4.9 percent or 10 out of 205), the fixed-dose insulin group (6.2 percent or 13 out of 210), and the variable insulin group (5.9 percent or 12 out of 204). After evaluating the available data, the investigators decided to discontinue use of tolbutamide in the study because they concluded that no benefit had been shown for these patients and there was evidence that the long term use of this drug was associated with a serious side effect.

A report on the findings of the UGDP was submitted to the Food and Drug Administration in March 1970. The report concluded that "the findings of this study provide no evidence that the combination of diet and tolbutamide therapy as described and used for mild non-insulin dependent diabetics is more effective than diet alone. Moreover, the findings suggest that tolbutamide and diet may be less effective, at least insofar as cardiovascular mortality is concerned, than diet alone or than diet plus insulin." The Food and Drug Administration reviewed the report and convened an ad hoc meeting of experts on May 21, 1970, to evaluate the findings. The report was scheduled for presentation at the annual meeting of the American Diabetes Association on June 14, 1970. The program and abstracts for the meeting of the American Diabetes Association were disseminated in May, however, and the general findings of the UGDP study became widely publicized in the press. In view of this publicity, FDA released a statement to the press on May 22, 1970, indicating that the agency agreed with the UGDP's stated conclusions and would require labeling changes for the oral hypoglycemic drugs to reflect results of the study.

In October 1970, FDA distributed a Current Drug Information Bulletin to physicians and other health professionals confirming its agreement with the stated conclusions of the UGDP study. The agency recommended that use of sulfonylurea agents be limited to those patients with symptomatic adult-onset, nonketotic diabetes who cannot be adequately controlled by diet or weight loss alone and in whom the addition of insulin is impractical or unacceptable.

The first report of the UGDP study was published in November 1970 as a supplement to Diabetes, the journal of the American Diabetes Association (ref. 1). An accompanying editorial statement representing the view of the American Diabetes Association (ref. 2) made the following therapeutic recommendations:

> The clearest indication for oral agents is diabetes of mild or moderate severity in a patient who proves to be poorly controlled with diet and who is unable or unwilling to take insulin. In adult-onset diabetes with hyperglycemia and glycosuria, symptomatic or not, and in the absence of ketosis, a trial with an appropriate diet should come first. If this does not establish satisfactory control, insulin is to be preferred to other therapeutic agents because it is more uniformly effective in controlling hyperglycemia and the UGDP study indicates that it may be safer.

A statement published at the same time by The American Medical Association Council on Drugs (ref. 3) included the following recommendations:

> Although some flaws exist in the UGDP study, it clearly demonstrates that every effort should be made by the physician to control the symptomatic, maturity-onset diabetic with diet alone. Should this fail, treatment with insulin or oral hypoglycemic agents should be undertaken. If oral hypoglycemic agents are selected for therapy the results of the UGDP study should be kept in mind. Therefore, the consideration of treatment with oral hypoglycemic agents should be secondary to the use of insulin.

In May 1971 the use of phenformin in the UGDP study also was discontinued because there was a significantly higher cardiovascular mortality in the phenformin group (12.7 percent or 26 out of 204) compared to the other treatment groups. The preliminary results with phenformin were published in August 1971 (ref. 4). An additional report by the UGDP published in November 1971 discussed the clinical implications of the UGDP study (ref. 5).

In June 1971 the Food and Drug Administration issued a Drug Bulletin outlining changes in the labeling for all sulfonylurea drugs. The Drug Bulletin stated that diet and reduction of excess weight are the foundation of therapy of diabetes mellitus, and that when the disease is adequately controlled by these measures, no other therapy is indicated.

The Bulletin also stated that the sulfonylurea agents are indicated in the treatment of adult-onset, nonketotic diabetes mellitus which cannot be adequately controlled by diet and reduction of excess weight alone and when, in the judgment of the physician, insulin treatment is not feasible.

From the time the results of the UGDP study were first reported, the study was subjected to intense criticism by both clinicians and statisticians (ref. 6 through 12). The basic scientific criticisms of the study were as follows:

1. Patient selection was inappropriate in that many patients had such mild diabetes that neither oral drugs nor insulin was indicated.

2. Total mortality in the tolbutamide group was not significantly different from that in the placebo group.

3. Excess cardiovascular mortality occurred in only a few clinics.

4. Randomization was not successful; therefore, the tolbutamide group was not comparable to the other groups at the outset of the study with respect to baseline cardiovascular risk factors.

5. With the exception of the variable insulin group, patients were maintained on a fixed drug dosage, contrary to the principles of good medical practice.

6. The use of tolbutamide and phenformin in the study was terminated prematurely, i.e., before definitive results were obtained.

7. The results of the study are contradicted by the studies of Keen (ref. 13 through 15) and of Paasikivi (ref. 16).

These criticisms were in turn analyzed by representatives of the UGDP (ref. 17) and by a statistician who had served as a consultant to the UGDP (ref. 18) and were rejected as a basis for invalidating the conclusions of the UGDP study. By this time, however, a widespread

belief had developed among many physicians that the UGDP study was somehow flawed in terms of its design and execution, and therefore could not serve as a proper basis for a warning to the medical profession.

Uncertainty about the scientific quality of the UGDP study has been a prominent feature of all critical commentary since 1970 and has clearly inhibited acceptance by the medical profession of the study's most troubling finding, namely, that the administration of either tolbutamide or phenformin to patients with maturity-onset diabetes was associated with an increase in cardiovascular mortality. Undoubtedly one reason many practicing physicians were surprised by and reacted critically to the findings of the UGDP study is that the reported increase in cardiovascular mortality--though statistically significant--is not of the magnitude which can be readily detected by the individual physician in the course of practice.

The Commissioner recognizes that a large number of physicians still do not accept the position of the Food and Drug Administration as expressed in the FDA Drug Bulletin, or the position of the American Diabetes Association and the American Medical Association Council on Drugs as expressed in the references cited. An outcome of this disagreement was a prolonged legal confrontation that precluded the inclusion of warnings in the labeling for oral hypoglycemic drugs similar to those appearing in the Drug Bulletin.

III. LEGAL CHALLENGE TO THE LABELING OF ORAL HYPOGLYCEMIC DRUGS

In November 1970 a group of physicians known as the Committee on the Care of the Diabetic was formed to oppose the proposed warning

labeling for oral hypoglycemic drugs. The group included some of the country's leading diabetologists.

In October 1971 the Committee on the Care of the Diabetic petitioned the Commissioner to rescind his position that labeling for oral hypoglycemic drugs must contain a warning of associated cardiovascular hazards. The committee maintained that the UGDP study constituted an improper basis for the agency's decision, because it had been criticized on scientific, clinical, statistical, and other grounds. The Committee on the Care of Diabetes cited "controverting data," particularly the studies of Keen et al. (ref. 13 through 15) and Paasikivi (ref. 16), which, it contended, demonstrated the safety of oral hypoglycemic therapy. The committee also insisted that labeling for these drugs must reflect a "fair balance" of scientific opinion and cite the alleged deficiencies of the UGDP study and the controversial nature of its conclusions as well as the data in controversy.

After thorough evaluation of all the materials submitted to the agency, the Commissioner formally replied to counsel for the Committee on the Care of the Diabetic on June 5, 1972. The Commissioner's letter responded to each of the criticisms raised by the committee concerning the UGDP study and the agency's position. The Commissioner reaffirmed the position of the Food and Drug Administration that an undiluted and unencumbered warning in the labeling of the oral hypoglycemic drugs regarding cardiovascular hazards was fully warranted by the available evidence.

The agency's position on labeling for these drugs was again stated in an FDA Drug Bulletin issued in May 1972. Based on the results for phenformin reported by the UGDP in 1971, the following labeling changes were to apply to the biguanide drugs as well as the sulfonylurea drugs:

> Because of the apparent increased cardiovascular hazard associated with oral hypoglycemic agents, they are indicated in adult-onset, nonketotic diabetes mellitus only when the condition cannot be adequately controlled by diet and reduction of excess weight alone, and when, in the judgment of the physician, insulin cannot be employed because of patient unwillingness, poor adherence to injection regimen, physical disabilities such as poor vision and unsteady hands, insulin allergy, employment requirements, and other similar factors.

On July 13, 1972, counsel for the Committee on the Care of the Diabetic requested a formal evidentiary hearing before the agency. The Commissioner advised the petitioners that they were not entitled to a hearing since their submission did not meet the statutory standard of "substantial evidence" and stated that the Commissioner's letters constituted final agency action.

Soon thereafter suit was filed in the United States District Court for the District of Massachusetts by a group of 178 physicians, many of them members of the Committee on the Care of the Diabetic, asking that the Food and Drug Administration be enjoined from requiring manufacturers to include a warning of associated cardiovascular hazards

in their labeling for oral hypoglycemic drugs (Bradley v. Richardson, Civil No. 72-2517 M (D. Mass. 1972)). A temporary restraining order was entered by the court on the same day. A hearing on the motion for a preliminary injunction was held before Judge Campbell on August 17, 1972, and, on August 30, 1972, he denied an injunction. Judge Campbell concluded that the plaintiffs had not demonstrated a reasonable probability of prevailing on the merits since the administrative action of the Food and Drug Administration, requiring an unencumbered warning, was a reasonable exercise of its statutory duty and the potential harm to users of the drugs was greater than any harm to the manufacturers or prescribers. Judge Campbell further observed that the Food and Drug Administration labeling requirements would not preclude physicians from exercising their best clinical judgment.

The plaintiffs filed another motion for a temporary restraining order and preliminary injuction on October 17, 1972, specifically requesting that the agency be enjoined unless the drug warning was redrafted to incorporate their views concerning the interpretation of the UGDP study. The plaintiffs argued that, without such a discussion, the labeling required by the Food and Drug Administration was misleading because it failed to reveal the existence of divergent opinion among experts, contrary to the agency's own regulation, § 1.3 (21 CFR 1.3). On November 3, 1972, the District Court issued a temporary restraining order, which became a preliminary injunction on November 7, 1972, restraining the agency from implementing the labeling.

On July 31, 1973, the United States Court of Appeals for the First Circuit vacated the District Court's injunction and remanded the case to the Food and Drug Administration for its further determination. In its opinion the Court ruled that the plaintiffs failed to exhaust their administrative remedies regarding the issues presented. The Court expressed its awareness of negotiations between the parties to arrive at a mutually acceptable solution even during litigation, and also expressed its belief that the remand could well produce the most informed and responsible solution possible (483 F.2d 410 (1st. Cir. 1973)).

In its opinion the Court of Appeals also noted apparent inconsistency between the agency's regulation on the disclosure of differences of medical opinion in § 1.3 and the substantial evidence requirements added to the Federal Food, Drug, and Cosmetic Act by the Drug Amendments of 1962. The Court directed the Commissioner to consider § 1.3 as it relates not only to the substantial evidence standard but also to the misbranding requirements of the act. The agency is revising § 1.3, by order published elsewhere in this issue of the FEDERAL REGISTER, to bring the regulation into conformity with these related provisions of the law. As revised, § 1.3 does not permit a statement of differences of opinion in required warnings in the labeling of drugs.

It should be noted that no manufacturer of oral hypoglycemic drugs has initiated proceedings challenging the Commissioner's authority to require changes in the labeling of its products, or attacking the scientific basis for the specific labeling changes that the agency proposed to require.

After the Court of Appeals vacated the preliminary injunction in July 1973, the Food and Drug Administration undertook additional discussions concerning the labeling of the oral hypoglycemic agents with interested individuals and groups. In October 1973, the Director, Bureau of Drugs, and other members of the Food and Drug Administration met with representatives of the Committee on the Care of the Diabetic, the American Medical Association, the American Diabetes Association, the National Institutes of Health, and manufacturers of hypoglycemic drugs to discuss procedures that would facilitate the issuance of appropriate labeling. Based upon the discussion and input from the agency's staff, proposed labeling revisions were circulated for comments in February 1974 to those who attended the meeting and to other interested persons. Addressees were also invited to meet with agency officials, if desired, to discuss the labeling. Four such meetings were held between March 21 and April 24, 1974. The minutes of these meetings have been placed on public display in the office of the Hearing Clerk.

The responses to the proposed labeling, including comments received at these meetings, revealed continuing major differences of opinion over the scientific validity of the UGDP study and over the asserted need for "fair balance" and the acknowledgment of "controversy" in the proposed warning. In addition, the Food and Drug Administration was advised that a major outside review, described below, of the UGDP study by a committee of the Biometrics Society was near completion.

The agency therefore decided to postpone implementation of the warning until this review was published. Since the UGDP study was the basis for the proposed warning, the Commissioner believed that this independent review of the statistical validity of the study should be available to all interested persons before taking definitive action. The review by the committee of the Biometrics Society required extensive reanalysis of the data in the UGDP study and was not published until February 10, 1975 (ref. 19). A more detailed report of the UGDP on phenformin was also published recently (ref. 20).

The Commissioner believes that sufficient time has passed to have permitted all interested persons to study these reports. Since no major new information in regard to the UGDP study is anticipated, the Commissioner believes it is now essential to effect all labeling changes that are appropriate and necessary on the basis of the UGDP study.

On June 11, 1975, and June 18, 1975, representatives of the Food and Drug Administration met with representatives of the Committee on the Care of the Diabetic to discuss late drafts of the Indications and

Warnings sections of the labeling proposed in this notice. The representatives of the Committee on the Care of the Diabetic included one of the plaintiffs in Bradley v. Weinberger and the plaintiffs' attorney. The purpose of these meetings was to engage in good faith negotiation in an attempt to resolve outstanding issues in conformity with the intent of the Court of Appeals. Memoranda of these meetings and of subsequent phone calls and drafts of labeling discussed at the meetings are on file in the office of the Hearing Clerk.

IV. REVIEW OF BIOSTATISTICAL ISSUES BY THE COMMITTEE OF THE BIOMETRICS SOCIETY

The UGDP study was subjected to intense adverse criticism (ref. 6 through 12) largely on the basis of its design and the statistical analysis of the results. For this reason, the National Institute of Arthritis, Metabolism, and Digestive Diseases, which financed the UGDP study, sought an independent review of the study. In 1972 a contract was awarded to the Biometrics Society, an international organization of biostatisticians, to make an in-depth assessment of the scientific quality of the UGDP study, particularly the biometric aspects of the design, conduct, and analysis of the trial, and a similar assessment of other controlled trials involving oral hypoglycemic agents. A committee of six members was selected to undertake this task. The committee visited the UGDP coordinating center and two of the clinical centers to study methods used in the trial, reviewed

published criticisms of the UGDP study in detail, interviewed both critics and supporters of the study, and made new analyses from the original data.

On the basis of this in-depth review, the Biometrics Society committee commented as follows on the major criticisms of the UGDP study:

1. The criticism that patient selection was inappropriate was considered to be "largely irrelevant to the primary issue raised by the critics," viz., the validity of the evidence pointing to excess mortality in the tolbutamide- and phenformin-treated groups. The committee argued that even "if it could be shown that the study group contained some non-diabetics* * * [a] drug found toxic in such subjects would not likely be counted safe for persons with well documented mild diabetes either."

2. Wih respect to the criticism that total mortality in the tolbutamide group was not significantly different from that in the placebo group, the committee concluded that this criticism "has some weight (although we do not interpret it as a criticism of the action of the UGDP) and that the toxic effect of the oral hypoglycemics cannot be affirmed with the certainty that would be present if total mortality were significantly different."

3. In response to the criticism that excess mortality occurred in only a few clinics, the committee presented calculations of the data to take account of the number of patients treated in each clinic and the duration of their treatment and concluded that "the excess mortality

is not in fact confined to a few clinics and that this particular criticism should not be taken to detract from the interpretation of the UGDP findings."

4. The contention that randomization was not successful was studied in detail by the committee which identified "a puzzling anomaly concerning the distribution of the two sexes to the four treatment groups within clinics." The committee reviewed the randomization procedure in detail and examined the log books containing records of the allocation of each patient. The committee's report reads: "We were not able to find an assignable cause for the surprising allocation of the sexes to treatments but have no reason to think that the study has been compromised by a breakdown in the randomization of patients to the treatment groups. Because of the imbalance of sexes in the treatment groups in some clinics, however, allowance for this has been made in our analysis." The committee went on to analyze the data by several different statistical approaches, including those used originally by the UGDP investigation. The committee concluded: "Our findings* * * take into account the differences between centers and the differences in length of treatment, as well as the baseline variables. They support the view of Cornfield [ref. 18] that there is no evidence that the baseline differences arising from the randomization contributed in any important way to the finding of adverse effect from tolbutamide."

5. The criticism that the oral hypoglycemic drugs were given in fixed dosage was rejected by the committee, with respect to conclusions regarding toxicity, as follows: "It is true that the use of a fixed dose of drug, which was also the approach adopted by Feldman et al. [ref. 21] and Keen and Jarrett [ref. 14], limits the generalization about therapeutic effects, but since the dose of tolbutamide is about equal to the average recommended for therapeutic use, an evaluation of its possible toxic effect is highly relevant."

6. Concerning the criticism that the use of tolbutamide and phenformin was terminated prematurely, the committee acknowledged that "It would have been easier to interpret the findings if there were more data on mortality." The committee also recognized, however, the ethical issues raised by continuing these drugs in the study and concluded: "We do not criticize the UGDP investigators for having made the decision when they did. Nevertheless, the result of that decision is to leave us with some residual uncertainty about the meaning of the findings, a point that is well understood by the UGDP investigators themselves."

7. In considering the criticism that the results of the UGDP study are contradicted by the studies of Keen (ref. 13 through 15) and of Paasikivi (ref. 16), the committee analyzed these studies in detail. With respect to the data of Keen and his colleagues, they concluded that, in their ongoing prospective study, neither cardiovascular mortality nor total mortality in the tolbutamide group is significantly different from

that in the placebo group. Because of imperfections in the randomization process and in the maintenance of blinding, and because of the preliminary nature of the data obtained to date, the committee concluded that "the provisional data that Dr. Keen has kindly sent us* * * do not throw doubt on the UGDP findings in regard to deaths from cardiovascular causes." In regard to the Paasikivi study, which appeared to show a beneficial effect of tolbutamide on mortality in the first year in patients who survived a first myocardial infarction, the committee concluded: "This study neither confirms nor contradicts the UGDP findings, as the population under consideration was not one of maturity-onset diabetics, and the patients taking tolbutamide had been exposed to a relatively small dose for a shorter time than that applied in the UGDP study." The studies of Feldman et al. (ref. 21) and of Tzagournis and Reynertson (ref. 22) were also briefly reviewed by the committee. Their conclusion was that in neither study has a sufficient number of deaths yet occurred to permit meaningful interpretation of results.

In addition to evaluating these criticisms of the UGDP study, the Biometrics Society committee conducted extensive new analyses of the UGDP data, taking into account the effect of various baseline variables and cardiovascular risk factors. These analyses confirmed that cardiovascular mortality was increased in the tolbutamide group. This increase was statistically significant in females, especially in women over the age of 53, but not in males. An important finding was that the highest death rate occurred in the group of patients who adhered most closely to the tolbutamide regimen and did not have their dose modified. Also when

the analysis was conducted according to an approach called the survival modeling method, which takes into account the proportion of time each patient received the assigned medication, women in the tolbutamide group had a statistically significant increase in both cardiovascular and total mortality. This does not mean that the study necessarily showed the drug to carry less risk in males. On this point the committee concluded: "The data do not support the same conclusions for men, but one possible reason is that the smaller number of patients in the male group results in lack of sensitivity to detect differences of moderate magnitude."

In the final section of its report, the Biometrics Society committee summarized its conclusions:

> 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* * *

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 criticism 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 reservations about the conclusion that the oral hyperglycemics [sic] are toxic must remain. Nonetheless, we consider the evidence of harmfulness moderately strong. The risk is clearly seen in the group of older women* * * 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* * *

> 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.

V. RECENT ADDITIONAL INFORMATION ON SAFETY OF ORAL HYPOGLYCEMIC DRUGS

The more detailed report on the results of the phenformin study was published recently by the UGDP (ref. 20). In addition to the higher mortality from all causes and from cardiovascular causes observed in the phenformin-treated group compared to the other treatment groups, evidence was presented that phenformin therapy resulted in increased blood pressure levels and heart rate, thus suggesting possible mechanisms by which this drug might influence cardiovascular mortality.

Recently, additional reports relating to the safety of oral hypoglycemic drugs have appeared:

1. At hearings before the Subcommittee on Monopoly of the Select Committee on Small Business, U.S. Senate, on January 31, 1975, Dr. P. J. Palumbo reported that a retrospective study of diabetic patients treated at the Mayo Clinic suggests that survival was lower in those patients treated with oral hypoglycemic agents, compared to those patients treated with insulin. The full study has not yet been published.

2. A retrospective study of diabetic patients treated at the Joslin Clinic, reported in a doctoral thesis (ref. 23), can be interpreted as providing results that are consistent with those of the UGDP. This study has not yet appeared in the medical literature.

3. A positive inotropic effect, i.e., increased force of muscular contraction, of sulfonylurea agents on the heart muscle has been demonstrated (ref. 24 and 25). The increased oxygen requirement resulting from such an effect could have a deleterious effect in patients with coronary artery disease. Limited animal studies also suggest that the sulfonylurea agents may affect the excitability of heart muscle (ref. 25), which could predispose the heart to develop abnormal rhythms, particularly in the presence of a decreased oxygen supply.

4. Results from a study on the chronic effects of tolbutamide in the rhesus monkey by R. W. Wissler et al. (FDA contract 72-114) indicate there is an increased frequency and severity of atherosclerotic lesions in the coronary arteries of the tolbutamide-fed monkeys compared to the control monkeys (ref. 26). The final report of this study is under review.

While neither of the two epidemiological studies is a prospective clinical trial such as the UGDP study, the preliminary reports indicate that further information casting doubt on the safety of the oral hypoglycemic drugs may be forthcoming. And, although the animal findings cannot be considered necessarily relevant to the issue of excess cardiovascular mortality in diabetic patients, they indicate that sulfonylureas may have potentially adverse effects on the cardiovascular system of certain animals which can be detected by appropriate pharmacological and toxicological tests.

In addition to these reports, two critiques of the Biometrics Society committee report have recently been published (ref. 27 and 28).

VI. DISCUSSION OF PROPOSED LABELING FOR ORAL HYPOGLYCEMIC DRUGS

The judgment of the Commissioner that changes must be made in the labeling of the oral hypoglycemic drugs to reflect the findings of the UGDP study is well known from previously published statements. The Commissioner is therefore proposing labeling in this notice for public comment and scheduling a public hearing to receive additional data, information, and views. After consideration of all materials submitted, the Commissioner will publish final labeling for oral hypoglycemic drugs in the FEDERAL REGISTER.

The warning proposed in this labeling for oral hypoglycemic drugs is based primarily on a thorough review and evaluation of the UGDP study. In proposing the overall labeling, the Commissioner has also carefully considered:

1. Published reviews, criticisms, and rejoinders to criticisms of the UGDP study.

2. Other scientific and clinical investigations of the oral hypoglycemic agents.

3. The advice of experts.

4. Comments submitted to the agency by interested persons.

The Commissioner reaffirms his conclusion that the UGDP study is an adequate and well-controlled clinical trial, which is the most extensive and detailed examination of long term administration of hypoglycemic agents yet undertaken. Although the study has shortcomings, which might be expected in any clinical trial of this complexity,

the shortcomings do not invalidate the central finding that there appears to be an increased risk of cardiovascular mortality associated with the administration of tolbutamide and of phenformin to maturity-onset diabetic patients, compared to treatment with diet alone or diet plus insulin. This conclusion has in the past been reached independently by the UGDP investigators, the FDA, and the Biometrics Society committee, and is again affirmed by the Commissioner. Other clinical trials of these oral hypoglycemic drugs are not comparable to the UGDP study and provide insufficient evidence to negate the findings of the UGDP study.

Accordingly, although comments concerning the validity of the UGDP study and its conclusion will be accepted, comments on this issue that contribute no new information and only reiterate published criticisms, which have already been extensively reviewed by the Food and Drug Administration, are not considered useful at this time.

The Commissioner proposes that a boxed warning concerning the possible increased risk of cardiovascular mortality be included in the labeling for these drugs. This warning is based on the findings of the UGDP study. The Commissioner emphasizes that the requirement for such a warning does not depend upon an absolute certainty that the findings of the UGDP study are correct. Prudence dictates that

a warning be issued whenever there is sufficient evidence from controlled or uncontrolled studies to believe that a drug may be hazardous or carry a risk and that such warning is necessary for safe and effective use of the drug by physicians and patients. The Federal Food, Drug, and Cosmetic Act provides no standard for the amount or character of scientific evidence required for the issuance of a warning. The decision to require a warning is a matter of judgment which must be made in light of both the available scientific evidence and the opinion of experts who interpret that evidence. The Commissioner believes that the UGDP study is a validly conducted trial and accepts the opinion of the Biometric Society committee and other experts that the increased cardiovascular mortality found in this trial to be associated with these drugs cannot reasonably be attributed to scientific shortcomings in the study. Under those circumstances, a clear warning is necessary even though a residual uncertainty over the correctness of the study may be present. Warnings may properly be required on the basis of evidence that falls short of conclusive proof.

In conformity with Food and Drug Administration policy that warnings must be presented in unambiguous terms without disclaimers or qualifications that would undermine or destroy their usefulness, there is no mention in the proposed warning of other studies involving the oral hypoglycemic drugs. The mention of studies in which increased cardiovascular mortality was not found would serve only to encumber the warning and would therefore not be consistent with revised § 1.3. Comments concerning the principle of

an unencumbered warning, which have been received and considered in conjunction with the proposed revision of § 1.3 published in the FEDERAL REGISTER of September 16, 1974 (39 FR 33229), are addressed in the final regulation published elsewhere in this issue of the FEDERAL REGISTER.

The proposed warning does, however, contain a statement acknowledging the controversy that exists over the interpretation of the UGDP study and states that, in spite of this, the UGDP findings provide adequate scientific basis for a warning. The purpose of this statement is to emphasize clearly the basis for the warning. Comments on specific wording in the proposed warning are invited by this notice. The Commissioner advises, however, that he does not intend to reopen consideration of the principle of an unencumbered warning which is embodied in the final regulation relating to § 1.3.

The Commissioner concludes that, from the standpoint of patient safety, it is prudent to apply the possible increased risk of cardiovascular mortality for tolbutamide and phenformin to other sulfonylurea and biguanide drugs in view of the similarities in chemical structure and mode of action for members within each of these two categories. This position was endorsed by the Endocrinology and Metabolism Advisory Committee of the FDA at its meeting on June 28, 1971, but additional comment at this time would also be appropriate.

The Commissioner also concludes that a patient population exists for which these drugs, properly labeled, can be considered as safe and effective. Marketing therefore may continue. The Commissioner is proposing, however, that this patient population be limited to patients with maturity-onset diabetes whose symptoms or blood glucose level cannot be controlled by diet alone and who cannot take insulin for one or more of the reasons identified in the labeling. This restriction in labeling has been opposed in the past on the ground that it interfered with the practice of medicine. The Commissioner recognizes that drug labeling impacts on the practice of medicine. For this reason the Food and Drug Administration has an obligation to ensure that drug labeling is as correct and accurate as possible and meets the statutory standard of describing the conditions of use under which the drug may be considered safe and effective. Those limitations on use that properly derive from a known hazard or potential risk must, in the interest of safety, be included in drug labeling. This principle is stated in the proposed regulations on prescription drug labeling (published in the FEDERAL REGISTER of April 7, 1975 (40 FR 15392)), time for comment on which has been extended to August 6, 1975, by notice published in the FEDERAL REGISTER of June 11, 1975 (40 FR 24909).

The Commissioner proposes the appended labeling for oral hypoglycemic agents of the sulfonylurea and biguanide categories as labeling providing the essential information for the safe and effective use of these drugs. Comments addressed to any portion of the labeling will be considered.

REFERENCES

Copies of all references cited below are on public display in the office of the Hearing Clerk, Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, MD 20852:

1. The University Group Diabetes Program, "A Study of the Effects of Hypoglycemic Agents on Vascular Complications in Patients with Adult-Onset Diabetes. I. Design, Methods and Baseline Results. II. Mortality Results," Diabetes, 19 (supp. 2):747-830, 1970.

2. Ricketts, H. T., "Editorial Statement," Diabetes, 19 (supp. 2): iii-v, 1970.

3. AMA Council on Drugs, "Statement Regarding the University Group Diabetes Program (UGDP) Study," Diabetes, 19 (supp. 2):vi-vii, 1970.

4. The University Group Diabetes Program, "Effects of Hypoglycemic Agents on Vascular Complications in Patients with Adult-Onset Diabetes. IV. A Preliminary Report on Phenformin Results," Journal of the American Medical Association, 217:777-784, 1971.

5. The University Group Diabetes Program, "Effects of Hypoglycemic Agents on Vascular Complications in Patients with Adult-Onset Diabetes. III. Clinical Implications of UGDP Results," Journal of the American Medical Association, 218:1400-1410, 1971.

6. Reeves, R. L., "Erroneous Interpretation of Data" (correspondence), Northwest Medicine, 69:470, 1970.

7. Hare, R. L., "Therapeutics--by Headline and Edict," Northwest Medicine, 70:118-119, 1971.

8. Feinstein, A. R., "Clinical Biostatistics. VIII. An Analytic Appraisal of the University Group Diabetes Program (UGDP) Study," Clinical Pharmacology and Therapeutics, 12:167-191, 1971.

9. Schor, S., "The University Group Diabetes Program. A Statistician Looks at the Mortality Results," Journal of the American Medical Association, 217:1671-1675, 1971.

10. Seltzer, H. D., "Tolbutamide Mortality in the Six Phenformin Clinics," (letter to the editor), Journal of the American Medical Association, 218:594, 1971.

11. Brandman, O., "University Group Diabetes Program and the Practicing Physician," Journal of the Medical Society of New Jersey, 68:909-911, 1971.

12. Seltzer, H. S., "A Summary of Criticisms of the Findings and Conclusions of the University Group Diabetes Program (UGDP)," Diabetes, 21:976-979, 1972.

13. Keen, H., R. J. Jarrett, C. Chlouverakis, and D. R. Boyns, "The Effect of Treatment of Moderate Hyperglycemia on the Incidence of Arterial Disease," Postgraduate Medical Journal, 44:960-965, 1968.

14. Keen, H., and R. J. Jarrett, "The Effect of Carbohydrate Tolerance on Plasma Lipids and Atherosclerosis in Man," in Atherosclerosis, R. J. Jones, editor, Berlin, Springer-Verlag, 1970, pp. 435-444.

15. Keen, H., "Factors Influencing the Progress of Atherosclerosis in the Diabetic," Acta Diabetologica Latina, 8 (supp. 1):444-456, 1971.

16. Paasikivi, J., "Long-Term Tolbutamide Treatment after Myocardial Infarction. A Clinical Biochemical Study of 178 Patients Without Overt Diabetes," Acta Medica Scandinavica, Supplement, 507:3-82, 1970.

17. Prout, T. E., G. L. Knatterud, C. L. Meinert and C. R. Klimt, "The UGDP Controversy. Clinical Trials Versus Clinical Impressions," Diabetes, 21:1035-1040, 1972.

18. Cornfield, J., "The University Group Diabetes Program. A Further Statistical Analysis of the Mortality Findings," Journal of the American Medical Association, 217:1676-1687, 1971.

19. "Report of the Committee for the Assessment of Biometric Aspects of Controlled Trials of Hypoglycemic Agents," Journal of the American Medical Association, 231:583-608, 1975.

20. The University Group Diabetes Program, "A Study of the Effects of Hypoglycemic Agents on Vascular Complications in Patients with Adult-Onset Diabetes. V. Evaluation of Phenformin Therapy," Diabetes, 24 (supp. 1):65-184, 1975.

21. Feldman, R., D. Crawford, R. Elashoff, and A. Glass, "Progress Report on the Prophylactic Use of Oral Hypoglycemic Drugs in Asymptomatic Diabetes: Neurovascular Studies," Advances in Metabolic Disorders, 2 (supp. 2):557-567, 1973.

22. Tzagournis, M., and R. Reynertson, "Mortality from Coronary Heart Disease During Phenformin Therapy," Annals of Internal Medicine, 76:587-592, 1972.

23. Kanarek, P. H., "Assessing Survival in a Diabetic Population," thesis, Harvard School of Public Health, Boston, January 1973.

24. Lasseter, K. C., G. S. Levey, R. F. Palmer and J. S. McCarthy, "The Effect of Sulfonylurea Drugs on Rabbit Myocardial Contractibility, Canine Purkinje Fiber Automaticity, and Adenyl Cyclose Activity from Rabbit and Human Hearts," The Journal of Clinical Investigation, 51:2429-2434, 1972.

25. Levey, G. S., K. C. Lasseter, and R. F. Palmer, "Sulfonylureas and the Heart," Annual Review of Medicine, 25:69-74, 1974.

26. Wissler, R. W., J. Borensztajn, G. S. Godfrey, G. Seymour, A. Rubenstein, C. H. Ts'ao, "A Study of the Chronic Effects of Tolbutamide in the Rhesus Monkey," FDA contract 72-114, February 15, 1975.

27. Bradley, R. F., H. Dolger, P. H. Forsham, and H. Seltzer, "Settling the UGDP Controversy?", Journal of the American Medical Association, 232:813-817, 1975.

28. O'Sullivan, J. B. and R. B. D'Agostino, "Decisive Factors in the Tolbutamide Controversy," Journal of the American Medical Association, 232:825-829, 1975.

VII. NOTICE OF PUBLIC HEARING

The Commissioner concludes that, to permit maximum public participation in the development of labeling requirements for oral hypoglycemic drug products, a public hearing shall be held to provide an opportunity for interested persons to present data, information, and views on the proposed labeling. This public hearing is ordered pursuant to § 2.400(a) (21 CFR 2.400(a)) and shall be conducted in accordance with the procedures established in Subpart E of Part 2 of the regulations. The Commissioner has designated J. Richard Crout, M.D., Director, Bureau of Drugs, to be the presiding officer at such hearing, to be held August 20, 1975, beginning at 9 a.m. in Conference Rm. E, Parklawn Bldg., 5600 Fishers Lane, Rockville, MD 20852.

Interested persons who wish to make an oral presentation at the hearing shall file a written notice of appearance with the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852 by close of business August 6, 1975. The

notice of appearance shall state the approximate amount of time requested by the person for presentation. It shall also give the telephone number of the person to be contacted regarding the schedule for presentation. Individuals and organizations with common interests are strongly urged to consolidate or coordinate their presentations because of the limitations of time.

By August 11, 1975, the Food and Drug Administration will communicate by telephone with each person who requested an opportunity to be heard, regarding the time his or her oral presentation is scheduled to begin and the amount of time allocated for his or her presentation. The Food and Drug Administration may require joint presentations by persons sharing common views. The Food and Drug Administration will prepare a hearing schedule, listing the participants and the time allotted to each, which shall be filed with the Hearing Clerk and a copy mailed to each participant.

The hearing will be transcribed. Any interested person may, consistent with the orderly conduct of the meeting, also record or otherwise make his or her own transcript of the meeting. Each participant may use the allotted time however he or she desires, consistent with decorum and order, and may present written data, information or views for inclusion in the record of the hearing. Any person who desires to submit an advance written statement may do so in quintuplicate to the Hearing Clerk. All written comments and statements submitted before

August 15, 1975, will be reviewed by the presiding officer prior to the hearing, so that full repetition at the hearing will be unnecessary. A participant may be accompanied by any number of additional persons.

If a participant is not present when his or her presentation is scheduled to begin, the participants following will be taken in order. An attempt will be made to hear any scheduled participant who misses his assigned time at the conclusion of the hearing. Other interested persons attending the hearing who did not request an opportunity to speak will be given an opportunity to make oral presentations at the conclusion of the hearing to the extent that time permits.

The presiding officer, as well as any other Food and Drug Administration employee serving with him as a panel, may question any participant during or at the conclusion of his presentation. No other persons attending the hearing may question a participant. The presiding officer may allot additional time to any participant if he concludes that it is in the public interest, but may not reduce the time allotted to anyone.

The record of the hearing will remain open until September 5, 1975, for the submission of any additional written statements or comments regarding oral presentations made at the hearing.

No written submission, or any portion thereof, made in response to this notice shall be received or held in confidence. The administrative record of this rule making proceeding shall consist of all relevant FEDERAL REGISTER notices and the documents to which they refer, all

written submissions made in response to this notice, and the transcript of the oral hearing made by the Food and Drug Administration. The administrative record of the proceeding shall be made available for public examination.

VIII. PROPOSED REGULATION FOR THE LABELING OF ORAL HYPOGLYCEMIC DRUGS

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 701(a), 52 Stat. 1050-1053, as amended, 1055 (21 U.S.C. 352, 355, 371(a))) and under authority delegated to him (21 CFR 2.120), the Commissioner proposes that Part 310 of Subchapter D of Title 21 of the Code of Federal Regulations be amended by adding a new § 310.510 as follows:

§ 310.510 Labeling for oral hypoglycemic drugs.

(a) An adequate and well-controlled clinical trial (the University Group Diabetes Program study) has indicated that there appears to be an increased risk of cardiovascular mortality associated with the administration of tolbutamide and of phenformin (oral hypoglycemic drugs of the sulfonylurea and biguanide categories, respectively) to maturity-onset diabetic patients as compared to treatment with diet alone or diet plus insulin. The Commissioner concludes that in view of the great similarities in chemical structure and mode of action for drugs within each of these two categories, it is prudent from a safety standpoint to consider that the possible increased

risk of cardiovascular mortality for tolbutamide and phenformin also applies to other sulfonylurea and biguanide drugs. Therefore, the labeling for oral hypoglycemic drugs shall describe properly the conditions for their use and include a warning concerning the possible increased risk of cardiovascular mortality associated with such use, as set forth in paragraphs (b) and (c) of this section.

(b) Labeling for oral hypoglycemic drugs of the sulfonylurea category shall be as follows:

DESCRIPTION

(Trade name, established name) is an oral blood-glucose-lowering drug of the sulfonylurea category. It is a white, crystalline compound, formulated as a tablet for oral administration. (Manufacturer to add structural formula and other appropriate information.)

ACTIONS

Administration of (drug) appears to lower the blood glucose initially by stimulating the release of insulin from the pancreas; the effect is thus dependent on functioning beta cells in the pancreatic islets. The mechanism by which (drug) lowers blood glucose during long term administration has not been clearly established. Many patients who at first demonstrate an adequate glucose-lowering effect with a sulfonylurea

agent subsequently prove to be no longer satisfactorily responsive, i.e., secondary failure may occur.

(Manufacturer to supply information about:

1. Absorption.

2. Metabolism and excretion.

3. Plasma half-life and the effect of hepatic or renal impairment on blood levels, metabolism, and excretion.

4. Peak and duration of glucose-lowering effect, indicating the duration of effect relative to the class of sulfonylurea agents, e.g., shortest acting, longest acting, etc.

5. Mechanism of drug interaction with agents that impair or potentiate drug effect.)

INDICATIONS

(Drug) is indicated to control symptoms due to hyperglycemia in patients with maturity-onset nonketotic diabetes mellitus whose symptoms cannot be controlled by diet alone and in whom insulin cannot be used because of patient unwillingness, erratic adherence to the injection regimen, poor vision, physical or mental handicap, insulin allergy, employment requirements, or other similar factors.

(Drug) may also be used to lower blood glucose in asymptomatic patients whose blood glucose elevation cannot be controlled by diet alone and in whom insulin cannot be used for any of the above reasons. In considering the use of (drug) in asymptomatic patients, it should be recognized that whether or not controlling the blood glucose is effective in preventing the long term cardiovascular or neural complications of diabetes is an unanswered scientific question.

The use of (drug) may be associated with an increased risk of cardiovascular mortality as compared to diet alone or diet plus insulin; see WARNINGS. For this reason, it should be used only

when the advantages in the individual patient justify the potential risk. The patient should be informed of the advantages and potential risks of (drug) and of alternative modes of therapy and should participate in the decision to use this drug.

The foundation of therapy in the obese maturity-onset diabetic is caloric restriction and weight loss. Proper dietary management alone is often effective in controlling the blood glucose and eliminating symptoms of polydipsia and polyuria. Use of (drug) must be considered by both the physician and patient as a treatment in addition to diet and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint.

Many patients who are initially responsive to oral hypoglycemic drugs become unresponsive or poorly responsive over a period of time, usually 1 to 5 years. (Drug) should be given only to patients demonstrated to be responsive to it; see DOSAGE AND ADMINISTRATION for discussion of secondary failure. Short term

administration of (drug) may be sufficient during periods of transient loss of control.

Concomitant Therapy with a Biguanide:

(Drug) may be used in conjunction with phenformin to control symptoms due to hyperglycemia in patients with maturity-onset nonketotic diabetes mellitus whose symptoms cannot be controlled by diet and maximum recommended doses of either drug alone and in whom insulin cannot be used for any of the reasons cited above.

In considering the use of concomitant therapy, it should be noted that both a sulfonylurea drug (tolbutamide) and a biguanide drug (phenformin) have been reported to be associated with increased cardiovascular mortality; see WARNINGS. In addition, phenformin can

produce lethal lactic acidosis in some patients. Thus the use of (drug) in association with phenformin carries a greater risk than the use of (drug) alone.

If a judgment is made that (drug) and phenformin are to be used together in a particular patient, it should be established that the patient is responsive to both drugs. This may be accomplished either by a trial of each drug separately or by adding the second drug and then tapering the dosage of the first, observing for diminished control of blood glucose. Once the need for both drugs is established, the desired control of blood sugar may be obtained by adjusting the dose of either drug. The possibility of hypoglycemia should be anticipated and appropriate precautions taken. See package insert for phenformin hydrochloride for CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.

CONTRAINDICATIONS

(Drug) is contraindicated in patients with:

1. Known hypersensitivity or allergy to the drug.

2. Diabetic ketoacidosis, with or without coma. Such patients should be treated with insulin.

WARNINGS

SPECIAL WARNINGS ON CARDIOVASCULAR MORTALITY

(This subsection of labeling to be boxed, set in boldface type, and placed at the beginning of WARNINGS section of labeling.)

The administration of oral hypoglycemic drugs may 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 maturity-onset nonketotic diabetes. The study involved 1,027 patients who were randomly assigned to one of five treatment groups (Diabetes, 19 (supp. 2): 747-830, 1970; Diabetes, 24 (supp. 1):65-184, 1975).

The UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) or diet plus a fixed dose of phenformin (100 milligrams per day) had a rate of cardiovascular mortality approximately twice that of patients treated with diet alone or diet plus insulin. Total mortality was increased in both the tolbutamide- and phenformin-treated groups, but this increase was statistically significant only for phenformin. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide adequate scientific basis for this warning.

Although only one drug in the sulfonylurea category (tolbutamide) and one in the biguanide category (phenformin) were included in this study, it is prudent from a safety standpoint to consider that this result may also apply to other oral hypoglycemic drugs in these categories, in view of the close similarities in mode of action and chemical structure among the drugs in each category.

(Drug) should be used in preference to insulin only in patients with maturity-onset diabetes whose symptoms or blood glucose level cannot be controlled by diet alone and only when the advantages in the individual patient justify the potential risk; see INDICATIONS. The patient should be informed of the advantages and potential risks of (drug) and of alternative modes of therapy and should participate in the decision to use this drug.

(Drug) is not effective in patients with juvenile diabetes or insulin-dependent diabetes at any age. Such patients should be treated with insulin. The concomitant long term use of insulin and (drug) in an individual patient is, in view of the potential risk of increased cardiovascular mortality with (drug), less safe on a benefit-risk basis than the use of insulin alone.

The effectiveness of any oral hypoglycemic drug, including (drug), in lowering blood glucose to a desired level decreases in a large number of patients as the drug is administered over a period of months or years, in part because the patient's blood glucose tends to rise over time and in part because of diminished responsiveness to the drug. This phenomenon is known as secondary failure to distinguish it from primary failure in which the drug is ineffective in an individual patient at the time of its initial administration. See DOSAGE AND ADMINISTRATION.

Renal or hepatic insufficiency may cause elevated blood levels of (drug) and increase the risk of serious hypoglycemic reactions.

Pregnancy: (Data and interpretation related to reproduction and teratology studies to be supplied by manufacturer).

Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. Neonatal hypoglycemia has been reported more frequently following use of the longer-acting agents. If (drug)

is used during pregnancy, it should be discontinued (time period to be supplied by manufacturer) before the expected delivery date.

PRECAUTIONS

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Particularly susceptible are elderly patients, patients with impaired hepatic or renal function, patients who are debilitated or malnourished, and patients with adrenal or pituitary insufficiency. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, or when more than one glucose-lowering drug is used.

(To be inserted for chlorpropamide only:) Because of the long half-life of chlorpropamide, patients who become hypoglycemic during therapy require careful supervision of the dose for at least 3 to 5 days, during which time frequent feedings are essential. It may be necessary to hospitalize such patients and give intravenous glucose.

Certain drugs may potentiate the hypoglycemic action of (drug), including phenylbutazone, oxyphenbutazone, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. See ACTIONS.

When such drugs are administered to a patient receiving (drug), the patient should be observed closely for hypoglycemia.

Loss of Control of Blood Sugar: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times it may be necessary to discontinue (drug) and administer insulin.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other oral diuretics, corticosteriods, and (to be supplied by manufacturer). When such drugs are administered to a patient receiving (drug), the patient should be carefully observed for loss of control.

Pseudo-albuminuria (tolbutamide only): Urine containing a tolbutamide metabolite may give a false positive reaction for albumin if the acidification-after-boiling test is used, because this procedure causes the metabolite to precipitate as flocculent particles. Use of the sulfosalicylic acid test circumvents this problem.

ADVERSE REACTIONS

Hypoglycemia: See PRECAUTIONS.

Gastrointestinal Reactions: Cholestatic jaundice may occur rarely; (drug) should be discontinued if this occurs.

Gastrointestinal disturbances, e.g., nausea, epigastric fullness, and heartburn are the most common reactions, occurring in (manufacturer to supply estimate of incidence). They tend to be dose related and may disappear when dosage is reduced.

Dermatologic Reactions: Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions occur (manufacturer to provide estimate of incidence). These may be transient and may disappear despite continued use of (drug); if skin reactions persist, the drug should be discontinued.

Porphyria cutanea tarda and photosensitivity reactions have been reported.

Hematologic Reactions: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported.

Metabolic Reactions: Hepatic porphyria, disulfiram-like reactions (manufacturer to supply further details).

(To be inserted for chlorpropamide only:)

Endocrine Reactions: On rare occasions (drug) has caused a reaction identical to the syndrome of inappropriate antidiuretic hormone (ADH) secretion. The features of this syndrome result from excessive water retention and include hyponatremia, low serum osmolality, and high urine osmolality.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with (drug) or any other agent. In addition to the usual monitoring of urinary glucose, the patient's blood glucose must also be monitored periodically:

a. To determine the minimum drug dosage that will lower the blood glucose adequately.

b. To detect primary failure, i.e., inadequate lowering of blood glucose when the drug is first used, even though dose has been raised to the maximum level recommended; and

c. To detect secondary failure, i.e., loss of adequate blood-glucose-lowering response after an initial period of effectiveness. (Drug) should be discontinued, with careful monitoring of blood glucose at least annually to be certain that (drug) is continuing to lower the blood glucose.

Short term administration of (drug) may be sufficient during periods of transient loss of control.

(Manufacturer to supply the following details of dosage for each sulfonylurea:

1. Usual starting dose.

2. Maximum dose.

3. Dose beyond which a response is usually not seen if patient has not already had some response.

4. Usual maintenance dose.

5. Dosage interval, with reasons, e.g., avoid GI tolerance, short half-life of drug, etc.

6. Caution regarding dosage in elderly.)

HOW SUPPLIED

(To be supplied by manufacturer.)

(c) Labeling for oral hypoglycemic drugs of the biguanide category shall be as follows:

DESCRIPTION

(Trade name, established name) is an oral blood-glucose-lowering drug of the biguanide category. It is a white, crystalline, water-soluble compound, formulated as (to be supplied by firm) for oral administration. (Manufacturer to add structural formula and other appropriate information).

ACTIONS

The mechanism of action of phenformin is not established but its ability to cause increased peripheral glucose uptake in vitro appears to be related to its inhibition of cellular oxidative processes. It does not stimulate insulin production. Many patients who at first demonstrate an adequate glucose-lowering effect with (drug) subsequently prove to be no longer satisfactorily responsive, i.e., secondary failure may occur.

(Manufacturer to supply information about:

1. Absorption.

2. Metabolism and excretion.

3. Plasma half-life and the effect of hepatic or renal impairment on blood levels, metabolism, and excretion.

4. Peak and duration of glucose-lowering effect.

5. Mechanism of drug interaction with agents that impair or potentiate drug effect.)

INDICATIONS

Identical to sulfonylurea label, except for substitution of the following section relating to concomitant therapy:

Concomitant Therapy:

Phenformin may be used in conjunction with a sulfonylurea to control symptoms due to hyperglycemia in patients with maturity-onset nonketotic diabetes mellitus whose symptoms cannot be controlled by diet and maximum recommended doses of either drug alone and in whom insulin cannot be used for any of the reasons cited above.

In considering the use of concomitant therapy, it should be noted that both phenformin and a sulfonylurea drug (tolbutamide) have been reported to be associated with increased cardiovascular mortality; see WARNINGS. Thus the use of phenformin in association with a sulfonylurea may carry a greater risk than the use of phenformin alone.

If a judgment is made that phenformin and a sulfonylurea are to be used together in a particular patient, it should be established that the patient is responsive to both drugs. This may be accomplished either by a trial of each drug separately or by adding the second drug and then tapering the dosage of the first, observing for diminished control of blood glucose. Once the need for both drugs is established, the desired control of blood sugar may be obtained by adjusting the dose of either drug. The possibility of hypoglycemia should be anticipated, and appropriate precautions taken. See package insert for the appropriate sulfonylurea for CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.

CONTRAINDICATIONS

(Drug) is contraindicated in patients with:

1. Known hypersensitivity or allergy to the drug.

2. A history of lactic acidosis.

3. Disease states associated with hypoxemia including cardiovascular collapse and acute myocardial infarction.

4. Severe renal disease.

5. Alcoholism.

6. Diabetic ketoacidosis with or without coma. Such patients should be treated with insulin.

WARNINGS

SPECIAL WARNING ON CARDIOVASCULAR MORTALITY

(Identical to boxed, boldface sulfonylurea labeling.)

(Drug) is not adequate therapy in patients with juvenile diabetes or insulin-dependent diabetes at any age. Such patients should be treated with diet and insulin. The concomitant long term use of insulin and (drug) in an individual patient is, in view of the risk of increased cardiovascular mortality with (drug), less safe on a benefit-risk basis than the use of insulin alone.

The effectiveness of any oral hypoglycemic drug, including (drug), in lowering blood glucose to a desired level decreases in a large number of patients as the drug is administered over a period of months or years, in part because the patient's

blood glucose tends to rise over time and in part because of diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient at the time of its initial administration. See DOSAGE AND ADMINISTRATION.

Lactic Acidosis: There have been numerous reports of lactic acidosis in patients receiving phenformin. Lactic acidosis is an often fatal metabolic acidosis characterized by elevated blood lactate levels, an increased lactate-to-pyruvate ratio, and decreased blood pH. Azotemia ranging from mild to severe is present in most of the reported cases of lactic acidosis. Azotemia can result from dehydration, and some patients developing lactic acidosis associated with azotemia have had normal serum creatinine levels when properly hydrated. The following specific precautions should be observed when administering phenformin:

a. Impairment of renal function increases the risk of lactic acidosis. Renal function tests, such as serum creatinine, should be performed prior to phenformin therapy and at least annually thereafter. Phenformin should not be used in patients with impaired renal function, e.g., serum creatinine over 1.5 milligrams/100 milliliters, except in extraordinary circumstances.

b. Cardiovascular collapse (shock), congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and also may cause prerenal azotemia. Use of phenformin in patients particularly prone to develop such conditions must be carefully considered and the risks weighed against possible benefits. When such events occur in patients on phenformin therapy, the drug should be discontinued promptly.

c. Gastrointestinal disturbances are the most common adverse reactions to phenformin therapy. These symptoms must be distinguished from the symptoms of developing lactic acidosis. Anorexia

and mild nausea are common side effects of phenformin, particularly upon initiation of therapy. Nausea, vomiting, malaise, or abdominal pain may herald the onset of lactic acidosis. The patient should be instructed to notify the physician immediately at the onset of any of these gastrointestinal symptoms or of hyperventilation. Phenformin should be withdrawn until the situation is clarified by determination of serum electrolytes and ketones, blood glucose, and, if indicated, blood pH, lactate, and pyruvate levels.

d. Lactic acidosis has a significant mortality and, when suspected, must be treated promptly by discontinuing phenformin and giving bicarbonate infusions and other appropriate therapy even before the results of lactate determinations are available. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis in the absence of ketonuria and ketonemia, uremia, and methanol or salicylate poisoning.

e. The physician should use special caution after initiating phenformin therapy, after increasing the drug dosage, and in circumstances that may cause dehydration leading to impaired renal function.

f. Alcohol is known to potentiate the effect of phenformin in elevating blood lactate levels, and patients should be warned against excessive alcoholic intake while receiving phenformin.

g. Impaired hepatic function has been associated with some cases of lactic acidosis. Particular caution must be observed when administering (drug) to patients with hepatic disease.

Pregnancy: (Data and interpretation related to reproduction and teratology studies to be supplied by manufacturer).

PRECAUTIONS

Hypoglycemia: Hypoglycemia is unusual in patients receiving (drug) alone, but may occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or when more than one hypoglycemic drug is used.

(Manufacturer to supply paragraph on potentiating drugs.)

Loss of Control of Blood Sugar: Identical to sulfonylurea labeling.

Change in Clinical Status of Previously Controlled Diabetic: A diabetic patient previously well-controlled on phenformin who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose, and, if indicated, blood pH, lactate, and pyruvate levels. Acidosis of either form necessitates withdrawing phenformin and initiating other appropriate corrective measures.

Starvation Ketosis: This must be differentiated from insulin-deficient ketosis and is characterized by ketonuria with little or no glucosuria and relatively normal blood glucose levels. This may result from excessive dosage of phenformin or insufficient carbohydrate intake.

ADVERSE REACTIONS

Hypoglycemia: See PRECAUTIONS.

Gastrointestinal Reactions: Gastrointestinal disturbances such as anorexia, nausea, vomiting, and diarrhea are the most common adverse reactions (manufacturer to supply frequency) and are dose related. These symptoms must be distinguished from the prodromata of lactic acidosis. See WARNINGS section for discussion of lactic acidosis. They may also cause dehydration and prerenal azotemia, which require discontinuation of the drug until renal function is again normal. Phenformin should be discontinued if vomiting occurs. An unpleasant metallic taste is a warning signal of impending gastrointestinal disturbances.

Dermatologic Reactions: (Manufacturer to supply data, including estimate of incidence.)

Miscellaneous Reactions: Fatigue and weakness. Anorexia, nausea, and vomiting may occur in association with the intake of alcohol.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetic mellitus with (drug) or any other agent. In addition to the usual monitoring of urinary glucose, the patient's blood glucose must also be monitored periodically:

a. To determine the minimum drug dosage that will lower the blood glucose adequately.

b. To detect primary failure, i.e., inadequate lowering of the blood glucose when the drug is first used, even though dose has been raised to the maximum level recommended.

c. To detect secondary failure, i.e., loss of adequate blood-glucose-lowering response after an initial period of effectiveness. Drug should be discontinued with careful monitoring of blood glucose at least annually to be certain that (drug) is continuing to lower the blood glucose.

Short term administration of (drug) may be sufficient during periods of transient loss of control.

(Manufacturer to supply the following details of dosage:

1. Usual starting dose.
2. Maximum dose.
3. Dose beyond which a response is usually not seen if patient has not already had some response.
4. Usual maintenance dose.
5. Dosage interval, with reasons, e.g., avoid GI intolerance, short half-life of drug, etc.
6. Caution regarding dosage in elderly.)

HOW SUPPLIED

(To be supplied by manufacturer.)

(d) Each holder of an approved new drug application for an oral hypoglycemic agent shall submit a supplement to his application under the provisions of § 314.8(d) of this chapter to provide for labeling as described in paragraphs (b) and (c) of this section. The labeling in such supplement shall be identical in wording to the labeling in paragraphs (b) or (c) of this section where precise wording is specified, shall provide information on each of the points where wording is delegated to the manufacturer, and shall contain no additional or extraneous information. Such supplement shall be submitted within 10 days after (effective date of the final regulation). Any oral hypoglycemic drug with labeling not in compliance with this section and shipped into interstate commerce after (60 days after effective date of the final regulation) shall be subject to regulatory action.

Interested persons may, on or before (insert date 60 days after date of publication in the FEDERAL REGISTER), submit to the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852, written comments regarding this proposal. Comments shall be filed in quintuplicate and shall be identified with the Hearing Clerk docket number found in the document heading. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: 1 July 1975.

H. M. Schmidt.

Public Citizen

June 10,1975

Alexander M. Schmidt, M.D.
Commissioner,
Food and Drug Administration
Federal Building 8
200 "C" St. S.W.
Washington, D.C. 20204

Dear Dr. Schmidt:

This letter is to urge immediate publication of a warning to patients and doctors about all oral drugs used to treat diabetes. New evidence from four previously unreported studies combined with previous evidence demands this action to prevent the unnecessary death of thousands of diabetics and waste of more than 100 million dollars a year on these drugs.

It is now five years since the University Group Diabetes Program (UGDP) reported that there was a significant excess cardiovascular mortality in patients taking an oral diabetes drug (tolbutamide-ORINASE). Although promulgation of an FDA-proposed warning label for all such drugs[1] was enjoined in 1972 by a Federal District Court, this was reversed in July, 1973 by the U.S. Court of Appeals. Thus, the FDA has delayed for almost two years the

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1. "Although the specific sulfonylurea drug studied by UGDP was tolbutamide, the conclusions apply equally to all sulfonylureas--Diabinase, Orinase, and Tolinase--because of their close chemical relationship." "...the conclusions apply to DBI and Meltrol as well" (FDA Drug Bulletin, May 1972).

LEADING ORAL "ANTIDIABETES" DRUGS
TOTAL PRESCRIPTIONS PER YEAR FOR U.S.[1]

	1972	1973	%CHANGE
Diabinase (Pfizer)	5,845,000	6,201,000	+7.8%
Orinase (Upjohn)	5,290,000	4,998,000	-5.5%
DBI (Geigy)	4,035,000	4,282,000	+6.1%
Dymelor (Lilly)	1,553,000	1,462,000	-5.8%
Tolinase (Upjohn)	1,468,000	1,975,000	+34.6%
Total Prescriptions (including all oral drugs)	18,369,000	19,381,000	+5.5%

(National Disease & Therapeutic Index, 1972 & 1973, LEA Inc., Ambler,PA.)

publication of a warning label which would, if properly worded, cause most adult diabetics to be taken off these dangerous, ineffective, and expensive drugs.

During this interval of irresponsible delay by the FDA, approximately 250 million dollars worth of these drugs have been consumed in this country alone and, according to experts, 20,000-30,000 unnecessary deaths due to these drugs have probably occurred.[2] Of the 1.5 million people currently using these drugs, it is estimated that 80% to 90%, at least, could be controlled as well or better--and certainly more safely--by diet or, in a very small number of cases, insulin.[3]

Although the published medical literature contains ample evidence of the increased risk of death and lack of efficacy of these drugs, the FDA is aware of four additional studies the results of which have not yet been made known to the public. A brief review of these studies follows:

1. Unpublished Study on Mortality in Joslin Clinic Patients

Although many doctors who have been wedded to the idea that these pills benefit diabetics have attacked the findings of the UGDP study, none have been as vocal as the doctors of the Joslin Clinic in Boston. Aside from organizing the law suit against the FDA to block promulgation of the warning label three years ago, Dr. Robert Bradley (Joslin Director) and his cohort have devoted considerable time to presentations at drug-company-financed meetings around the country aimed at maintaining doctors "faith" in these drugs. It is thus all the more striking to find that a study of the Joslin Clinic's own patients yields results similar to those found by the UGDP.

A Harvard Ph.D. thesis by Paula Kanarek entitled "Assessing Survival in a Diabetic Population" and dated January 1973 was a retrospective study of 6300 patients at the Joslin Clinic. Begun after the UGDP study, its stated purpose was to study the effect of various types of therapy on the survival of diabetic patients, particularly to see "if individuals treated with tolbutamide (ORINASE) are more likely to die from cardiovascular causes..."

The results of the study showed that:

a)"For individuals who survive at least 5 years, however, the relative survival experience for persons receiving tolbutamide is worse in all cases than that of those on diet..." (p. III-16)

b)"...certainly in all risk categories, the probability of dying from cardiovascular causes in 5-10 years was consistently higher in the tolbutamide group than in the diet group (III-17)

2. Senate Hearings on Oral Hypoglycemic Drugs, Sept. 1974, p.10803.

3. J.A.M.A., 232, 854, May 26, 1975.

c)"...the results of this observational study suggest that the findings of the UGDP may be generalized to other diabetic populations." (III-23)

2. FDA-Sponsored Study of the Effect of Tolbutamide on Development of Coronary Artery Disease in Monkeys

This study, FDA contract #72-114,was done by researchers headed by Dr. Robert Wissler, Professor of Pathology at the University of Chicago. Begun in 1972, the final report was submitted to FDA in February, 1975.

Monkeys were placed on an "Average American Diet" and one-half were given tolbutamide at a dosage comparable to that taken by diabetics. The study was continued for two years with the following findings:

a) Coronary artery disease was found two times more often in animals taking tolbutamide than in animals on diet alone.

b) The coronary artery disease caused by the drug was three times more severe than that developing spontaneously from the diet alone.

Although the UGDP and Joslin studies showing increased death in humans from cardiovascular disease due to these drugs are clear enough, the Wissler study is the first experimental confirmation of the mechanism whereby the human deaths ahve occured. Since it has been known for more than 30 years that most diabetics die from cardiovascular complications, such animal studies should have preceded marketing.

3. A Study by Dr. C.R. Wu,, et al., of New Jersey Medical School, presented May 3, 1975 in Atlantic City at the American Federation for Clinical Research meeting also looked at the effect of tolbutamide on the heart of diabetic dogs. At therapeutic doses (equivalent to those taken by diabetic patients) the function and structure of the heart was worsened by 1 year of treatment with tolbutamide.

4. Unpublished Study of Joslin Clinic Patients Showing Lack of Efficacy of 4 Oral Diabetes Drugs.[4]

In addition, we have just obtained a copy of a study by researchers at the Joslin Clinic which clearly demonstrates that the oral antidiabetic drugs fail to achieve their intended "beneficial" purpose, namely lowering of blood sugar.

365 adult-onset diabetics were placed on an individualized diet and given either a placebo, tolbutamide (ORINASE), chlorpropamide

4. The Effects of Long Term Therapy with Oral Hypoglycemic Agents on the Oral Glucose Tolerance Test Dynamics in Chemical Diabetics (Tan, Graham, Bradley et.al.)

(DIABINASE), phenformin (DBI) or acetohexamide (DYMELOR). At the end of four years on diet and either placebo or one of the four drugs, there was no evidence that any of the four drugs improved glucose tolerance more than diet and a placebo.

This study, although completed more than 2 1/2 years ago and presented in summary form at a meeting of the American Diabetes Association June 23, 1973, has never been published. It is likely that one or both of the following factors are responsible for its non-publication:

1. The Joslin Clinic is the center of advocacy (aside from the drug companies) for the use of these diabetes drugs.

2. The study was supported by Upjohn (makers of Orinase and Tolinase), Lilly (Dymelor) and Pfizer (Diabinase).

The degree to which the Joslin Clinic adheres to their "faith" in these drugs despite all the evidence--including data from their own patients--to the contrary can be seen in the testimony of Joslin Director Dr. Robert Bradley before the Senate hearings last fall:

> "Data from the UGDP Study have thus far contributed nothing to the controversy regarding the effectiveness of blood sugar control and...the results cannot at present be extrapolated to the diabetic population at large." Select Committee on Small Business (p. 10986).

If the UGDP study didn't convince Dr. Bradley, surely the combination of increased mortality and lack of efficacy of these drugs in his own Clinic should.

WARNING LABEL AND MALPRACTICE

At the heart of opposition by both drug industry and doctor opposition to the proposed warning label is the question of medical malpractice. A strong label, warning against using the drugs unless an adequate trial on diet therapy has been attempted and making doctors (and patients) aware of the increased risk of cardiovascular death, would likely become grounds for malpractice if these caveats were not heeded.

On April 15, 1974, we commented on the way FDA had already weakened the warning label proposed for comment on Jan.28, 1974 from the earliest draft published in the FDA Drug Bulletin, May 1972. (See enclosed).

In testimony before Senator Nelson last fall, Dr. Thomas Chalmers, Dean of Mount Sinai Medical School discussed labelling:

> "The new FDA labelling should be strong enough to warn all physicians that they are distinctly putting their patient at risk by using oral agents when diet or insulin will suffice. The wording

should be such that doctors will be compelled to protect themselves from a later malpractice suit by obtaining truly informed consent from their patients, and by demonstrating in the patient's record that the patient's symptoms could not be controlled by diet and/or insulin." (Nelson Hearings, p. 10999).

Faced with such a warning label, most doctors, in the interests of their patients (and themselves) would make a much greater effort to avoid use of these dangerous drugs.

In summary, it is long past the time for FDA to have issued a strong warning label for these drugs. Any further delay should result in sanctions against all FDA officials who have been responsible.

Sincerely,

Sidney M. Wolfe, M.D.

Anita Johnson, esq.

When Friends or Patients Ask About . . .

William H. Crosby, MD, *Coordinator*

The FDA and Hypoglycemic Drugs

John K. Davidson, MD, PhD

THE NELSON Committee hearings in the US Senate (Sept 18 to 20, 1974) explored the *safety, effectiveness,* and *use* of hypoglycemic drugs. A dozen witnesses, including the Food and Drug Administration (FDA) Commissioner Dr. Alexander Schmidt, gave testimony concerning the implications of the University Group Diabetes Program (UGDP) articles for medical practice. Concern was expressed because the FDA Bureau of Drugs had not required appropriately written package inserts warning physicians and the drug-consuming public of the dangers inherent in the indiscriminate use of sulfonylureas and phenformin hydrochloride. There was agreement that caloric restriction with weight reduction is the preferred method of treatment for the maturity-onset diabetic who is above ideal body weight, and that such therapy is always safe and with intensive education and follow-up is usually effective.

The UGDP investigators ended the *tolbutamide* (sulfonylurea) study in 1969 and the *phenformin* study in 1971, when careful statistical analysis showed a death rate more than twice that expected for each drug when compared to the death rates in the three other groups in the study (*placebo,* a *standard dose of insulin* that resulted in a moderately elevated mean fasting blood glucose level, and a *variable dose of insulin* that resulted in a near-normal mean fasting blood glucose level). Death rates in the placebo and insulin groups were similar. There were no significant differences in the rate of development or progression of chronic complications (retinopathy, nephropathy, neuropathy, arteriopathy) in the survivors of any of the five treatment groups.

Are Oral Hypoglycemic Drugs Safe and Effective?

In addition to the increased cardiovascular mortality with tolbutamide therapy or with phenformin therapy of approximately 1% per year, there are many other adverse effects of oral hypoglycemic drugs. These include prolonged sulfonylurea-induced hypoglycemia and phenformin-induced lactic acidosis, both of which have terminated fatally in a number of patients.

Extrapancreatic effects of the sulfonylureas include hypothyroidism, skin rashes and photosensitivity, corneal opacities, blood dyscrasias, increased fibrinolytic activity, hyponatremia, water retention, jaundice, liver-enzyme inhibition, heart effects (including inotropism, increased oxygen need, and microgranulomas), elevated blood pressure, altered electroencephalogram in epilepsy, and increased stomach-acid secretion.

The sulfonylurea drugs compete for carrier-protein binding sites with many other drugs, including sulfonamides, salicylates, phenylbutazone, monoamine oxidase inhibitors, thiazides, and barbiturates. The pharmacological effect of all of these drugs, including the sulfonylureas, may be increased when they are displaced from their combining sites; thus, combination drug therapy may have many unanticipated toxic consequences. The difficulties in maintaining stable anticoagulation therapy in the pres-

The Author: John K. Davidson received his BS degree in 1943 and MD degree in 1945 at Emory University, Atlanta. He was a research fellow of the American Diabetes Association from 1961 to 1965 at the University of Toronto, where he won the Starr medal in 1963 for his work on nonsuppressible insulin-like activity and studies of bete cell function. He received the PhD degree in Physiology in 1965 at the University of Toronto, and joined the faculty with appointments in physiology and medicine. He returned to Emory University in 1968, where he is now director of the Diabetes Unit at Grady Memorial Hospital and professor of medicine. He has been on the Board of Directors of the American Diabetes Association since 1970, and directed its sixth Allied Health Postgraduate Course in Atlanta in 1974. His research interests are in insulin immunity, immunologic insulin resistance and its treatment with sulfated insulin, and investigations of various techniques of implementing effective diet therapy and weight reduction in obese maturity-onset diabetics.

If you wish to suggest a topic or write an answer for this feature, write to William H. Crosby, MD, Scripps Clinic and Research Foundation, La Jolla, CA 92037.

Reprint requests to Department of Medicine, Emory University School of Medicine, 69 Butler St SE, Atlanta, GA 30303 (Dr. Davidson).

ence of sulfonylureas and the potentiation of alcohol by sulfonylureas with an occasional disulfiram-like reaction are well substantiated.

Phenformin increases anaerobic glycolysis and lactate production and may produce lactic acidosis; it increases blood pressure, heart rate, and need for digitalis; and it decreases gluconeogenesis and glucose absorption.

There has been a striking increase in death rate and a decrease in life expectancy in maturity-onset diabetics in America, Europe, Asia, Africa, and Australia during the last 20 years. These changes have paralleled the increasingly widespread neglect of diet therapy and the almost unbridled enthusiasm among many physicians and patients for the use of sulfonylureas and phenformin as treatments of choice.

If a drug is to be considered *safe*, it should not shorten life expectancy nor be associated with fatal side effects or with severe drug reactions. The increased number of cardiovascular deaths in the UGDP study, the not uncommon occurrences of irreversible hypoglycemic brain damage and death with sulfonylureas and fatal lactic acidosis with phenformin, and the previously noted decreased life expectancy of the maturity-onset diabetic population throughout the world are the dramatic consequences of unrestricted use of oral hypoglycemic drugs. Thus, one is forced to the conclusion that both sulfonylureas and phenformin are unsafe.

It has been known for a long time that primary and secondary drug treatment failures are common with the sulfonylureas and phenformin; these failures have usually necessitated insulin therapy. As early as 1957, it was noted that blood glucose levels were frequently as low on placebo as on tolbutamide therapy. In a 1974 report, blood sugar levels did not rise in 30 of 50 patients when single-blind placebo was substituted for chlorpropamide. In 20 patients, the level rose modestly on a placebo regimen; however, in only four of the 20 patients did chlorpropamide help attain fasting normoglycemia (blood glucose level, < 140 mg/100 ml).

If a drug is to be considered *effective*, it should prevent or delay the appearance of complications or prolong life, as well as lower the blood glucose level in a dependable fashion. Since sulfonylureas and phenformin apparently shorten life expectancy, do not prevent or delay complications, and do not lower the blood glucose level in an optimal fashion in the majority of patients, neither sulfonylureas or phenformin can be considered effective therapy, despite the claims of several drug companies and some physicians to the contrary.

Safe and Effective Alternatives

Appropriate caloric restriction (including periods of fasting for up to one week) usually lowers the blood glucose level dramatically in the obese diabetic. With intensive instruction and follow-up, a diet adherence rate of 96% has been reported recently. Success rates in reducing the weight of obese diabetic patients at Grady Memorial Hospital and Emory University School of Medicine in Atlanta have varied in different groups of patients from 50% to 90%, with the most intensively instructed and monitored patients having the greatest degree of success (unpublished data). To modify successfully a patient's long-established habits of food intake, it is mandatory that the physician be competent in calculating ideal body weight and in writing the correct dietary prescription. The patient's adherence to diet is facilitated by use of an easily understood diet manual and intensive instruction over a long period of time by physician, nurse, and dietitian. Patients at Grady Hospital are now given about 25 hours of individual and group instruction over a one-year period. Diet therapy is universally *safe*, and when pursued aggressively it is *effective* in a large majority of maturity-onset diabetics.

In the diabetic above ideal body weight who is not acutely decompensated (plasma glucose level, 500 mg/dl or higher, or moderate to large acetonuria), only a one-week fast and intensive follow-up caloric restriction is needed. In addition to appropriate diet and exercise therapy, optimal insulin therapy is needed in (1) the acutely decompensated diabetic (even those above ideal body weight), (2) the hyperglycemic maturity-onset diabetic at or below ideal body weight, (3) the hyperglycemic pregnant diabetic, and (4) the hyperglycemic juvenile-onset diabetic. The prime therapeutic objective when insulin is used is to attain normoglycemia as frequently as possible, with hypoglycemia being as infrequent as possible. The slight discomfort of insulin injections is a minor price to pay for the generally acknowledged physiologic actions and life-sustaining properties of the hormone. Insulin therapy, optimally used, is *safe*, and it is almost universally *effective* in lowering the blood glucose level.

Responsibility for Indiscriminate Use

At the present time, about 1,500,000 Americans are being treated with oral hypoglycemic drugs. At the Nelson Committee hearings, different witnesses estimated that from less than 1% to 20% of the patients being treated with these agents were actually helped by such therapy. Depending on which opinion one accepts as valid, this means that from 1,200,000 to 1,485,000 Americans are being inappropriately treated and should have their oral agent therapy discontinued. The drugs are probably being used excessively because the physician wants to do something when he makes a diagnosis of diabetes, and the patient wants something done. The easiest thing to do is to write a prescription for a pill, because it takes only a little time and it necessitates no significant change in the patient's life-style. Thus, the physician writes a prescription for a medication that he has been led to believe is safe and effective, when it is almost certainly unsafe and is frequently ineffective.

The FDA has not required properly written package inserts for the sulfonylureas and phenformin because of a legal barrier erected by litigation instituted by the Committee on the Care of the Diabetic. For this reason, physicians and the drug-consuming public have not been honestly and fully informed of the dangers inherent in the continued widespread use of these drugs. This legal barrier

has now been removed. Commissioner Schmidt has indicated that when the audit of the UGDP study by the Biometrics Society is published [Feb 10 issue of *JAMA*.—Ed], the FDA will move swiftly and forcefully to order labeling of the sulfonylureas and phenformin to reflect the results of the UGDP study. He anticipates that this action will discourage future indiscriminate use of the drugs.

If the drugs *are* used in the future, it would be prudent for the physician to have the patient sign an informed consent agreement indicating that he has been informed of the possible hazards associated with such drugs and that he accepts the full responsibility for the effects of such therapy.

For physicians who are concerned about the consequences of discontinuing the use of oral hypoglycemic agents by their patients, there is a reassuring precedent for such action. Four years ago, in the wake of the UGDP report, oral agent therapy was abandoned at Grady Hospital, involving 1,500 patients. Eighteen months later, the blood glucose levels of 60% of these patients were satisfactorily controlled on diet therapy *alone*. Since 1972, the emphasis on diet therapy and weight reduction has been intensified, and during the last year insulin therapy has been discontinued in all patients who are above ideal body weight.

Additional Readings

A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes, University Group Diabetes Program. *Diabetes* 19(suppl 2):747-830, 1970.

Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes: IV. A preliminary report on phenformin results, University Group Diabetes Program. *JAMA* 217:777-784, 1971.

Prout TE: Adverse effects of the oral hypoglycemic drugs, in *Proceedings of the Eighth Congress of the International Diabetes Federation*. Amsterdam, Excerpta Medica, 1974, pp 612-623.

Hurwitz D, McCuistion AC: Tolbutamide: A double-blind study of its effect in diabetes. *N Engl J Med* 257:931-933, 1957.

Lev-Ran A: Trial of placebo in long-term chlorpropamide-treated diabetics. *Diabetologia* 10:197-200, 1974.

Weinsier RL, Seeman A, Herrera MG, et al: Diet therapy of diabetes: Description of a successful methodologic approach to gaining diet adherance. *Diabetes* 23:669-673, 1974.

Davidson JK, Goldsmith MP: *Diabetes Guidebook: Diet Section*. Columbus, Ga, Litho-Krome Co, 1971.

JAMA
75 YEARS AGO

May 26, 1900

Carcinoma in Early Life

[Walter L. Bierring, MD, pp 1295-1298]

Carcinoma is usually regarded as the malignant tumor of later life, having its legitimate age limit at 35, though it is most frequently met with after 40 years of age.

With increasing study of the malignant neoplasms, age is gradually losing its hold as a criterion of difference between sarcoma and carcinoma, the former being found at almost any age, while carcinoma is beginning to be noticed more frequently during the earlier decades of life. . . .

Carcinoma in early life often has a slow course, and like that of later years may be latent for a considerable length of time. That cancer in early life is becoming more frequent is very evident; whether it keeps pace with the general increase in carcinoma will be difficult to determine. Certainly a collective study of the statistics reveals the unfortunate fact that the mortality rate of carcinoma is on the increase. Roswell Park calls attention to the statistics of New York State, showing 2,363 deaths in 1887 against 4,456 in 1898. In England and Wales, where careful records are kept, the rate of occurrence of cancer has increased from 1 in 5,646 population in 1840 to 1 in 1,306 in the year 1896, an increase of five times in fifty years. This increase can hardly be ascribed as due to improvements in methods of diagnosis, for rather the reverse is the case, since many cases that were formerly diagnosed as cancer are now properly classified where they belong in other lists.

While the etiology of cancer remains obscure, there is but little hope that the future will offer any abatement in this progressive increase. As careful observation continues to note the occurrence of carcinoma in the earlier decades of life, there is removed from the list of predisposing causes, the influence of age.

It has been an attractive explanation to attribute to the lessened physiologic resistance in connective tissue the rôle of permitting atypical proliferation of epithelium beyond its normal limits. With advancing age the submucous, subcutaneous and interstitial connective tissues undergo atrophic changes, while the covering or lining epithelial elements seem to retain their usual vitality. When glands reach the limit of their functional rôle in the organism, the danger from carcinoma is most marked, while it diminishes again when complete atrophy has taken place. When cancer occurs thus in the developing decades of life, the above influences can hardly be considered. . . .

In the entire field of pathology, no subject has proved more alluring to physician and investigator than the etiology of carcinoma. It was no wonder that the development of bacteriologic methods gave a mighty impetus to the search for an etiologic agent, the result of which is well known. Numerous forms of cell inclusions—cancer bodies—have been observed and variously interpreted. . . .

As yet it is evident that the real cause of carcinoma has not been demonstrated. Perhaps it will be necessary to completely modify our culture methods. Perhaps our optical aids are inadequate in magnifying power, but unless the light comes soon, the 19th century will close with the genesis of cancer as much a mystery as when the century began.

GOVERNMENT Rx's

FDA proposes important revision

According to a recent FDA-proposed regulation on labeling (package insert), a food, drug, device, or cosmetic is "misbranded" if the labeling does not reveal:

1. facts that appear in other statements (et al) about the product;
2. consequences which may result from using the product (either as prescribed or as it is usually used).

However, the regulation's prohibitions are more important than its requirements. Material facts do not, according to the FDA, "*permit* or require a statement of *differences of opinion* with respect to warnings (including contraindications, precautions, adverse reactions, and other information relating to possible product hazards) required in labeling for food, drugs, devices or cosmetics under the act." (Italics ours.) Furthermore, the proposed regulation does not "*permit* or require a statement of differences of opinion with respect to the effectiveness of a drug unless each of the opinions expressed is supported by substantial evidence of effectiveness . . . ."

In the regulation's preamble, the FDA gives us significant insight into why they have made the above proposal. The current regulation states that "the existence of a difference of opinion among experts qualified by scientific training and experience, as to the truth of a representation made or suggested in the labeling is a fact (among other facts) the failure to reveal which may render the labeling misleading if there is a material weight of opinion contrary to such representation." (In other words, according to the regulation they want to revise, differences of opinion are required.)

In 1971, the FDA published a notice that the labeling for oral hypoglycemic drugs used in the treatment of adult onset diabetes must contain a warning against cardiovascular consequences reportedly associated with the use of these drugs. Later that year a group of physicians petitioned the FDA to withdraw or modify this requirement, because they believed that the warning was unjustified, and that if it were required, it should be accompanied by a statement of the differences of opinion among experts about the necessity for the warning. The FDA Commissioner denied the petition, and manufacturers of oral hypoglycemic drugs had to include the warning in their labeling. The FDA felt that an undiluted statement was justified, since there was significant clinical evidence to support the warning, and that the physicians who presented the petition did not have enough evidence to dispute the need for the warning. The physicians then brought suit to enjoin the labeling change on the grounds that, by not including the difference of opinion, the drug would be misbranded according to the above regulation.

The FDA contended that since statements of drug effectiveness and truthful labeling were supposed to be based on "substantial evidence" rather than medical opinion, the labeling suggested by these physicians would be misleading. However, the district court entered a preliminary injunction prohibiting the FDA from requiring the warning because, the court concluded, there was a reasonable likelihood that the labeling proposed by the FDA did not comply with current regulations.

When the FDA appealed, the United States Court of Appeals cited the inconsistency between the way the current FDA regulation reads and the "substantial evidence" requirements that had been added to the Food

and Drug Act by Congress in 1962. The court then voided the injunction and gave the case back to the FDA for "further determination."

Now the FDA had to either allow inclusion of conflicting opinions about the oral hypoglycemics drug warning or revise the regulation. They decided to revise the regulation.

According to the 1962 Food and Drug Act:

> "If an article is alleged to be misbranded because the labeling is misleading, then in determining whether the labeling is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling relates under the conditions of use prescribed in the labeling thereof or under such conditions of use as are customary or usual."

And:

> "Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users: Provided, That where any requirement of clause (1) of this paragraph, as applied to any drug or device, is not necessary for the protection of the public health, the Secretary shall promulgate regulations exempting such drug or device from such requirement."

The law also (as everyone probably knows by now) states that a new drug may not be approved for marketing if it is unsafe or ineffective for the conditions for which it is supposed to be used.

The FDA finds the use of the word "may" (underlined in the quotation above) particularly significant, since it implies lack of universal agreement among experts. The word "may" thus is supposed to make it unnecessary to include the specific medical controversy surrounding the warning. The FDA comments that warnings have been required on drug

(continued on p. 82)

labels by the Food and Drug Administration when there is significant medical evidence of a possible health hazard without waiting for a causal relationship to be established by definitive studies, which in some instances may not be feasible or would take many years. It states that in this way, physicians are fully informed of known potential dangers and the public is better protected.

These warnings must be stated in clear and unambiguous terms without disclaimers or qualifications that the FDA says would undermine or destroy their meaning and usefulness, and that all such warnings are by their very nature, about *possible* danger only. These warnings are often the subject of intense debate, but the FDA has never permitted drug labeling to reflect such debate, and, they say, this debate and disagreement should appear in professional journals and symposia but not in drug labeling. The prescription drug label warning is only for the guidance of a physician—it does not constitute a legal requirement and, the FDA adds, a physician does not violate federal law when he prescribes a drug contrary to a warning in its approved labeling.

In 1938, when the Federal Food and Drug Cosmetic Act was passed, personal expert judgment was the standard for determining drug effectiveness. The only way to satisfy that standard when the experts' opinions differed was to state both sides of the issue in the labeling for the drug. In the regulation preamble, however, FDA states that by 1960, the scientific principles of modern drug testing using statistically valid controlled studies had become fully developed and accepted, and claims of drug effectiveness (and thus the truthfulness of drug labeling) should be determined by adequate and well-controlled investigations, including clinical investigations by qualified experts.

The stated purpose of requiring scientific studies was to eliminate individual clinical observation and opinion as the measure of a drug's effectiveness, since the opinions of individual physicians reflecting their personal experience, empirical observation, and traditional practice do not satisfy the requirements of sound scientific investigation and thus do not conform to the standards established by the Drug Amendments of 1962. FDA notes that the Drug Amendments of 1962 are clearly intended to supersede the earlier reliance on medical opinion, and that therefore regulations should reflect the new standard.

In commenting on the concept of "fair balance" argued by the physicians in attacking the labeling for oral hypoglycemic drugs, FDA states that a draft of proposed new regulations will soon be published in the *Federal Register*. These regulations will implement "fair balance" for prescription drug labeling in the same way that present regulations do for prescription drug advertising. In both advertising and labeling, the required "balance" refers to how information on drug safety and effectiveness is presented and not to differences of judgment about that information.

The FDA concludes that the present regulation is inconsistent with current legal requirements and with contemporary medical and scientific principles. Since Congress has determined that the effectiveness of new drugs must be established by substantial evidence, the FDA thinks that a difference of medical opinion about labeling claims of effectiveness is not legally sufficient and is not a material fact unless the opinion is supported by evidence which meets the legal standard. The FDA goes on to say that some controversy exists in the medical profession about most statements in prescription drug labeling, and that permitting or requiring statements of these opinions on all such matters would destroy the present usefulness of prescription drug labeling.

The Commissioner thus concludes that there is no justification for presenting differences of medical opinion in any warning statements relating to possible product hazards. The FDA feels that the law presupposes a difference of medical opinion, since warnings of drug dangers will be required even though the danger itself may not be established but merely potential. Furthermore, they think there is no reason to allow these warnings to be discounted by including an opinion that the warning is really not necessary at all.

For these reasons the FDA proposes that the standing regulations be revised. (39 *Federal Register* 33229, Sept. 16, 1974)

Controversy in Internal Medicine II Ed. by Ingelfinger, Ebert, Finland, and Relman. W.B. Saunders Co. Phila. 1974

Oral Antidiabetic Agents Have a Limited Place in Management and May Be Harmful*

ALBERT I. WINEGRAD, REX S. CLEMENTS, JR., and ANTHONY D. MORRISON

University of Pennsylvania School of Medicine

The manner in which most physicians now manage their patients with adult-onset diabetes might best be termed "benign neglect." In part, this is a consequence of the continuing controversy over the aims and the efficacy of presently available therapy. Just how benign current practice really is remains to be determined; however, it includes certain aspects that are difficult to justify, such as the common misuse of the sulfonylurea compounds and the biguanide derivatives.

The indications for continued medical intervention are not so obvious in adult-onset diabetics as in juvenile diabetics since, irrespective of their age at diagnosis, patients with the adult-onset form of the disease exhibit little tendency to ketoacidosis. There is general agreement that efforts to lower the blood glucose are indicated in patients who are symptomatic as the result of hyperglycemia, and that delay in the effective treatment of symptomatic hyperglycemia in adult-onset diabetics may be a major factor in the development of hyperglycemic nonketotic coma. At the time of diagnosis, patients with adult-onset diabetes are a heterogeneous group not only with regard to symptoms, but also with regard to the presence of the complications of diabetes and the coexistence of other conditions (e.g., hypertension and arteriosclerotic cardiovascular disease) that might be expected to alter their prognosis. There is little agreement as to benefit of therapy other than that designed to relieve symptoms directly related to hyperglycemia.

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What Is the Value of "Control"?

Physicians are divided on the value of attempts to achieve an approximation of normal glucose metabolism in the hope that this will influence the development or progression of the late complications. (It is symptomatic of the state of the field that measures to modify other demonstrable abnormalities, such as hyperlipoproteinemias, have received minimal consideration.) Much of the present controversy over the value of "control" is nonsense. The players in this philosophical sport are trapped by the definitions and unstated assumptions that constitute the rules of this game. In the treatment of adult-onset diabetics, convenience is the overriding consideration in the minds of most physicians, which may be understandable since the value of treatment in asymptomatic patients is disputed. The effort and expense required to achieve and to document an approximation of normal blood glucose concentrations throughout the day preclude this type of treatment for most patients. None of the reported clinical trials designed to evaluate the value of "control" has made a serious attempt to achieve normalization of blood glucose fluctuations. The frequency with which this goal can be achieved in a large population of adult-onset diabetics by presently available means has never been evaluated. In essence we have been subjected to a heated dispute over the value of a form of therapy that is only rarely attempted and even more rarely achieved.

Recent studies suggest that fluctuations in the blood glucose concentration in nondiabetic subjects on a normal diet are restricted to a relatively narrow range. However, when evaluating blood glucose concentrations in adult-onset diabetics, physicians almost invariably apply arbitrary standards that bear little relationship to the levels observed in nondiabetics. In addition, it is commonly assumed that if there were a relationship between the blood glucose level and the pathological processes responsible for complications, it should be apparent from comparisons of groups of patients who have had persistently differing degrees of *abnormal* blood glucose levels. Although the basis of this belief is difficult to perceive, it is rarely questioned. A blood glucose concentration that fluctuates between 110 mg. per cent and 180 mg. per cent in a 39 year old man throughout the day cannot be considered normal, even though most physicians would consider this good or excellent "control."

One of the undisputed aspects of the recent reports of the University Group Diabetes Program (UGDP)[1, 2] is the record of the quality of "control" achieved in adult-onset diabetics treated in university medical centers by a variety of therapeutic regimens, most of which are similar to those now commonly employed. None of the treatment groups in the UDPG study had a normal fasting blood glucose at any time during the initial four plus years of the study. Diurnal fluctuations in blood glucose on the patients' usual diet and with their usual physical activity were not assessed. However, at regular intervals the patients were given a 50-gm. oral glucose load one half hour after their morning medication, and the blood glucose was determined one hour later. Although the *lowest* mean blood glucose level at one hour was observed in the patients treated with adjusted insulin dosages, even in this group the mean one-hour value was in excess of 200 mg. per cent in more than half the tests during the initial four plus

years. It is difficult to assemble totally appropriate age and sex matched control data, but in a recent study of normal males with no family history of diabetes (ages 22 to 28), the mean blood glucose one hour after a 50 gm. glucose load was 90.6±5.7 mg. per cent,[3] and in the studies of Neel et al.[4] the mean blood glucose one hour after a 100 gm. glucose load in patients with no family history of diabetes (ages 30 to 39) was 104.3±7.1 mg. per cent in males and 93.7±6.9 mg. per cent in females.* The data available would suggest that most of the patients in the UDPG study had persistently abnormal fluctuations in blood glucose concentration irrespective of the treatment prescribed. Although the UDPG study was a pioneer effort to improve the quality of clinical trials, it shares one of the common deficiencies of such studies in that it included no group of patients who had an essentially normal range of blood glucose fluctuation throughout the day.

Another frivolous aspect of the current controversy is the simplistic fashion in which the pathogenesis of the late complications of diabetes is viewed by most physicians. Each of the diverse clinical syndromes lumped into this unfortunate term has a very complex pathological basis, and in some instances a distinction must be made between processes responsible for acute symptoms and those which operate in the production of predisposing pathological lesions. There is little to support the widespread belief that each of the late complications is primarily a reflection of diabetic microangiopathy. There is no convincing evidence that alterations in capillary structure play a determining role in the pathogenesis of the common symmetrical peripheral neuropathic syndromes associated with diabetes mellitus,[5] nor is there convincing evidence that this process contributes to the increased frequency with which arterial occlusions occur in specific portions of the vascular system. In patients dying of diabetic nephropathy the pathological findings almost invariably include alterations other than those unique to diabetes mellitus; thus, arteriolosclerosis and intimal fibrosis of the renal arteries are often present.[6] Therefore, in any organ system, the pathological changes that are associated with diabetes mellitus may very well be subject to modification by independently determined genetic and environmental factors. However, this is rarely considered in efforts to evaluate the factors responsible for the clinical course in diabetics. As an example, although the recent studies of Hazzard et al.[7] would suggest that inherited abnormalities in lipoprotein metabolism are commonly associated with myocardial infarction, the distribution of patients with such abnormalities has not yet been assessed in clinical trials of diabetic therapy.

Another reason why caution must be exercised in the evaluation of clinical trials is the problem of asymptomatic but irreversible pathology in the patients studied. It is notoriously difficult to date the onset of an abnormality in glucose tolerance in adult-onset diabetics, and this problem is magnified by the recent realization that asymptomatic adult-onset diabetes may occur in children and young adults and does not appear to progress to the ketosis-prone type of the

* The effects of sex and increasing age on fasting blood glucose levels, and on the response to a 100-gm. oral glucose tolerance test in patients with no family history of diabetes have been well documented in patients up to age 39.

disease.[8] Thus, the presence of asymptomatic pathology in newly diagnosed adult-onset diabetics cannot be used as a telling argument against a relationship to the metabolic abnormalities associated with diabetes mellitus.

The failure to consistently observe improvement in specific diabetic complications following the institution of "stricter control" is frequently used as evidence that the pathogenesis of these conditions is unrelated to the consequences of an impaired insulin secretory mechanism. To cite but one example of the limitations of this reasoning, recent studies have demonstrated that the majority of a group of newly diagnosed adult-onset diabetics with normal standard neurologic examinations and without symptoms of neuropathy could be shown to have widespread functional abnormalities in their peripheral nervous system when suitably sensitive techniques were employed.[9] Biopsies of peripheral nerves from asymptomatic adult-onset diabetics without clinical evidence of neuropathy have also revealed pathological changes similar to those found in the nerves of patients with clinical neuropathy (although of a lesser degree).[10] Thus, the development of the clinical manifestations of diabetic neuropathy may represent a late stage in the pathological process and have irreversible elements. Whether or not patients with clinically apparent peripheral neuropathy respond to efforts to improve "control" can provide little information concerning its pathogenesis or its prevention. The host of invasive techniques which would be required to assemble suitably characterized subjects for study (e.g., coronary angiography, renal and peripheral nerve biopsies, fluoroscein retinography, and so forth) almost precludes meaningful large scale clinical trials.

Many physicians also believe that the controversy over the relationship between the metabolic derangements that result from an altered insulin secretory mechanism and alterations in the capillary basement membrane in diabetics has been resolved and that the two are clearly unrelated. This stems from the provocative studies of Siperstein and associates, who were the first to apply quantitative techniques to the assessment of capillary basement membrane thickness (CBMT).[11] They recognized the inherent technical problems in attempting to measure CBMT in many organs and demonstrated that skeletal muscle biopsies provide a means of obtaining suitable material for study from large numbers of patients. Their data indicated that muscle CBMT was significantly greater in diabetics and that the degree of thickening appeared to be unrelated to the duration of known disease or to its "severity." Moreover, their studies suggested that in patients genetically at high risk for the development of diabetes mellitus, increased muscle CBMT was present prior to the development of a detectable abnormality in glucose tolerance. Siperstein's work has been a major contribution and stimulus. However, some of his observations and interpretations have been seriously challenged by Kilo et al., who have concluded that muscle CBMT is usually within normal limits at the outset of clinical diabetes mellitus and increases with duration of disease.[12] There are differences in methodology and in patient selection in these studies, and the resulting controversy has not been resolved. The studies of Østerby suggest that in the kidney the alterations in glomerular capillary structure are not present at the outset of clinical diabetes in young adults but progress with increased duration of the disease.[13] Thus, it would be premature to conclude that the demonstrable metabolic abnormalities

in diabetes mellitus are totally unrelated to the development or progression of alterations in capillary structure. A similar conclusion would have to be drawn with regard to data available from studies of experimental diabetes in animals, particularly in view of recent preliminary reports of the production of retinal capillary microaneurysms in rats with chronic streptozotocin diabetes.[14]

From this cursory review it would appear that at the present time the physician treating adult-onset diabetics has a clear responsibility to prevent symptomatic hyperglycemia; the advantages of maintaining a normal or nearly normal range of blood glucose fluctuations remain to be evaluated but cannot be excluded. The choice of therapeutic aims must be a conscious decision by the physician, and one in which an informed patient participates. The patient's age, the presence of other serious medical problems, the presence or absence of specific clinical complications, and the patient's motivation are practical considerations.

The Importance of Weight Control

Whether the physician believes that the prevention of symptomatic hyperglycemia is an adequate goal in a given patient, or whether a strenuous effort is undertaken to achieve a normalization of glucose metabolism, the relationship between increased body weight and hyperglycemia that so frequently exists in adult-onset diabetics must be considered. In the UGDP study the adult-onset diabetics averaged +33 per cent of ideal body weight at the outset.[15] It has been observed repeatedly that many adult-onset diabetics will exhibit improvement in their degree of hyperglycemia if a significant reduction in body weight can be achieved. (Whether this is due to weight reduction per se or to a decrease in carbohydrate intake remains to be determined.[16, 17]) The UGDP studies provide an indication of the effectiveness of present efforts to achieve weight reduction and the resultant improvement in diabetic "control." All the patient groups in the UGDP study exhibited a fall in mean body weight at the time of the first follow-up visit. However, the maximum decrease for any group was 4.2 lbs (less than 3 per cent of initial mean weight), which was observed in the patients treated with diet plus a placebo. In this group the early weight loss was not sustained, and the mean body weight remained close to 98 per cent of the initial weight throughout the subsequent four plus years. The initial weight loss was associated with a fall in both the mean fasting blood glucose level and in the glucose level observed one hour after the ingestion of 50 gm. of glucose. Subsequently both of these parameters of "control" rose progressively throughout the remainder of the study. Although the patients receiving tolbutamide or insulin (in fixed or varying dosages) also received dietary instruction, their initial weight loss was less than that observed in the placebo group, and no further reduction in mean body weight was observed during the subsequent four years. These data suggest that current efforts to achieve weight reduction in adult-onset diabetics are ineffective, at least as currently practiced in medical outpatient clinics.

The difficulties encountered in achieving weight reduction in chronically

obese nondiabetic subjects have been well documented, and the psychiatric implications of food to some patients are recognized; however, it is not certain that the experience with these chronically obese patients provides a meaningful index of the results that could be obtained in patients with adult-onset diabetes. Weight reduction remains the safest and cheapest means of achieving "control" sufficient to prevent hyperglycemic symptoms in the majority of adult-onset diabetics. Moreover, in the absence of significant weight reduction, the efficacy of other agents employed to lower blood glucose appears to be considerably reduced. The manner in which weight reduction is usually undertaken ensures failure in a large percentage of patients. Diet instruction is confusing and reflects the pseudoscience that presently surrounds the question of an appropriate diet for adult-onset diabetics.

Dietary instructions should be as simple as possible. The justification for modifications in dietary composition remains to be established: however, in the face of evidence of persistent abnormalities in plasma lipoproteins, we suggest modifications similar to those recently outlined by Fredrickson and his co-workers.[18] One of the factors that may contribute to the failure of diet therapy is the long period between follow-up visits—three-month intervals being not uncommon. The commercial weight reduction groups have demonstrated the value of reinforcement provided by frequent weight checks, and brief visits in which weight is checked by an office nurse can be helpful in many patients. Increased physical activity is often dismissed as of little benefit; however, for most 40 year old Americans a 15-minute daily walk would represent a significant increase in physical activity. A conscientious effort to increase physical activity is, in our hands, a significant factor in those patients in whom a reduction in weight and improved glucose levels are achieved. (It is of interest that a recent study, thus far reported only in abstract, suggests that the abnormal pattern of insulin secretion observed in markedly obese nondiabetics can be normalized by physical training without a decrease in body fat.[19])

Although there are many adult-onset diabetics in whom lifelong patterns of overeating and limited physical activity are practically immutable, the fact remains that serious efforts to encourage reduced caloric intake and increased physical activity have been abandoned by many physicians. There is little justification for the use of any pharmacologic agent in asymptomatic adult-onset diabetics until the possibility of attaining improved "control" by weight reduction has been given an adequate trial. It is now common practice, however, to begin sulfonylurea or phenformin treatment from the outset in asymptomatic adult-onset diabetics. One of the results of this practice is that the necessity for weight reduction is minimized in the patient's mind. Moreover, the patient is instructed that the oral hypoglycemic agents may provoke hypoglycemic symptoms which can be relieved by the ingestion of free carbohydrate. For many patients, who are understandably anxious about their newly diagnosed disease, this becomes a sanctioned invitation to unrestricted caloric intake. It is not surprising that significant weight reduction and maintenance of normal body weight are rarely achieved under these conditions, for both physicians and patients have come to view the nature and amount of the drug ingested as the major consideration in "controlling" adult onset diabetes.

Limited Effectiveness of Oral Hypoglycemic Agents

If the physician resorts to pharmacologic agents to prevent symptomatic hyperglycemia in adult-onset diabetics before demonstrating the necessity for their use, then one might hope that he would at least document the effectiveness of the agent employed. Since a fixed dosage of 1.5 gm. per day of tolbutamide was employed, the data derived from the UGDP study are not completely applicable. However, all the sulfonylureas have a relatively narrow effective dosage range, and the experience of this study is probably not too unrepresentative of the long-term efficacy of sulfonylureas in adult-onset diabetics in whom significant weight reduction is not achieved. In the UDGP study there was an initial improvement in fasting blood sugar and also in the blood glucose level observed one hour after a glucose load. This improved "control" paralleled the initial and transient weight loss which had occurred in these patients. Subsequently there was a progressive rise in mean fasting blood glucose and over the remaining four plus years it rarely differed from that of the group receiving a placebo by more than 15 mg. per cent (the mean values in both groups being persistently abnormal). The blood glucose level after a glucose load also tended to increase progressively in the patients treated with tolbutamide, and the mean value was rarely more than 20 mg. per cent different from that of the placebo group. At the end of four plus years the mean value in the group treated with tolbutamide was 244 mg. per cent, whereas the value for the placebo group was 251 mg. per cent. Thus, one may question whether the use of tolbutamide under these conditions significantly reduced the frequency with which *abnormal* blood glucose levels were present in these patients, or with which symptomatic hyperglycemia developed.

The mechanisms responsible for the development of refractoriness to sulfonylurea therapy in patients in whom an initial response is observed are still uncertain, and the data on its incidence are difficult to interpret.[20] Values ranging from 0.3 to 30 per cent have been reported, and there is a suggestion that the incidence increases with known duration of diabetes. The uncertainty results, in part, from differences in patient selection, in criteria for failure, and in the extent to which other factors such as weight gain and dosage were considered. Unfortunately physicians exercise little selectivity in administering sulfonylurea or biguanides to adult-onset diabetics, ignore the limitations imposed by obesity, and are slow to raise the question of efficacy. One can only guess at the number of patients presently receiving these drugs in whom their withdrawal would not significantly alter the daily fluctuations in blood glucose levels. Our own experience would suggest that it represents a significant fraction of the patients who have received the drug for a prolonged period and in whom obesity persists.

In general, both physicians and patients are reluctant to stop oral hypoglycemic therapy once it has been instituted. In many instances random blood glucose values of 200 to 300 mg. per cent are observed over a period of months to years before the physician reluctantly concludes that the drug has become ineffective. The usual course under these circumstances is to resort to another sulfonylurea in the hope of finding one that is "effective," and often to combine this with a biguanide. The pernicious aspect of the current misuse of the sulfo-

nylureas and the biguanides is that many patients are subjected to the expense and potential hazard of long-term treatment to attain a relatively limited goal—freedom from hyperglycemic symptoms—while the agents are used under conditions in which their efficacy is restricted and is only rarely adequately assessed.

The foregoing comments should not be misinterpreted. There are a number of adult-onset diabetics in whom the use of the sulfonylureas can produce further improvement in the range of fluctuations of blood glucose over that resulting from the correction of obesity. These agents may also be effective in some nonobese adult-onset diabetics. We do not eschew the use of sulfonylureas in efforts to prevent symptomatic hyperglycemia, or to achieve an approximation of normal fluctuations in blood glucose. In both instances, however, the consequences of effective weight reduction should first be demonstrated if obesity is present. If the addition of a pharmacologic agent is required, the relative merits either of insulin or of a sulfonylurea must be considered. We do not believe that the biguanides have an established place in the treatment of diabetics.

Many physicians are reluctant to accept the fact that the sulfonylureas and the biguanides are not appropriate agents in circumstances in which rapid correction of the metabolic abnormalities is required. An obvious instance is when ketonemia develops either in association with an acute infection or following the institution of therapy for an unrelated disease that requires the use of agents that can impair endogenous insulin secretion and/or decrease its apparent effectiveness. In these circumstances insulin is indicated, since neither the sulfonylureas nor the biguanides provide significant protection against the development of ketoacidosis. Even in the more common situation in which the previously untreated patient presents with marked polydipsia, polyuria, and weight loss without ketonemia, one cannot predict with any certainty whether the patient will respond to sulfonylurea or biguanide therapy. Under these circumstances, and particularly if there is an associated illness that predisposes to dehydration, it is wiser to use insulin for the acute correction of hyperglycemia and the relief of symptoms. Nonetheless, many physicians attempt trials at treatment with the sulfonylureas or the biguanides with a resulting delay in effective therapy that in some instances may contribute to the development of hyperglycemic nonketotic coma.

The use of insulin to achieve acute improvement does not imply that the patients will necessarily require exogenous insulin once they have been stabilized for a significant period. When there is a demonstrated requirement for the addition of a pharmacologic agent to correct symptomatic hyperglycemia, there is a curious reluctance to employ insulin in the management of adult-onset diabetics. This stems, in part, from the misconception that these patients are invariably insulin hypersecretors and that insulin resistance is a major factor in the pathogenesis of this syndrome. The bulk of the present evidence (which Kipnis has admirably reviewed[21]) clearly indicates that most adult-onset diabetics exhibit an impaired insulin secretory mechanism when compared with appropriately matched age, sex, and weight groups. Moreover, although obesity in both the normal and diabetic individual is associated with an apparent decrease in the biologic effectiveness of insulin, the diabetic state per se does not appear to be associated with any significant degree of insulin antagonism (if one excludes specific circumstances such as

ketoacidosis). Insulin remains the preferred pharmacologic agent because of its assured and continued efficacy and its protective value in circumstances in which acute impairment of endogenous insulin secretion and/or effectiveness may arise. Since 1972 there have been improvements in the purity of the commercial insulin preparations available, as the result of the application of methods developed to separate insulin, pro-insulin, and related peptides. Preliminary data suggest that these newer preparations *may* significantly reduce the immunologic responses to the administration of porcine and bovine insulin and the associated clinical problems.[22, 23] However, the present methods for the administration of insulin to adult-onset diabetics are far from ideal. We have no practical method of reproducing the timed relationship between food ingestion and insulin secretion that occurs in normals nor of selectively exposing the liver to the pulses of insulin that normally occur in portal venous blood after eating. Therefore, there is little reason to believe that present forms of insulin treatment reproduce normal physiology.

The primary advantage of the sulfonylureas is that they can be administered orally. The resulting convenience is a real but not necessarily compelling consideration when there is a manifest requirement for a pharmacologic hypoglycemic agent. The specific circumstances in a given patient should determine the choice, and while our own preference is to employ insulin, there is no good reason why a carefully controlled trial—preferably with one of the shorter acting sulfonylureas—should not be undertaken. The physician should, however, consider the possibility that contraindications to the use of sulfonylureas may exist (e.g., renal impairment or liver disease) and that sulfonylurea therapy may influence the metabolism of other pharmacologic agents (e.g., bishydroxycumarin and sulfonamides). The limitations of our knowledge concerning the role of insulin deficiency in certain situations lead us to prefer the use of insulin in patients with manifest symmetrical peripheral neuropathy with or without associated chronic foot ulcers, and in individuals in whom repeated skin infections or poorly healing surgical wounds are present. However, it must be admitted that this is clearly a prejudice on our part.

Hazards of Treatment with Sulfonylureas

Insulin or sulfonylurea therapies are not without hazard. With insulin the major concerns are hypoglycemia and problems resulting from the administration of foreign protein(s). The safety of treatment with the sulfonylureas is, however, the point most fiercely disputed at the moment. It should be apparent from the initial section of this discussion that we have serious reservations about the conclusions that can be drawn from any of the published clinical studies, irrespective of the elegance of the statistical methods employed to deal with their inherent deficiencies. A causal relationship between the treatment prescribed in the UDPG study and the subsequent clinical course of these patients would be difficult to establish on the basis of the information available. The excess cardiovascular mortality observed in the groups treated with tolbutamide and phenformin cannot be dismissed, since the manner in which these agents were

employed mirrors the misuse of these agents in common practice. If subsequent data provided by the UDPG group provide evidence of an unusual form of coronary artery disease in the patients treated with tolbutamide and phenformin, or of an unusual propensity to cardiac arrhythmias, to pulmonary emboli, or to shock in the patients who died of cardiovascular disease, the case may be strengthened. However, although we feel that the sulfonylureas have a limited role in the treatment of adult-onset diabetes, we would not abandon their use on the basis of the findings of the UDPG study. Nevertheless, this study has served the useful purpose of reminding physicians that the use of sulfonylureas and biguanides is not without hazard, and that as with any pharmacologic agent, the possibility of unanticipated effects must be considered.

Hypoglycemia and hypersensitivity reactions have been the major problems encountered in the use of the sulfonylureas. Hypoglycemia resulting from these drugs can be prolonged and may be fatal; this is particularly true of long acting compounds such as chlorpropamide. Many of the reported instances have resulted from the unwarranted administration of this agent to patients with impaired renal function.[24] In addition, it has been recognized that chlorpropamide can induce a syndrome characterized by hyponatremia, impaired mental function, and evidence of inappropriate antidiuretic hormone activity.[25] The pernicious aspect of this syndrome is that in elderly patients (in whom it has been most frequently observed) the impaired mental function could easily be attributed to other causes. There is little reason to believe that the effects of the sulfonylureas are restricted to the pancreatic β-cells. Specific compounds have been shown to alter thyroid function,[26] to modify adenyl cyclase activity in cardiac muscle,[27] to augment antidiuresis,[25] and to alter lipolytic activity in isolated adipose tissue.[28] However, with the exception of the UGDP study, the reported incidence of serious problems resulting from the use of the shorter acting sulfonylureas has been remarkably low. Nonetheless, the prolonged administration of sulfonylureas to adult-onset diabetics does entail an obvious risk. As with any pharmacologic agent, this risk must be justified in terms of the indications for its use, and is not acceptable unless the agent is demonstrated to be effective.

Why Do We Use the Biguanides?

As we have previously mentioned, we find it difficult to justify a role for the biguanides in the treatment of diabetics and would discourage their use. It is doubtful that these agents would be employed at all if it were not for the fact that they can be administered orally. While there are gaps in our knowledge of the manner in which insulin and the sulfonylureas lower blood glucose levels in diabetics, there is some reassurance that these effects are mediated, in part, by the correction of metabolic abnormalities resulting from an altered insulin secretory mechanism. Whether the long-term effects of the sulfonylureas result primarily from an action on the pancreatic β-cells is a point that is difficult to document, but the ability of these agents to stimulate insulin secretion in adult-

onset diabetics in whom they are effective is undisputed. In contrast, the manner in which phenformin lowers blood glucose in human diabetics, or in animals with alloxan diabetes, remains an enigma, but the fragmentary data available are not reassuring. An effect on insulin secretion has been excluded, although some residual endogenous insulin secretion is necessary for phenformin to be effective in lowering blood glucose. Kruger et al. have reported that phenformin impairs intestinal glucose absorption in man;[29] this compound also increases peripheral glucose utilization, albeit with an increased rate of lactate production.[30] The applicability of data derived from other species must be questioned because of the marked species variation in susceptibility to the hypoglycemic effects of phenformin. Thus, Kreisberg and associates dispute any effect of phenformin on decreasing hepatic glucose production or release in man.[30] However, at high concentrations phenformin does inhibit gluconeogenesis in isolated perfused rat liver.[30] In none of the isolated tissues in which the effects of phenformin have been examined is there clear evidence that phenformin restores a pattern of metabolism resembling that observed in the animal with a normal insulin secretory mechanism.

More to the point, biguanides are ineffective in the prevention of keto-acidosis, and there is no evidence that they have the assured efficacy of insulin in the management of acute symptomatic hyperglycemia. It is obviously not a suitable agent to use in those patients in whom a serious effort to achieve a normal range of blood glucose fluctuation is undertaken with the aim of correcting the underlying derangements in tissue metabolism that may contribute to the pathogenesis of the late complications. In patients in whom efforts at weight reduction have failed to remove the threat of symptomatic hyperglycemia, biguanides have no obvious advantage over insulin or the sulfonylureas (unless one wishes to view its effects on glucose absorption as an advantage). There is thus no obvious requirement for biguanides in the treatment of adult-onset diabetes, unless one will accept its use as an adjuvant to ineffective treatment with sulfonylureas. Since suitable alternatives are available, the justification for the additional risk entailed in this practice escapes us. The UDPG study reported a significant excess cardiovascular mortality in the groups treated with phenformin, but again the causal nature of this relationship is difficult to establish. However, there remains the distinct possibility that phenformin may represent a pharmacologic hazard in a group of patients who tend to develop general or local circulatory insufficiency. We believe this may contribute to the association between phenformin administration and the development of clinical lactic acidosis.[31]

Lactic Acidosis

The pathogenesis of lactic acidosis in those instances in which there is no obvious evidence of local tissue hypoxia is poorly understood. However, it is clear that in many tissues the rate of lactate production under normal conditions is in

a range that represents only a small fraction of the tissues' total capacity. In many tissues the rates of conversion of glucose to pyruvate and lactate are kept at a small fraction of total capacity by chemical signals generated as a consequence of the operation of the Krebs cycle and the electron transport system in which oxygen is the final acceptor. The effect of anoxia on the rate of lactate production in a tissue such as muscle results from a decrease in the signals which are usually generated as a consequence of respiration and an increase in glycolysis. Under these conditions the end product of glycolysis appears primarily as lactate, since a secondary consequence of impaired respiration is an increase in the cytoplasmic free NADH/NAD ratio, which is one of the factors determining the ratio of lactate/pyruvate in the cytoplasm. There is no doubt that in lactic acidosis, as in diabetic ketoacidosis, the rate of production of a normal product can be increased to levels that threaten the organism's existence. Lactate released into the circulation by other tissus is removed in large part by the liver, where it is utilized to a considerable degree for the resynthesis of glucose. The only value of this simplistic outline is to stress the point that factors that permit the expression of the tremendous latent capacity for lactate production in many tissues, or which impair the capacity of the liver to dispose of lactate, may eventuate in lactic acidosis. It is well established in adult-onset diabetics that chronic phenformin administration results in significant elevation of blood lactate concentrations. While in most patients the levels observed give little cause for concern, the effect does appear to be dose related.[32] There is, therefore, the possibility that at sufficiently high concentrations phenformin might induce lactic acidosis in humans either by increasing peripheral lactate production or by decreasing hepatic utilization, or both. This would appear to be the case since there are well documented instances in which phenformin was taken for suicidal purposes, with the subsequent development of lactic acidosis.[33]

The biguanides are unlikely to be the sole cause of the increased frequency of lactic acidosis in diabetics, since this syndrome has been observed in patients who are not receiving these drugs. Adult-onset diabetics are, as a group, individuals at increased risk to the development of a number of acute conditions which may produce local circulatory changes conducive to the development of either increased lactate production or impaired disposition. It seems difficult to exclude the possibility that, under these circumstances, the presence of biguanides may potentiate the development of lactic acidosis. The efforts to exclude this possibility are not totally convincing; thus, the failure of biguanides to potentiate markedly the rise in blood lactate in rats exposed to low oxygen tensions ignores the relative insensitivity of this animal to the effects of these compounds. We find ourselves in agreement with Oliva, who concluded: "It remains possible that the association of phenformin and lactic acidosis is coincidental since lactic acidosis may occur in diabetic subjects not taking phenformin, as well as in non-diabetic subjects. The weight of the indirect evidence, however, strongly suggests that phenformin plays a causal or contributory role in the production of lactic acidosis."[31] It is interesting that the only death specifically ascribed to lactic acidosis in the UDPG study occurred in a patient in the group receiving phenformin.[2] In sum, since phenformin fills no unique requirement in the treatment of adult-onset diabetes, since its mode of action is uncertain but unlikely

to be corrective of derangements resulting from an impaired insulin secretory mechanism, and since its relationship to lactic acidosis is unsettled, there is no valid reason to employ it in these patients.

Summary

The present state of treatment for adult-onset diabetes is admittedly inadequate, except for the prevention of symptomatic hyperglycemia. The data derived from clinical studies and from experimental work provide no basis for excluding the possibility that normalization of blood glucose fluctuations may significantly modify the development and progression of diabetic complications. However, the value of this form of therapy has never been adequately tested, and its immediate aims are difficult to achieve with present methods. It is an approach that should be considered primarily in younger diabetics without evidence of irreversible pathology who are capable of making an informed commitment to this form of treatment.

In the majority of adult-onset diabetics the aim of therapy is of necessity restricted to the prevention of symptomatic hyperglycemia, and irrespective of the arbitrary assessments of "control" employed, most of these patients will have blood glucose levels which persistently fluctuate in the abnormal range. The use of any pharmacologic agent in this group of patients should be justified by excluding the possibility that reduced caloric intake and increased exercise will not remove the threat of symptomatic hyperglycemia.

In present practice the sulfonylureas and the biguanides are often used without adequate indication and under circumstances in which they are unlikely to be of any benefit. In addition, patients are exposed to the expense and potential hazard of prolonged treatment with these agents without adequate concern for their efficacy.

Insulin is the drug of choice when ketoacidosis threatens, or when an acute improvement in symptomatic hyperglycemia is required. In asymptomatic patients with a demonstrated requirement for a pharmacologic hypoglycemic agent, we believe insulin to be preferred, but a well controlled trial of a sulfonylurea is not necessarily contraindicated. Biguanides have no role in the treatment of diabetes mellitus.

References

1. The University Group Diabetes Program: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. I: Design, methods and baseline results. II: Mortality results. Diabetes *19* (Suppl. 2):747–830, 1970.
2. Knatterud, G. L., Meinert, C. L., Klimt, C. R., et al.: The University Group Diabetes Program: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. IV. A preliminary report on phenformin results. J.A.M.A. *217*:777–784, 1971.
3. Förster, H., Haslbeck, M., and Mehnert, H.: Metabolic studies following the oral ingestion of different doses of glucose. Diabetes *21*:1102–1108, 1972.

4. United States Department of Health, Education, and Welfare, Public Health Service, Division of Chronic Diseases: *Genetics and the Epidemiology of Chronic Diseases.* Washington, D.C., Government Printing Office, PHS Publication No. 1163, 1965, p. 113.
5. Winegrad, A. I.: Diabetic neuropathy. (Editorial.) New Eng. J. Med. *286*:1261–1262, 1972.
6. Warren, S., Le Compte, P. M., and Legg, M. A.: *The Pathology of Diabetes Mellitus.* Philadelphia, Lea & Febiger, 1966, pp. 200–201.
7. Hazzard, W. R., Goldstein, J. L., Schrott, H. G., et al.: Hyperlipidemia in coronary heart disease: Lipoprotein characteristics of a classification based on genetic analysis. J. Clin. Invest. *51*:43a–44a, 1972.
8. Fajans, S. S.: What is diabetes? Definition, diagnosis, and course. Med. Clin. N. Amer. *55*:793–805, 1971.
9. Chochinov, R. H., Ullyot, G. L. E., and Moorhouse, J. A.: Sensory perception thresholds in patients with juvenile diabetes and their close relatives. New Eng. J. Med. *286*: 1233–1237, 1972.
10. Chopra, J. S., Hurwitz, L. J., and Montgomery, D. A. D.: The pathogenesis of sural nerve changes in diabetes mellitus. Brain *92*:391–418, 1969.
11. Siperstein, M. D., Unger, R. H., and Madison, L. L.: Studies of muscle capillary basement membranes in normal subjects, diabetic and prediabetic subjects. J. Clin. Invest. *47*:1973–1999, 1968.
12. Kilo, C., Vogler, N., and Williamson, J. R.: Muscle capillary basement membrane changes related to aging and to diabetes mellitus. Diabetes *21*:881–905, 1972.
13. Østerby, R.: Diabetic glomerulopathy. A quantitative electron microscopic study of the initial phases, Diabetes: Proceedings of the Seventh Congress of the International Diabetes Federation, Buenos Aires, August 23–28, 1970 (International Congress Series No. 231). Edited by R. R. Rodriguez and J. Vallance-Owen. Amsterdam, Excerpta Medica, 1971, pp. 793–803.
14. Leuenberger, L., Cameron, D., Stauffacher, W., et al.: Ocular lesions in rats rendered chronically diabetic with streptozotocin. Ophthal. Res. *2*:189–204, 1971.
15. Goldner, M. G., Knatterud, G. L., and Prout, T. E.: The University Group Diabetes Program: Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. III. Clinical implications of the UGDP results. J.A.M.A. *218*: 1400–1410, 1971.
16. Grey, N., and Kipnis, D. M.: Effect of diet composition on the hyperinsulinemia of obesity. New Eng. J. Med. *285*:827–831, 1971.
17. Brunzell, J. D., Lerner, R. L., Hazzard, W. R., et al.: Improved glucose tolerance with high carbohydrate feeding in mild diabetes. New Eng. J. Med. *284*:521–524, 1971.
18. Levy, R. I., Fredrickson, D. S., Shulman, R., et al.: Dietary and drug treatment of primary hyperlipoproteinemia. Ann. Intern, Med. *77*:267–294, 1972.
19. Björntorp, P., Fahlén, M., Grimby, G., et al.: The effects of physical training and acute physical work on plasma insulin in obesity. Europ. J. Clin. Invest. *2*:274, 1972.
20. Krall, L. P.: The oral hypoglycemic agents. *In* Marble, A., White, P., Bradley, R. F., and Krall, L. P. (eds.): *Joslin's Diabetes Mellitus.* Philadelphia, Lea & Febiger, 1971, p. 315.
21. Kipnis, D. M.: Insulin secretion in normal and diabetic individuals. Advances Intern. Med. *16*:103–134, 1970.
22. Schlichtkrull, J., Brange, J., Christiansen, A. H., et al.: Clinical aspects of insulin-antigenicity. Diabetes *21*(Suppl. 2):649–656, 1972.
23. Root, M. A., Chance, R. E., and Galloway, J. A.: Immunogenicity of insulin. Diabetes *21* (Suppl. 2):657–660, 1972.
24. Seltzer, H. S.: Drug-induced hypoglycemia: A review based on 473 cases. Diabetes *21*:955–966, 1972.
25. Weissman, P. N., Shenkman, L., and Gregerman, R. I.: Chlorpropamide hyponatremia: Drug-induced inappropriate antidiuretic-hormone activity. New Eng. J. Med. *284*: 65–71, 1971.
26. Brown, J., and Solomon, D. H.: Effects of tolbutamide and carbutamide on thyroid function. Metabolism *5*:813–819, 1956.
27. Lasseter, K. C., Levey, G. S., Palmer, R. F., et al.: The effect of sulfonylurea drugs on rabbit myocardial contractility, canine purkinje fiber automaticity, and adenyl cyclase activity from rabbit and human hearts. J. Clin. Invest. *51*:2429–2434, 1972.
28. Stone, D. B., Brown, J. D., and Cox, C. P.: Effect of tolbutamide and phenformin on lipolysis in adipose tissue in vitro. Amer. J. Physiol. *210*:26–30, 1966.

29. Kruger, F. A., Altschuld, R. A., Hallobough, S. L., et al.: Studies on the site and mechanism of action on phenformin. II. Phenformin inhibition of glucose transport by the rat intestine. Diabetes *19*:50–52, 1970.
30. Kreisberg, R. A., Owen, W. C., and Siegal, A. M.: Hyperlacticacidemia in man: Ethanol-phenformin synergism. J. Clin. Endocrinol. *34*:29–35, 1972.
31. Oliva, P. B.: Lactic acidosis. Amer. J. Med. *48*:209–225, 1970.
32. Craig, J. W., Miller, M., Woodward, H., et al.: Influence of phenethylbiguanide on lactic, pyruvic, and citric acids in diabetic patients. Diabetes *9*:186–193, 1960.
33. Davidson, M. B., Bogarth, W. R., Challoner, D. R., et al.: Phenformin hypoglycemia and lactic acidosis. New Eng. J. Med. *275*:886–888, 1966.

IN VITRO EFFECTS OF TOLBUTAMIDE ON THE SYMPATHO-ADRENAL SYSTEM. Chung-Yi Hsu, Gary Brooker, Michael J. Peach, and Thomas C. Westfall, Charlottesville, Va. (Introduced by Joseph Larner,* Charlottesville, Va.)

High concentrations of tolbutamide (6.6 mM and 10 mM) provoked massive discharge of catecholamines from the perfused cat adrenal gland. Differential estimation of secreted catecholamines revealed preferential release of epinephrine by these concentrations of tolbutamide. At concentrations within the therapeutically effective range (0.1 to 1.0 mM), tolbutamide depressed basal, nicotine-, KCl-, and glucagon-induced catecholamine release from the cat adrenal glands and nicotine- and KCl-, induced ^{3}H-norepinephrine release from perfused guinea pig hearts in a dose dependent manner. This inhibitory action of tolbutamide was quickly reversed following removal of the drug from the perfusion solution. Prolonged perfusion for 20 min or longer with tolbutamide resulted in a sustained depression of catecholamine secretion from the cat adrenal. Withdrawal of the drug caused catecholamine secretion to reach a steady state level which was higher than the level observed just before tolbutamide perfusion was begun. This rebound phenomenon was occasionally manifested by an outburst of catecholamine release. Carboxytolbutamide, the major metabolite of tolbutamide, showed no effect on basal as well as stimulated catecholamine secretion. If tolbutamide acts similarly in vivo on the sympathoadrenal system, then the detailed concentration versus time relationships of tolbutamide could be of considerable importance in its pharmacological action and possible toxicological effects.

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SCIENCE

Inhibition of Catecholamine Release by Tolbutamide and Other Sulfonylureas

Chung-Yi Hsu, Gary Brooker, Michael J. Peach and Thomas C. Westfall

Inhibition of Catecholamine Release by Tolbutamide and Other Sulfonylureas

Abstract. *Tolbutamide and other sulfonylureas inhibited spontaneous and nicotine-induced release of catecholamines from the perfused cat adrenal gland and nicotine-induced release of [^{3}H]norepinephrine from isolated guinea pig hearts. Of the sulfonylureas tested, the order of potency of this inhibitory effect paralleled the hypoglycemic action. These results raise the possibility that the inhibition of the sympathoadrenal system may contribute in part to the hypoglycemic action of sulfonylureas.*

Sulfonylureas are oral hypoglycemic agents which have been utilized extensively in the treatment of adult-onset diabetes mellitus. The primary action of this group of agents has been attributed to the direct stimulation of pancreatic beta cells to release insulin (*1*). However, the poor correlation between their insulin-releasing effect and diabetic control has led to speculation of extrapancreatic actions of sulfonylureas (*2*). Herein we report an effect of tolbutamide and other sulfonylureas on the spontaneous and nicotine-induced release of catecholamines from isolated cat adrenal glands (*3*) and on nicotine-induced release of [^{3}H]norepinephrine ([^{3}H]NE) from isolated guinea pig hearts (*4*). These observations suggest that sulfonylureas have a direct inhibitory action on the sympathoadrenal system.

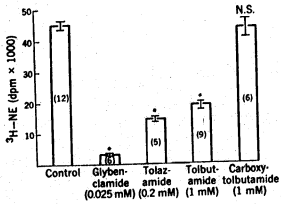

Fig. 1. The effects of four sulfonylureas on the release of [^{3}H]NE induced by nicotine in isolated guinea pig hearts, measured in disintegrations per minute. Release of [^{3}H] was stimulated by a single injection of nicotine. Five minutes before and after injection, one of the sulfonylureas or the vehicle used to dissolve sulfonylureas (control) was present. Asterisk denotes difference from control is significant at $P < .001$. *N.S.*, not significant.

Isolated cat adrenal glands were retrogradely perfused with phosphate-buffered Locke's solution, and the adrenal catecholamine secretion was monitored by a modification of the procedure of Robinson and Watts (*5*). This experimental procedure has been reported in detail previously (*6*). The effect of tolbutamide on the spontaneous secretion of catecholamines was observed by perfusing the glands with Locke's solution containing tolbutamide (0.1, 0.3, or 1 m*M*) for 5 minutes. To study the effect of sulfonylureas on the nicotine-induced release of catecholamines, each gland was stimulated twice by perfusion with nicotine ($10^{-6}M$) for 1 minute. Five minutes before and 5 minutes after the first stimulation by nicotine, the adrenal was perfused with either tolbutamide (0.3 or 1 m*M*) or tolazamide (0.2 m*M*). The administration of nicotine was repeated 30 minutes after termination of the perfusion with sulfonylureas and served as a control response.

Endogenous norepinephrine stores in isolated guinea pig hearts were prelabeled with [^{3}H]NE. Hearts were stimulated to release [^{3}H]NE by single injections of nicotine (4×10^{-7} mole) 20 minutes after [^{3}H]NE labeling. The perfusate effluents from the hearts were continuously collected and analyzed for [^{3}H]NE by liquid scintillation spectrometry (*7*). To study the effect of sulfonylureas on nicotine-induced release of myocardial [^{3}H]NE, sulfonylureas (tolbutamide, 1 m*M*; carboxytolbutamide, 1 m*M*; tolazamide, 0.2 m*M*; glybenclamide, 0.025 m*M*) were individually added to the perfusion fluid from 5 minutes before to 5 minutes after the injection of nicotine.

The spontaneous output of catecholamines from the cat adrenal gland usually became stable 1 hour after the initiation of perfusion with Locke's solution. Tolbutamide (0.3 or 1 m*M*) caused a decline in spontaneous catecholamine output (see Table 1). This inhibitory effect of tolbutamide was reversible. Nicotine-induced release of adrenal catecholamines was also suppressed by tolbutamide. When adrenal glands were stimulated consecutively at 30-minute intervals by the same dose of nicotine ($10^{-6}M$ for 1 minute), the response to the second stimulation was

Table 1. Effect of tolbutamide and tolazamide on spontaneous and nicotine-induced release of total catecholamines from isolated cat adrenal glands. Each gland served as its own control. The data are expressed as percent of control. The number of glands studied is indicated in parentheses after the mean ± S.E.M.

Drugs (m*M*)	Catecholamines released (% of control)	
	Spontaneous*	Nicotine-induced†
Tolbutamide		
0.1	95 ± 2 (3)	
0.3	72 ± 6 (5)‡	77 ± 5 (4)‡
1.0	62 ± 8 (5)‡	56 ± 10 (7)‡
Tolazamide		
0.2		51 ± 7 (3)‡

* [Rate of spontaneous output in the presence of sulfonylurea (ng/min) divided by the rate of spontaneous output in the absence of sulfonylurea (ng/min)] × 100. Control spontaneous output was 230 ± 30 ng/min. † [Nicotine-induced release in the presence of sulfonylurea (ng) divided by nicotine-induced release in the absence of sulfonylurea (ng) × 100. Control nicotine-induced release was 12,210 ± 1,330 ng. ‡ Signifiant at $P < .01$

only 60 to 70 percent of the initial response (data not shown). When tolbutamide (0.3 or 1 m*M*) was present only during the initial exposure to nicotine, the second response to nicotine was then greater than the first. Tolazamide (0.2 m*M*) exerted a similar inhibitory action (see Table 1).

Nicotine-induced release of [^{3}H]NE from the isolated guinea pig hearts was also inhibited by several sulfonylureas (tolbutamide, tolazamide, and glybenclamide). The order of potency in inhibiting catecholamine release by these sulfonylureas was glybenclamide > tolazamide > tolbutamide (Fig. 1). Carboxytolbutamide, a major metabolite of tolbutamide without hypoglycemic action (*8*), showed no inhibitory effect on induced [^{3}H]NE release.

In vivo studies have led to the postulate that sulfonylureas may possess a direct stimulatory action on the adrenal medulla (*9*). Since epinephrine release is increased by insulin-induced hypoglycemia (*10, 11*), the previous in vivo observations with sulfonylureas may be an indirect result of the hypoglycemia following insulin release. The present in vitro studies demonstrate that sulfonylureas act directly to inhibit the release of catecholamine from the feline adrenal medulla and from the adrenergic nerve terminals in guinea pig hearts. This effect of sulfonylureas was observed when catecholamine secretion was stimulated by nicotine or other secretagogues such as glucagon or KCl (*3, 4*). Pittman and Hazelwood selected doses of insulin and tolbutamide which caused similar degrees of hypoglycemia in chickens and found elevated plasma epinephrine levels only in those animals in which the hypoglycemia was induced by insulin (*11*). This absence of epinephrine release in response to tolbutamide-induced hypoglycemia suggests that this drug probably inhibits adrenal catecholamine release in intact animals.

In general the metabolic effects of catecholamines oppose the actions of insulin (*12*). Physiological concentrations of catecholamines are known to inhibit insulin release (*13*). It was interesting to note that for the two sulfonylureas tested in cat adrenal glands and for the four tested in guinea pig hearts, the order of potency in inhibiting catecholamine release paralleled their hypoglycemic potency (*1, 9*).

Results from the present experiments raise the possibility that this extrapancreatic action on the sympathoadrenal system may contribute in part to the hypoglycemic effect of sulfonylureas.

CHUNG-YI HSU, GARY BROOKER
MICHAEL J. PEACH
THOMAS C. WESTFALL
Department of Pharmacology, School of Medicine, University of Virginia, Charlottesville 22903

References and Notes

1. E. F. Pfeiffer, K. Schöffling, H. Ditschuneit, R. Zeigler, in *Oral Hypoglycemic Agents*, G. D. Campbell, Ed. (Academic Press, New York, 1969), p. 39.
2. J. M. Feldman and H. E. Lebovitz, *Arch. Intern. Med.* **123**, 314 (1969).
3. C.-Y. Hsu, *Fed. Proc.* **33**, 524 (1974).
4. ———, T. C. Westfall, M. J. Peach, *Pharmacologist* **16**, 191 (1974).
5. R. L. Robinson and D. T. Watts, *Clin. Chem.* **11**, 986 (1965); R. L. Robinson, *J. Pharmacol. Exp. Ther.* **156**, 252 (1967).
6. M. J. Peach, F. M. Bumpus, P. A. Khairallah, *J. Pharmacol. Exp. Ther.* **176**, 366 (1971).
7. T. C. Westfall and M. Brasted, *ibid.* **182**, 409 (1972).
8. J. M. Feldman and H. E. Lebovitz, *Diabetes* **18**, 529 (1969).
9. A. Bänder, *Aust. N.Z. J. Med.* **1** (Suppl. 2), 22 (1971); W. E. Duling, E. H. Morley, J. E. Nezamis, *Proc. Soc. Exp. Biol. Med.* **93**, 132 (1956).
10. U. S. von Euler and R. Luft, *Metabolism* **1**, 528 (1952); A. Goldfien, M. S. Zileli, R. H. Despointes, J. E. Bethune, *Endocrinology* **62**, 749 (1958).
11. R. P. Pittman and R. L. Hazelwood, *Comp. Biochem. Physiol.* **45A**, 141 (1973).
12. J. W. Ensinck and R. H. Williams, in *Handbook of Physiology*, sect. 7, vol. 1, *Endocrine Pancreas*, D. E. Steiner and N. Freinkel, Eds. (Williams & Wilkins, Baltimore, 1974), p. 665.
13. D. Porte, Jr., and R. P. Robertson, *Fed. Proc.* **32**, 1792 (1973).
14. We thank Drs. W. E. Duling and K. Gundersen of the Upjohn Company for supplying the sulfonylureas used in these studies. Supported by NIH-NS 10260, PHS NHLI HL 12706, NIH P17 AM17042-01, and Hoffmann-LaRoche, Inc.

27 September 1974

A STUDY OF THE CHRONIC EFFECTS OF TOLBUTAMIDE IN THE RHESUS MONKEY

FDA # 72-114

By:

Jayme Borensztajn, M.D., Ph.D.
Assistant Professor
Department of Pathology
University of Chicago

Arthur Rubenstein, M.D.
Professor
Department of Medicine
University of Chicago

Godfrey S. Getz, M.D., Ph.D.
Professor
Departments of Pathology
and Biochemistry
University of Chicago

Chung Hsin Ts'ao, Ph.D.
Assistant Professor
Department of Pathology
Northwestern University

Seymour Glagov, M.D.
Professor
Department of Pathology
University of Chicago

Robert W. Wissler, Ph.D., M.D.
Donald N. Pritzker Professor
Department of Pathology
University of Chicago

February 15, 1975

A. INTRODUCTION

The aim of this project was to study the effects of chronic administration of tolbutamide to normal Rhesus monkeys maintained on an atherogenic diet. The rationale for carrying out such a project was derived from the observations of the University Group Diabetes Project which suggested that diabetic patients treated with tolbutamide had an increased incidence of fatal events related to myocardial infarction when compared to patients managed on placebo or insulin (1). These studies raised the possibility that tolbutamide administration might accelerate the development of atherogenic processes.

To test this possibility the Rhesus monkey model was chosen because of ample evidence showing that atherosclerosis can be produced in this species by simple dietary manipulations, and that the qualitative aspects of the resulting lesions closely resemble atherosclerosis in man.

The "Average American Table Prepared Diet" was used for this study because it was considered to be better to use a relatively mild (and slow) atherogenic dietary regimen if one wanted maximum opportunity for a drug to show either a positive or negative effect. Furthermore, it was thought best to work with dietary ingredients similar to those that people in the U.S.A commonly consume. Three chronic (2 year) experiments conducted in this laboratory over a ten year period have indicated that this ration was well accepted by the Rhesus monkey and consistently resulted in mild to moderate atheromatous change with blood lipid levels not too far above levels commonly found in people consuming this type of diet.

Study of coronary artery lesions

The coronary artery sections were taken at nine predetermined sites in the main coronary artery (Figure G.6.) and were sectioned on the freezing (CO_2) microtome and stained with Oil Red O for fat. The other nine adjoining sections that were obtained from the same sites were embedded in paraffin and stained by hematoxylin and eosin and Gomori trichrome aldehyde fuchsin. They revealed a very unexpected and disturbing trend; coronary artery lesions in the treee main coronary arteries were almost two times more frequent and almost exactly three times more severe in the tolbutamide-treated animals than in the control animals in relation to the amount of lipid deposited in the intima and media (Table G.6.).* The intimal proliferation noted in the coronary arteries of the tolbutamide tested animals was also somewhat more severe than in the controls but this difference was not statistically significant. Figure G.7. presents photomicrographs of average types of coronary lesions stained for lipids in paired animals. Lower and higher magnification in the same lesions shows the intimal proliferation and lipid deposition in sections of the two types of monkeys. Moderate intimal proliferation and lipid deposition in the intimas and innermost media can be seen in animals treated with tolbutamide.

Pancreatic islet evaluation

The pancreatic islets of those animals were carefully examined by means of two stains, the Gomori trichrome-aldehyde-fuchsin stain and the Gomori chrome alum hematoxylin stain. These histological preparations were made from three Bouin's fixed complete cross sections of the pancreas, taken from its tail, body and head.

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*The detailed microscopic evaluations for these coronary lesions as done independently by each pathologist are presented pair-by-pair in Appendix IV.

TABLE B.1.

PLAN OF THE EXPERIMENT IN RHESUS MONKEYS FED AVERAGE AMERICAN DIET WITH OR WITHOUT TOLBUTAMIDE

GROUP	NUMBER OF ANIMALS	DIET FED FOR A PERIOD OF 18 MONTHS
I	9 (7)[A]	AVERAGE AMERICAN DIET - 250 G/DAY
II	9 (7)	AVERAGE AMERICAN DIET AND TOLBUTAMIDE[B] 20 MG/KG/DAY - PAIR FED

A. THE EXPERIMENT WAS STARTED WITH 9 ANIMALS PER GROUP, BUT 2 ANIMALS DIED AT 14 MONTHS AND THEIR CONTROLS WERE AUTOPSIED AT THE SAME TIME.

B. TOLBUTAMIDE - UPJOHN COMPANY

56-592 O - 75 - pt. 28 - 21

TABLE G.6.

MICROSCOPIC FINDINGS IN CORONARY ARTERIES OF RHESUS MONKEYS FED AVERAGE AMERICAN DIET WITH OR WITHOUT TOLBUTAMIDE

GROUP	NO. OF ANIMALS	DIET	FREQUENCY*	SEVERITY**
I	9 (7)	AVERAGE AMERICAN DIET	31 ± 6.3	0.18 ± 0.03
II	9 (7)	AVERAGE AMERICAN DIET AND TOLBUTAMIDE	65 ± 4.5	0.56 ± 0.06
			$p < 0.01$	$p < .001$

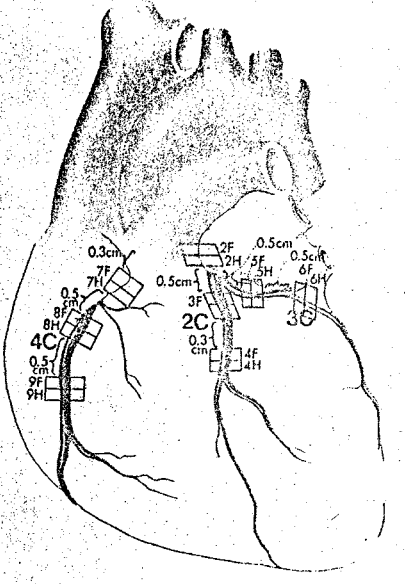
* FREQUENCY DATA WERE OBTAINED BY CALCULATING MEAN AND STANDARD ERROR FROM INDIVIDUAL PERCENTAGE VALUES FROM EACH SITE SAMPLED.

** SEVERITY WAS OBTAINED BY GRADING EACH SECTION EXAMINED FROM 0 TO 4+ AND THEN MEAN AND STANDARD ERROR WERE CALCULATED.

FIGURE G.6.

THE SAMPLING OF THE CORONARY ARTERIES

1C ORIFICE OF THE RIGHT AND LEFT CORONARY ARTERY



2C ANTERIOR DESCENDING BRANCH OF THE LEFT CORONARY ARTERY

3C CIRCUMFLEX BRANCH OF LEFT CORONARY ARTERY

4C RIGHT CORONARY ARTERY

MICROSCOPIC FINDINGS IN CORONARY ARTERIES OF RHESUS MONKEYS
FED AVERAGE AMERICAN DIET WITH OR WITHOUT TOLBUTAMIDE

(Combined Readings)

MAJOR MICROSCOPIC FINDINGS	ANIMALS	I AVERAGE AMERICAN DIET SECTIONS										II AVERAGE AMERICAN DIET WITH TOLBUTAMIDE SECTIONS									
		1	2	3	4	5	6	7	8	9	TOTAL	1	2	3	4	5	6	7	8	9	TOTAL
LIPID DEPOSITION	1	0.5	0.5	0.5	0	0	0	0	0	0.5	4/9	0.5	0.5	0.5	0	1.0	1.0	0.5	0	0.5	7/9
	2	1.0	0	0	0	0	0	0	0	0	1/9	0.5	0.5	0.5	0.5	0	0.5	0	0.5	0	6/9
	3	1.0	0.5	0	0.5	0.5	0	0	0	0	4/9	0.5	0.5	0	0	0	0.5	0	0	0	3/9
	4	0.5	0.5	0	-	0.5	0	0.5	0.5	-	5/7	0.5	0	0.5	0.5	0.5	0	1	0	0	5/9
	5	0	0	0	0	0	-	0	0	0.5	1/8	1.0	1.0	0	-	1.0	0.5	0.5	-	0	5/7
	6	0.5	0.5	-	-	0	0	0	0.5	0	3/7	0.5	2.0	2.0	0	2.0	2.0	2.0	0.5	1.0	8/9
	7	0	0	0	0	0	0	0.5	0	0	1/9	1.0	2.0	0.5	0.5	0.5	1.0	0.5	0.5	0	8/9
	TOTAL	5/7	4/7	1/6	1/5	2/7	0/6	2/7	2/7	2/6	19/58	7/7	6/7	5/7	3/6	5/7	6/7	5/7	3/6	2/7	42/61

% of involvement (Frequency & Severity) = 31 ± 6.3 = 65 ± 4.5

$p < 0.001$

TOLBUTAMIDE INDUCED ALTERATION OF LEFT VENTRICULAR FUNCTION IN DIABETES. C.F. Wu.* B. Haider. S.S. Ahmed. H. A. Oldewurtel.* M.M. Lyons.* and T.J. Regan.**
Department of Medicine , New Jersey Medical School, Newark, New Jersey.

The cardiovascular effects of chronic sulfonylurea use are in dispute. We have examined this question in an animal model of mild alloxan diabetes in which we have previously observed that left ventricular function is abnormal during enhanced preload or afterload but is normal at rest. A group of 7 male alloxan diabetics with fasting normoglycemia was followed an average of 12 months and compared with a diabetic group equivalent in intensity and duration but treated with tolbutamide soon after the onset of diabetes (N=7). The dose was 250 mg/day at meal time, achieving peak plasma levels of 42±3.1 µg/ml without subsequent hypoglycemia. These were compared with a group of 8 healthy control dogs. After a year, left ventricular function was assessed in the intact anesthetized state using indicator dilution. Heart rate and aortic pressure were comparable in the 3 groups. The treated diabetics had a significantly higher LVEDP 12.5±1.4 mm.Hg than the untreated diabetics at 6.1±0.8 mm Hg (P .002), while end-diastolic and stroke volume were similar. The end-diastolic pressure/volume ratio was significantly higher than controls in the tolbutamide group at 0.14±.03 vs .07±.01 (P .05), but was unchanged in untreated diabetics. Enhanced stiffness of myocardium in treated diabetics appeared to be correlated with greater accumulation of PAS positive material in the interstitium. Thus, tolbutamide at doses which improved glucose tolerance in diabetics was associated with reduced left ventricular function and altered morphology.

Clinical Research Vol. XXII, #3 April 1975
Abstract for presentation at American Federation for Clinical Research, May 3, 1975 Atlantic City, N.J.
pp 215A

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

MAY 30 1975

Senator Gaylord Nelson
Chairman, Monopoly Subcommittee
United States Senate
Washington, D.C. 20510

Dear Senator Nelson:

This is in further response to your request of April 1, 1975 for information concerning seven potential criminal prosecutions based on false advertising charges which were forwarded by the Food and Drug Administration (FDA) to the Justice Department, but in which prosecution was declined.

Upon a careful examination of our records, it has been determined that of the seven cases you mentioned six cases dealt with drug advertising charges and the seventh with a company's failure to report certain "alarming" findings with respect to a drug. As requested, you will find enclosed FDA's letters of transmittal and the Department of Justice's negative responses, except that in the cases involving Wyeth Laboratories and the American Cyanamid Company, no letters reflecting the Department of Justice's declinations are available. In these two cases, the basis for the negative decision in each can be gleaned from subsequent correspondence in which FDA asks for reconsideration of the determinations.

For your convenience, also enclosed are summaries of five of the six cases, each of which makes reference to the firm name, date of referral, and the particular product involved. The sixth case, involving the Bristol-Myers Company, is so summarized in the first paragraph of FDA's letter of transmittal.

If we can be of further assistance in any way, please let us know.

Sincerely yours,

Robert C. Wetherell, Jr., Director
Office of Legislative Services

Enclosure

CASES CLOSED BY DECLINATION OR UNSATISFACTORY SETTLEMENT

Name of defendants or products: Wyeth Labs.
F.D.C. No.: 52677.
Date Referred to Dept. of Justice: 12–5–66.
Judicial District: E. Pa.
Problem: Dept. of Justice in Washington, D.C. declined prosecution on false and misleading advertising charges relating to the drug Serax because seizure resulted in correction and because FDA intended to publish new advertising regulation.

We recommended prosecution for the following reasons:

1. The defendant had been warned by a notice of hearing under 21 U.S.C. 335, which issued about six months prior to the publication of the ads involved in Count 2, against the use of false and misleading ads such as were involved in Count 2.

2. The ads involved in this prosecution were false and misleading as follows:

(a) the ads referred to a study, in support of a claim of effectiveness in geriatric patients, in which no proper controls were exercised, only a small portion (14%) of which were geriatric patients, and the dosage administered exceeded the dosage permitted by the approved New Drug Application labeling;

(b) the ads falsely claimed that the drug was over 90% effective;

(c) the ads recommended the drug for use in anxiety-linked depression, which use was not set forth in the approved New Drug Application Labeling;

(d) the ads failed to emphasize that the drug should be used cautiously by elderly patients because of the possibility of serious hypotensive reactions.

As a result of such false and misleading ads, physicians who relied on them could be led into an error of medical judgment in prescribing Serax for their patients.

Name of defendants or products: American Cyanamid Co.
F.D.C. No.: 53050.
Date Referred to Dept. of Justice: 11–7–66.
Judicial District: S. N.Y.
Problem: U.S. Attorney declined prosecution on advertising charges relating to aristocort tablets and Pathibamate tablets because law and regulations were vague and emissions of side effect and contraindication information in the ads were not sufficiently grave.

A letter of protest was sent by us on 11–6–68 explaining that the law and regulations were not vague and that the warning information omitted from the advertisements for the drugs was important for the physician to know in order to provide safe patient care. The ad relating to the aristocort tablets did not state that such tablets may produce such potentially serious side effects as acne, spontaneous fractures, aggravation of infection, psychotic disturbances, thromboembolism, gastrointestinal hemorrhage. The ad relating to the Pathibamate tablets did not state that hypotensive crisis, anuria, anaphylaxis and proctitis are possible side effects and that the tablets are contraindicated in cases of known hypersensitivity to meprobamate.

We did state in our protest letter that in view of the age of the case we would have to agree that it was unlikely that pressing this case to prosecution would improve the advertising practices of the defendant and of the industry.

Name of Defendant or Product: Rexar Pharmacal Co.
F.D.C. No.: 53053.
Date Referred to Dept. of Justice: 1–17–67.
Judicial District: E. N.Y.
Problem: Dept. of Justice in Washington, D.C. declined prosecution on advertising charges relating to Obetral tablets since the side effects we charged to be omitted were not believed to be required by the law but were only "precautions"; prosecution also declined on new drug charges against Oby-Rex capsules because of age of offenses and because factual situation was unattractive for criminal case.

A letter of protest was sent by us on 4–18–68 stating that the warning information omitted from the Obetrol advertisement and which was described as "Precautions" in the full disclosure labeling of the Obetrol tablets was in fact "side effect" information which was required by the law and regulations to be

set forth in the advertisement. The omitted warning information related to information that the physician needed to know, namely, that the drug should be used with caution in individuals with anorexia, psychopathic personality, history of homocidal or suicidal tendencies, and emotionally unstable individuals known to be susceptible to drug abuse.

With respect to the new drug charge on the Oby-Rex capsules and tablets we stated that such drug was a potent amphetamine mixture with well recognized hazards, which had not been shown or recognized to be safe in the 30 mg. dosage for which the drug was intended. To place such unproved dosage on the market in utter disregard of the new drug procedure was, we believed, a substantial violation of the law.

The Department of Justice replied to our letter of protest and stated that it remained of the opinion that prosecution was not feasible.

Name of Defendant or Product: Syntex Labs.
F.D.C. No.: 53222.
Date Referred to Dept. of Justice: 3–16–67.
Judicial District: New Jersey.

Problem: We had recommended prosecution on the basis that the labeling for Norinyl, an oral contraceptive drug, failed to bear adequate directions for use, and that the advertisements for such drug did not bear information relating to the side effects and contraindications of the drug as required by law. The Department of Justice in Washington declined prosecution with respect to the advertisements on the ground that the information omitted did not relate to side effects and contraindications as we alleged but instead to matters which were not so categorized in the approved New Drug Application labeling.

We protested this decision on the basis that Congress intended that the advertising provision of the law should apply to all matters relating to side effects and contraindications and not be restricted to fixed artificial categories of information under those headings.

The Department of Justice affirmed its decision on the advertising charges but did approve prosecution on charges of inadequate directions in the labeling of the drug, and forwarded the case to the U.S. Attorney for prosecution on this basis.

The U.S. Attorney declined prosecution because it appeared doubtful to him that we could prove that the labeling of the drug consisting of the Physician's Desk Reference monograph was substantially different from the approved New Drug Application labeling, and thereby establish that the drug failed to comply with the conditions for exemption from the requirement of adequate directions for use.

We protested this decision on the basis that some of the most vital safety information in the approved labeling had been omitted from the PDR monograph. The United States Attorney subsequently affirmed his decision against prosecution.

Name of Defendant or Product: Merck & Co.
F.D.C. No.: 54763.
Date Referred to Dept. of Justice: 3–21–68.
Judicial District: E. Pa.

Problem: We recommended prosecution based on defendant's failure to immediately report to FDA the defendant's findings with respect to the drug MK–665. We considered such findings to be "alarming" within the meaning of the NDA regulation and therefore findings which should be immediately reported because they disclosed the development of cancer in animals which had been tested with the drug.

The Department of Justice declined prosecution because it did not agree with our interpretation of the NDA regulation relating to immediate reports on "alarming findings."

Name of Defendant or Product: Warner-Lambert Pharm. Co.
F.D.C. No.: 53548.
Date Referred to Dept. of Justice: 2–15–68.
Judicial District: New Jersey.

Problem: We recommended prosecution on the basis that the labeling of the drug Peritrate was false and misleading and failed to bear adequate directions

for use, that such drug was a new drug recommended for certain uses and no approval of a new drug application was effective with respect to such uses; and that the advertisements for the drug did not present true statements of the effectiveness of the drug since such ads contained false and misleading representations concerning the efficacy of the drug for acute myocardial infarction and for stimulating collateral circulation.

In addition we recommended prosecution with respect to the drug Proloid on the basis of advertisements which would mislead physicians into believing that Proloid was the drug of choice in the treatment of myxedema and that cardiac complications could be avoided.

The Department of Justice in Washington declined prosecution because it disagreed with our interpretations of what the Peritrate and Proloid ads represented and suggested and because the defendant had ceased the advertising and labeling practices complained of with respect to Peritrate.

OCTOBER 24, 1966.

In reply refer to F.D.C. No. 53050.
The Honorable ATTORNEY GENERAL,
Department of Justice,
Washington, D.C.

DEAR MR. ATTORNEY GENERAL: We request the institution of criminal proceedings under the Federal Food, Drug, and Cosmetic Act, against Lederle Laboratories Division, American Cyanamid Company, a corporation, Pearl River, New York.

The offenses complained of occurred during the period from about October 18, 1964, to about September 15, 1965, and involve the introduction into interstate commerce at Pearl River, New York, for delivery to Kansas City, Missouri, and Hillside and Newark, New Jersey of three articles of drugs: Artane (Trihexyphenidyl Hydrochloride) Elixir, Aristocort (Triamicinolone) tablets, and Pathibamate–400 (Tridihexethyl Chloride-Meprobamate) tablets.

There are transmitted herewith a suggested form of criminal information and the following exhibits:

(1) Copies of Notice of Hearing.

(2) Copies of bottle labels for Artane Elixir, Aristocort tablets and Pathibamate tablets.

(3) Copies of package insert labeling (the approved New Drug Application labeling) for Aristocort and Pathibamate.

(4) Copies of package insert labeling for Artane Elixir.

(5) Copies of cartons for Aristocort tablets and Pathibamate tablets.

(6) Copy of the advertisement for Aristocort tablets which appeared in the *Journal of the American Medical Association* for August 16, 1965, and a copy of the advertisement for Pathibamate tablets which appeared in the *Archives of Internal Medicine* for September, 1965.

SECTIONS OF ACT INVOLVED

The Information charges violation of 21 U.S.C. 331(a) in that the defendant caused the introduction into interstate commerce of articles of drug which were adulterated and misbranded (Artane Elixir) or misbranded (Aristocort tablets and Pathibamate tablets). Further, the articles were prescription drugs within the meaning of 21 U.S.C. 353(b)(1)(B) (Artane Elixir), or of 21 U.S.C. 553(b)(1)(C) (Aristocort and Pathibamate).

It is alleged that the Artane Elixir was adulterated within the meaning of 21 U.S.C. 351(c) in that its strength differed from that which it was represented to possess, and also misbranded under 21 U.S.C. 352(a) in that it did not contain the quantity of trihexyphenidyl hydrochloride declared on the label.

It is also alleged that the Aristocort tablets and the Pathibamate tablets were misbranded within the meaning of 21 U.S.C. 352(n) in that the defendant failed to include in the advertisements caused to be issued by it with respect to the drugs in the August 16, 1965, issue of the *Journal of the American Medical Association* (Aristocort), and the September, 1965, issue of the *Archives of Internal Medicine* (Pathibamate), a true statement of information in brief summary relating to side effects, contraindications and effectiveness of such drugs as required by regulations, 21 CFR 1.105 (e) and (f)(2).

BACKGROUND INFORMATION

"Artane" is a trademark held by Lederle Laboratories for the drug, trihexyphenidyl hydrochloride. At the time of the alleged violation, Artane was commonly prescribed for the management of all forms of Parkinsonism and for the prevention and control of extrapyramidal disorders due to central nervous system drugs.

"Aristocort" is a trademark held by Lederle Laboratories for the drug, triamcinolone. At the time of the alleged violation, Aristocort was commonly prescribed in the treatment of rheumatoid arthritis and associated syndromes, acute bursitis, fibrositis, myositis, tendinitis, and torticollis, vasomotor and allergic rhinitis, bronchial asthma, pulmonary emphysema, and pulmonary fibrosis, agioneurotic edema, urticaria and serum sickness, dermatoses, psoriasis, disseminated lupus erythematosus and other collagen diseases, nephrotic syndrome, rheumatic fever, leukemia and other lymphomatous diseases, hemolytic diseases, eye disorders, congestive heart failure and edema.

"Pathibamate" is a trademark held by Lederle Laboratories for the drug, tridihexethyl chloride in combination with meprobamate. At the time of the alleged violation, Pathibamate was commonly prescribed in the treatment of organic and functional disorders of the gastrointestinal tract, especially when accompanied by anxiety, neurosis, or tension states and in the management of gastric and duodenal ulcers.

Lederle Laboratories submitted to the Food and Drug Administration a new-drug application for Aristocort which was approved on October 24, 1957, and one for Pathibamate which was approved on April 22, 1957. Artane Elixir was originally marketed under the provisions of an approved new-drug application, but in September, 1955, the article was no longer considered a new drug.

EVIDENCE OF ADULTERATION

Examination at laboratories of the Food and Drug Administration of a sample Artane Elixir which had been shipped in interstate commerce by the defendant revealed that the article contained about 75% of the amount of active ingredients declared on the labeling.

EVIDENCE OF MISBRANDING

The medical journal advertising for Aristocort tablets appearing in the August 16, 1965, issue of the *Journal of the American Medical Association* did not contain a true statement in brief summary of the side effects, contraindications and effectiveness of Aristocort tablets, in that reference to the following information, which appeared in the labeling accepted as part of the approved new-drug application for Aristocort, was omitted:

1. The administration of anti-inflammatory steroids, such as Aristocort, has catabolic effects, and this, coupled with the anorexia frequently associated with the use of Aristocort, may produce a weight loss, and a steroid myopathy with advanced muscle weakness.

2. Aristocort may produce the following potentially serious side effects: moon face, striae, acne, buffalo hump, osteoporosis, spontaneous fractures, amenorrhea, aggravation of infection, psychotic disturbances, thromboembolism, gastrointenstinal hemorrhage, hyperglycemia, headache, insomnia, fatigue, hirsutism, vertigo and rarely necrotizing angitis; and necrotizing esophagitis and acute pancreatitis have occurred during corticosteroid therapy and may be caused by such therapy.

3. Caution should be exercised in the prolonged use in children because of the possibility of growth suppression.

4. It is important that therapy be withdrawn gradually after prolonged treatment. Adequate supportive measures, increase in dose or ACTH supplementation are indicated when undue stress occurs during or after triamicolone therapy and, if severe reactions or idiosyncracies are encountered, the drug should be discontinued and appropriate measures instituted.

5. Edema may occur, particularly in situations where the glomerular filtration rate cannot increase, such as in renal disease.

The advertisement for Aristocort further caused the drug to be misbranded within the meaning of 21 U.S.C. 353(n), in that the promotional text did not fairly show the effectiveness of the drug and lacked fair balance in its presentation as required by regulation 21 CFR 1.105(e), in that: (1) it implied that patients previously considered untreatable because they are "steroid risks"

become treatable with "Aristocort", without revealing the fact that patients with edema associated with a poor glomerular filtration rate are just as untreatable with Aristocort as they are with any other steroid, and (2) through the use of the statement: "Classic problems, such as salt and water retention, edema, overstimulated appetite, excessive weight gain, hypertension and euphoria, are unlikely to occur," without reporting that one of the major characteristics of this drug is its tendency to produce weight loss far more often than other steroids, due either to excretion of water, depression of appetite or protein catabolism, which weight loss is undesirable in some patients.

The advertising for Pathibamate tablets appearing in the September 1965, issue of *Archives of Internal Medicine* caused the drug to be misbranded within the meaning of 21 U.S.C. 352(n), in that it did not adequately present the information, as found in the labeling accepted as part of the approved new-drug application, concerning those side effects and contraindications which are pertinent to the uses suggested in the advertisement and for any other use for which the drug is commonly prescribed, as required by regulation 21 CFR 1.105(e) in that the following information is omitted:

1. Hypotensive crises, anuria, anaphylaxis, and stomatitis and proctitis are possible side effects.

2. Allergic or idiosyncratic reactions may develop in patients who have had only 1 to 4 doses of meprobamate and have not had previous contact with the drug.

3. The drug is contraindicated in cases of known hypersensitivity to meprobamate.

4. If severe reactions or idiosyncracies occur, use of the drug should be discontinued; and the drug should be administered cautiously to patients ". . . who are hypersensitive to sympathomimetic compounds, who have coronary or cardiovascular disease or who are severely hypertensive."

EVIDENCE OF VIOLATIVE SHIPMENT

Counts I and II: (Artane Elixir)

The sample was collected at Lederle Laboratories' branch warehouse located at 6100 East 60th Street, Kansas City, Missouri, by Inspector Donald L. Oglesbay. The sample was identified by the branch manager of Lederle Laboratories' branch warehouse at Kansas City, Missouri, who furnished the collecting inspector with documents showing that Artane Elixir sampled was shipped by Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York, on October 13, 1964, via Cooper-Jarrett, Inc.

Count III: (Aristocort)

The sample was collected at the New Jersey Wholesale Drug Company, 645 Glenwood Avenue, Hillside, New Jersey, by Inspector Kendrick M. Cole. The lot sampled was identified by William Prairie, the warehouse manager of New Jersey Wholesale Drug Company, Hillside, New Jersey, who said that the shipment was received from Lederle Laboratories Division, Pearl River, New York, on September 3, 1965, via a truck of the Oostydyke Trucking Company. On November 9, 1965, Inspector Cole obtained a copy of the August 16, 1965, issue of the *Journal of the American Medical Association* together with an appropriate affidavit from Peter J. Bonanno, M.D., whose office is located at 741 Teaneck Road, Teaneck, New Jersey.

Count IV: (Pathibamate)

The sample was collected at Bonis Division of Ketchum & Company, 119 Plane Street, Newark, New Jersey, by Inspector Kendrick M. Cole. The sampled lot was identified by Sylvanus Ficklin, warehouse manager of Konis Division of Ketchum & Company, Newark, New Jersey, who said that the shipment sampled was received on September 17, 1965, from Lederle Laboratories Division, Pearl River, New York. On November 15, 1965, Inspector Cole obtained from F. Weisbrod, M.D., 61 South Munn Avenue, East Orange, New Jersey, page 64–A of the September 1965 issue of *Archives of Internal Medicine* together with an appropriate affidavit signed by Dr. Weisbrod.

HEARING PURSUANT TO 21 U.S.C. 335

On December 1, 1965, Mr. Bertram H. Lebeis, Legal Department, American Cyanamid Company, appeared at a hearing held in the Food and Drug Admini-

stration offices in New York, New York, and submitted a written response dated November 30, 1965.

Mr. Lebeis said that the nature of the charges were understood and a discussion was had of the misbrandings by the journal advertisements of the Aristocort tablets and the Pathibamate tablets. Mr. Lebeis then requested, and received, additional time in which to submit a supplemental response. The supplemental written response was received on December 14, 1965. In its written response dated November 30, 1965, Lederle Laboratories stated that the Artane Elixir was put into 3800 pint bottles on June 8, 1964, that tests performed by the firm's quality control section disclosed that the bottles filled at the end of the run contained less of the labeled amounts of the active ingredients than permitted, and that these subpotent bottles were destroyed. 3,117 bottles, however, were released for sale. Lederle Laboratories believed that all the subpotent material had been rejected and that it acted in good faith in releasing the balance.

With regard to the charges that the medical journal advertising for Aristocort and Pathibamate tablets caused these drugs to be misbranded, Lederle Laboratories said that it was apparent that a medical journal advertisement is neither intended nor required to instruct the practitioner how to practice his profession or to remind him of things which are a part of the "common law" of medicine.

Lederle Laboratories then proceeded to deny the charges, contending that: (1) statements in the advertising relating to side effects, precautions and contraindications served to adequately call to the reader's attention the required warning information in the labeling; (2) the information omitted represented that which is part of a physician's overall fund of medical knowledge; and (3) the drug has one of the best records for not causing edema, and therefore there was no necessity for the warning that edema might occur in situations such as renal disease.

With regard to the charges that the advertisement for Aristocort lacked a fair balance in its presentation, Lederle Laboratories contended that the advertisement did not imply that the otherwise untreatable patient became treatable with Aristocort, but rather that the advertisement carefully pointed not to all, but to "large numbers" and to "many" in the untreatable group who were able to benefit from Aristocort therapy. Lederle Laboratories also said, that the advertisement pointed out that patients with certain diseases or conditions could not be treated with other steroids, *viz.*, overweight, with cardiac disease, with hypertension, with pulmonary fibrosis associated with congestive heart failure, and that it was for these patients that weight loss was desirable and for them alone that the drug is called to the attention of the physician.

CONCLUSIONS

We believe that the factors which have been set forth in some detail above show that the advertisements used by this firm have not met the standards required by law. The omissions and deceptive statements involved were numerous and serious. Moreover, the side effects and contraindications were already well known to the company as they were set down in the New Drug Application labeling. Advertising prescription drugs should be a very special operation—wholly unlike advertising the 1967 model automobiles or the tars and nicotines of cigarettes. It should be based on the scientific data that allowed the drug to enter the market—you need look and can look no further than the labeling accepted in the New Drug Application for the allowable claims and the required warnings. In drug advertising the law does not provide for product touting or "puffing" when it entails a compromise in the requirement of full disclosure. The advertisements involved in the charges contain half-truths designed more to boost sales than to provide a physician with the information essential to the proper and safe prescription of the drug. Busy physicians should and must be able to rely on statements concerning a product without referring back to the original source to look for inconsistencies and contraindications.

We also believe that the Artane Elixir was substantially subpotent, and such fact was known to the firm through the tests it performed on the drug. Defendant clearly acted in callous disregard of the public health by shipping a drug known to be subpotent.

The manufacturers of potent drugs, better than others, know the potential hazards of their products. We believe the prosecution is fully warranted.

WITNESSES

The principal witnesses in this case will be the Government inspectors who collected the samples; Government chemists who examined the Artane Elixir sample; cooperating physicians who subscribe to the *Journal of the American Medical Association* or the *Archives of Internal Medicine;* and medical officers of the Food and Drug Administration's Bureau of Medicine who can testify as to the approved new-drug applications, approved labeling, and the serious nature of the alleged medical journal advertising misbrandings.

It is requested that, if the information is amended, we will be provided with a copy thereof. Upon request, this office shall render such further assistance as may be possible.

Sincerely yours,

WILLIAM W. GOODRICH,
Assistant General Counsel,
Food and Drug Division.

NOVEMBER 6, 1968.

Re American Cyanamid Co., Inc., FDC 53050. Your ref. FMV:JWK:jbg: 21–51–518.

Hon. FRED M. VINSON, Jr.,
Assistant Attorney General,
Department of Justice,
Washington, D.C.

DEAR MR. VINSON: Thank you for your letter of October 30, 1968, enclosing a copy of the United States Attorney's letter of July 1, 1968, declining prosecution in this case.

The reasons given for declining prosecution are that the case is old, that the law and regulations are vague, and that the Company's failure to include side effect and contraindication information in its advertisements did not appear to have sufficiently grave medical seriousness to persuade a jury that criminal action had occurred.

It is true that the case is old. We sent it to your office in November 1966. We contacted the United States Attorney urging him to file the case, sent a physician to New York to explain the medical significance of the advertising failures, and supplied a memorandum to him pointing out the medical failures.

The law is not vague. The regulations are clear enough to cover what happened here.

The regulations required the Company to include in all advertisements a brief summary relating to side effects, contraindication and effectiveness and to achieve a fair balance in presenting information related to effectiveness and side effects and contraindications. Quite pertinent here is 21 CFR 1.105(f), which requires that any advertisement for a new drug approved prior to October 10, 1962, "shall present information from [the approved new drug] labeling concerning those side effects and contraindications that are pertinent with respect to the uses recommended or suggested in the advertisement and for any other use or uses for which the dosage form advertised is commonly prescribed."

It is clear to us that the advertisements here involved failed to comply with regulation 1.105 (a) and (f)(2). The details of the inadequacies are set out in the information we sent you and in the memorandum we supplied to the United States Attorney.

The warning ideas that were omitted from the advertisements were required in the labeling as a condition of the approval of the drugs for marketing through the new drug procedures. That they present information which the physician must have in mind for safe patient care cannot be successfully disputed.

The Company had no reason to be in doubt as to what information was required in the advertisements. It had only to go to its approved labeling and fairly summarize that information in the advertisements. The best that can be said for Lederle is that in its summarizations it made a choice of what information it thought the physician needed. But that choice was not available to it. The regulations, which have the force of law, required a summary of the approved prescribing information in the package insert labeling.

To say that "moon face", "buffalo hump", "acne" and some of the other distressing side effects of corticosteroids are unimportant because they merely

are cosmetically undesirable is to ignore the realities of good patient care. And, as the United States Attorney notes, there were several more serious side effects that were neglected in the advertisements.

Your letter of October 30, 1968 states that you have no basis for disputing the judgment of the United States Attorney because we have not supplied you with a narrative account of expected testimony of witnesses, copies of exhibits, and a brief of legal points.

We did not go to the expense of preparing this case for trial before it was even filed. The exhibits have been sent to you with our letter of November 7, 1966. If they have been misplaced, we will replace them. We didn't know what points to brief because we did not have the United States Attorney's questions.

We write to you at this length to be sure that the file is not left indicating that there are some facts we have not supplied or arguments we have not made. But we will have to agree with you that the age of this case and the reluctance of the Department of Justice to prosecute the action makes it seem unlikely that pressing this case will improve the advertising practices of this Company or the Pharmaceutical Industry.

Yours very truly,

WILLIAM W. GOODRICH,
Food, Drug, and Environmental Health Division.

U.S. DEPARTMENT OF JUSTICE,
U.S. ATTORNEY,
SOUTHERN DISTRICT OF NEW YORK,
New York, N.Y., February 25, 1970.

Re *U.S.* v. *American Cyanamid Co.*, t/a Lederle Laboratories, Div., F.D.C. No. 53050 118–943 A et al.
DEPARTMENT OF HEALTH, EDUCATION AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
Brooklyn, N.Y.
Attention JEROME J. DONOVAN, *Hearing Officer*

DEAR SIRS: In checking the file in this matter we find a letter dated September 25, 1968, in which you ask for the status of this matter. I have no indication that this letter was answered. However, this is to advise you that on April 29, 1968 prosecution was declined and the file was closed.

Very truly yours,

WHITNEY NORTH SEYMOUR, Jr.,
United States Attorney.
By SILVIO J. MOLLO,
Chief Assistant, United States Attorney.

OCTOBER 30, 1968.

Re American Cyanamid Co., Inc., F.D.C. No. 53050.
MR. WILLIAM W. GOODRICH,
Assistant General Counsel,
Department of Health, Education, and Welfare,
Washington, D.C.

DEAR MR. GOODRICH: We are in receipt of a further communication from the United States Attorney for the Southern District of New York, setting forth his reasons for declining prosecution in the above matter. Since the material submitted to us by your office has not been augmented as we suggested in our letter to you dated June 4, 1968, we have no basis on which to dispute any of the judgments of the United States Attorney.

Therefore, we have acquiesced in his decision and have closed this matter without prosecution.

Sincerely,

FRED M. VINSON, Jr.,
Assistant Attorney General,
Criminal Division.
By HAROLD P. SHAPIRO,
Chief, Administrative Regulations Section.

JUNE 24, 1966.

In reply refer to F.D.C. No. 52397.
The Honorable ATTORNEY GENERAL,
Department of Justice,
Washington, D.C.

DEAR MR. ATTORNEY GENERAL: We request the institution of criminal proceedings under the Federal Food, Drug, and Cosmetic Act against Bristol-Myers Company, a corporation trading and doing business under the name of Bristol Laboratories Division of Bristol-Myers Company at Syracuse, New York. The offenses complained of occurred on or about May 11, 1965 and September 9, 1965 and involved the introduction into interstate commerce at South Hackensack, New Jersey, for delivery to Pittsburgh, Pennsylvania, of prescription drugs, namely, "Salutensin", a combination of Saluron (hydroflumethiazide), Reserpine, and Protoveratrine A, and "Prostaphlin" (sodium oxacillin), both of which were misbranded.

There are transmitted herewith a suggested form of criminal information and the following exhibits:

A. Copies of Notices of Hearings.

B. Bottle labels.

C. Package inserts (the Salutensin approved NDA labeling and the Prostaphlin approved antibiotic labeling).

D. Copy of Prostaphlin monograph on pages 563 and 564 of the Physicians' Desk Reference, 1965 Edition.

E. Copy of Salutensin advertisement in the American Journal of Cardiology of November, 1964.

F. Copies of Salutensin Mailing Pieces.

G. Copy of Salutensin monograph on page 654 of the Physicians' Desk Reference, 1965 Edition.

H. Copy of Salutensin Mailing Piece SH 4950–1 (October 1961).

SECTIONS OF THE ACT INVOLVED

The Information charges violations of 21 U.S.C. 331(a) in that the defendant caused the introduction into interstate commerce of the above mentioned drugs which were misbranded as hereinafter described.

I—*Salutensin:* The drug was misbranded when introduced into interstate commerce within the meaning of 21 U.S.C. 352(n) in that defendant failed to include in an advertisement caused to be issued by it in the November 1964 edition of the American Journal of Cardiology a true statement of information in brief summary form relating to the drug's effectiveness, side effects, and contraindications as required by regulation 21 CFR 1.105 (e) and (f). The drug was further misbranded within the meaning of 21 U.S.C. 352(f)(1) in that its labeling failed to bear adequate directions for use, the drug not being exempt from such requirement since it was a prescription drug which was also a new drug subject to 21 U.S.C. 355 and the labeling namely two mailing pieces identified as SH 3852 RV and SH 3919 RV–2 and the monograph appearing in the 1965 Edition of the Physicians' Desk Reference was not, as required by regulations, substantially the same as the labeling authorized by the new drug application for the drug.

II—*Prostaphlin:* The drug was misbranded within the meaning of 21 U.S.C. 352(f)(1) in that the labeling of the drug failed to bear adequate directions for use. Nor was the drug exempt from such requirement since it was a prescription drug which was an antibiotic drug subject to 21 U.S.C. 357 and its labeling, namely its monograph, set forth in the 1965 edition of the Physicians' Desk Reference, was not, as required by regulations 21 CFR 1.106(b)(4), substantially the same as the labeling required as a condition for its certification nor did it provide adequate information for use under which a physician could use the drug safely and for the purposes for which it was intended. (See 21 CFR 146.2). It was further misbranded under 21 U.S.C. 352(1) in that the monograph appearing in the 1965 Physicians' Desk Reference is labeling which had not been submitted to the Commissioner of Food and Drugs as required by the Antibiotic Regulations, 21 CFR 146.2(b). (See also 21 CFR 146.4(a)(1)).

BACKGROUND INFORMATION

I—"Salutensin" is a trade-mark held by Bristol Laboratories for the drug, which is a mixture of Saluron (hydroflumethiazide), Reserpine, and Protovera-

trine A. At the time of the alleged violation, Salutensin was commonly prescribed for the treatment of hypertension and cardiovascular disease.

Bristol Laboratories submitted to the Food and Drug Administration a new-drug application for Salutensin which was approved on June 20, 1960.

The advertisement for Salutensin which appears in the November 1964 edition of the American Journal of Cardiology is a two page ad containing representatons relating to the effectiveness of the drug and statements concerning certain side effects and precautions applicable to it.

Salutensin Mailing Pieces, which are identified as "SH 3852 RV" and "SH 3919 RV–2", were designed by Bristol Laboratories. These four page mailing pieces were printed in September 1963. They contain representations relating to the effectiveness of the drug and statements concerning certain side effects and precautions applicable to the drug. The two aforesaid mailing pieces were distributed for Bristol Laboratories by Fisher-Stevens, Inc., a service organization, of Clifton, New Jersey as follows:

(1) On May 26, 1964, 75,131 of the "SH 3852 RV" Mailing Pieces were mailed to all General Practitioners, Doctors of Internal Medicine, and Cardiologists under 65 in private practice in the United States.

(2) On July 15, 1964, 75,145 of the "SH 3919 RV–2" Mailing Pieces were mailed out to the above identified physicians in the United States.

The May 1964 mailing was sent to 4,899 and the July 1964 mailing to 4,794 physicians in the state of Pennsylvania. Fourteen percent of these Pennsylvania physicians are located in Allegheny County which includes the city of Pittsburgh.

The 1965 edition of Physicians' Desk Reference, published by Medical Economics Inc., contains on page 564 a monograph for Salutensin. The PDR is published annually in cooperation with the subscribing manufacturers. The purpose of the PDR is to make available to the physician "essential prescription information on major pharmaceutical specialties". Information appearing in the PDR, however, is solely that furnished by the manufacturer. This is made clear by the "foreward" in the 1965 Edition which contains the following statement: "The function of the publisher is the compilation, organization, and distribution of the information. Each product description has been prepared by the manufacturer, and edited and approved by the manufacturer's Medical Department, Medical Director, or Medical Consultant."

An approved package insert for Salutensin bearing the date June 1963 details the side effects, warnings and precautions that are associated with the drug. It is clear that the manufacturer, Bristol-Meyers, had ample time prior to submission of the monograph for the 1965 edition of the PDR and before distribution of the two mailing pieces, to include this information contained in the approved package insert.

II—"Prostaphlin" is a trade-mark held by Bristol Laboratories for the antibiotic drug, sodium oxacillin. At the time of the alleged violations, Prostaphlin was commonly prescribed in the treatment of infections due to penicillin G-resistant Staphlococcus aureus, including skin and soft tissue infections, respiratory tract infections, genitourinary tract infections, osteomyelitis, bacteremia, septicemia and enterocolitis due to penicillin G-resistant staphlococci.

The 1965 edition of the Physicians' Desk References contains on pages 563 and 564 a monograph for Prostaphlin. As already indicated the information supplied in the PDR is wholly provided by the manufacturers of the drugs involved. The package insert labeling for Prostaphlin represents one of the specimens of labeling which were submitted to the Commissioner of Food and Drug on January 27, 1965 with a request for certification of the batch of Prostaphlin identified by Lot No. B 5312 from which the alleged shipment of Prostaphlin was subsequently made. Such labeling contained the four relevant hazards, contraindications, side effects, and precautions complained of herein. The copy of the Prostaphlin package insert bears the date August 1963. This proves conclusively that the firm knew about these conditions and had more than adequate time to include them in the 1965, and probably even in the 1964, Edition of the Physicians' Desk Reference.

EVIDENCE OF MISBRANDING

I—Salutensin:

21 U.S.C. 352(n) (*Regulation 1.105 (e) & (f)*).—In regard to the advertisement in the November 1964 American Journal of Cardiology, examination has shown that the advertisement failed to contain a true statement in "brief

summary" relating to side effects, warnings and contraindications. The following important ideas relating to patient safety which are set out in the approved NDA labeling were not expressed in the "brief summary" part of the advertisement:

a. "Severe depression is a contraindication to the use of reserpine."

b. "If progressive increases in serum nitrogen (BUN, NPN, creatinine) occur, therapy should be discontinued.

c. "If patients are to undergo elective surgery requiring general anesthesia, reserpine should be discontinued at least 2 weeks beforehand."

d. "This drug should be used cautiously in hypertensive patients with renal insufficiency, particularly if such patients are digitalized."

e. "If there is evidence of myocardial irritability (extrasystoles, bigeminy or AV block), reduce the dose or discontinue SALUTENSIN regardless of whether the patient is on digitalis."

f. "Caution is also necessary when conditions exist which are known to alter serum electrolyte concentrations, e.g. vomiting and diarrhea."

g. "Decreases in serum potassium are more apt to occur in cases of fluid retention caused by hepatic cirrhosis and steroid administration."

h. "Increases in excretion [of sodium and chloride caused by hydroflumethiazide] may produce alterations in the concentrations or serum electrolytes resulting in hypochloremia, hypocloremic alkalosis, hyponatremia or hypokalemia." (The ads statement, "alteration in electrolyte balance . . . may occur" does not make it clear that sodium and chloride might be reduced to levels below normal and that there is a possibility of a serious clinical condition).

i. "Rarely, it may be necessary to stop thiazide therapy before hypokalemia can be alleviated."

j. "In states of pre-coma of hepatic origin, thiazide diuretics may precipitate coma."

The promotional text of the advertisement contains faulty and misleading representations as follows:

a. The claims that the use of Salutensin will "get blood pressure down sooner" and that use of Salutensin will yield "more successful management of hypertension," than "just thiazide-reserpine" have not been approved for labeling, nor is there evidence in the New Drug Application to support them.

b. Referring to the combination of thiazide, reserpine and protoveratrine-A the ad states: "Clinically, the advantages of such a combination have been summed up as follows: 'The concomitant use of reserpine and the thiazides and veratrum has greatly widened the therapeutic and toxic range, making veratrum more effective and simple to administer * * *' It is unfortunate that more physicians do not take advantage of veratrum, thiazide, and reserpine to lower the arterial pressure simply, effectively and without side effects." The ad uses reference #2 (Finnerty) for the two-sentence statement quoted above. Such statement is objectionable for the following reasons:

(1) The reader is led to believe that Finnerty used proteveratrum A in his study. In fact, he prescribed Veriloid (alkavervir) and Unitensin (cryptenamine). (Protoveratrine A is a purified single alkaloid isolated from Veratrum album. Alkavervir is a partially purified extract containing a mixture of alkaloids, obtained from Veratrum *viride*. Cryptenamine is an alkaloid derived from an extract of Veratrum *viride*.)

(2) The ad misleads by quoting Finnerty out of context. The reader is led to believe that the author was advising the reader that the combination of veratrum, reserpine and thiazide lowers blood pressure, effectively and without side effect when a "simple" dosage schedule, supposedly like the one Bristol recommends, is followed. A review of Finnerty's article showed this not to be the case, for in the several sentences located between the two sentences quoted, the author gives these detailed instructions: the patient should eat at the same time every day; the patient should not eat for two hours after taking veratrum; a good beginning dosage of veratrum is 2 mg. three times a day, e.g., after breakfast, mid-afternoon and at bedtime, and then gradually increased over a period of two to three weeks—up to but not exceeding 4 mg. three times a day.

Also related to the problem of effectiveness and safety are the author's statements, elsewhere in his article, that the "thiazide" (chlorthalidone—which, incidentally, is not a thiazide) component of his combination therapy was given in a single 50 mg. daily dose (note that the recommended dosage range for the hydroflumethiazide in Salutensin is higher and the schedule permits the dose

of the diuretic to be given up to four times a day); that it was necessary to administer supplemental potassium to those digitalized patients who had been given a trial of other thiazides—other than chlorthalidone—to avoid arrhythmias, that a marked increase in toxic reactions occurs when more than 0.25 mg. of reserpine per day is administered (note that the dosage range recommended in the package insert for the reserpine component in Salutensin may be much higher than that recommended by Finnerty); that because mental depression from reserpine has resulted in suicides, monthly checkup is mandatory; that the combination of veratrum, thiazide and reserpine is indicated in moderately severe hypertension, and that he does not advocate the combination in mild or severe hypertension.

21 U.S.C. 352(f)(1) [*Reg. 1.106(b)(4)*]: Salutensin is a prescription drug within the meaning of 21 U.S.C. 353(b)(1)(C) in that it is limited to prescription use by its approved new drug application. Accordingly, since adequate directions for lay use cannot be written for a prescription drug, it is clear that the labeling for Salutensin here involved did not bear adequate directions for lay use as required by 21 U.S.C. 352(f)(1). Furthermore, the Salutensin involved here was not exempt from 21 U.S.C. 352(f)(1) as provided for by regulations 21 CFR 1.106(b) since it failed to comply with the condition for exemption set forth in subparagraph 4(i) of such regulations. This condition requires that any labeling of a prescription drug shall contain adequate information for use including indications, effects, dosages, routes, methods and frequency and duration of administration and any relevant hazards, contraindications, side effects and precautions under which practitioners licensed by law to administer the drug can use the drug safely and for the purpose for which it is intended and, if the drug is subject to 21 U.S.C. 355, the labeling providing such information shall be substantially the same as the labeling authorized by the approved new drug application for such drug.

In the case of Salutensin, examination of the Mailing Piece designated as "SH 3852 RV", which is labeling for the drug as described in regulations 21 CFR 1.105(1), has disclosed that such labeling is not substantially the same as that which is set forth in the approved new drug application for the drug.

1. This mailing piece deviates substantially from the approved package insert labeling by failing to disclose the following side effects, warnings and precautions:

a. Reduction of serum electrolyte concentrations may occur with Salutensin "resulting in hypochloremia, hypochloremis alkalosis, hyponatemia . . ." The warning in the mailing piece that "alterations in electrolyte balance . . . may occur" does not clearly inform the reader that the electrolytes, sodium and chloride, can be depressed below normal levels to cause these potentially serious clinical states.

b. "If indicated, potassium loss often may be easily replaced by including potassium-rich foods in the diet (tomato juice or orange juice or other citric juice, banana, etc.). Patients unable or unwilling to take fruit juice may be given potassium chloride 1 Cm 2 to 4 times daily by mouth. Rarely, it may be necessary to stop thiazide therapy before hypokalemia can be alleviated."

c. Some patients may have "insomnia" and "nightmares."

2. The promotional text of this mailing piece contains these faults:

a. The claims that the use of Salutensin will "get blood pressure down sooner", and that the use of Salutensin will result in "more successful management of hypertension", than "just thiazide-reserpine" have not been approved for labeling, nor is there evidence in the NDA to support them.

b. This mailing piece also refers to the work by Finnerty (reference #2) in such manner as to mislead the reader.

c. The company's description of the work by Smith (reference #3) exaggerates a claim for efficacy yet fails to mention side effects reported by the author.

(1) The reader is not told that the subjects in this study were hospitalized and had an average age of 77 years. Without this information he is prevented from correctly evaluating the results of the author, and from posing the question of whether or not these patients could be expected to show similar blood pressure reductions on just one of the ingredients of Salutensin, i.e. the reserpine or the hydroflumethiazide.

(2) Further, the mailing piece fails to reveal that the physicians attending these patients were allowed to adjust the dosage of the drug within a range of 1 to 4 tablets daily. This information is clearly set out in the approved package insert. The failure to reveal this in the mailing piece is misleading because the

headline implies that the results were obtained with "only one or two tablets a day."

(3) The mailing piece does not show fair balance. It attempts to exaggerate safety with a quotation from one paper (Finnerty), but, in an attempt to exaggerate efficacy claims, presents the report by Smith without revealing that twelve of the author's 45 patients had side effects such as nausea, vertigo, weakness and dizziness while on Salutensin, and that dosage in these cases had to be reduced in order to reduce the side effects. Further, the original Smith report in the NDA points out that several patients had side effects which were not "minimized" by reduction in dose and that two additional patients had side effects while on Salutensin; one with nausea, and another with abdominal pain. The Smith report shows that some patients on Salutensin experienced side effects on dosages (2 tablets daily) within the range recommended by the company.

Examination of the Salutensin Mailing Piece designated as "SH 3919 RV-2" disclosed the following:

1. The information in this mailing piece is lacking in its treatment of the drug's side effects, etc., as described above in the analysis of mailing piece No. SH 3852 RV.

2. The promotional section of this mailing piece contains the same faults as described above in relation to mailing piece No. SH 3852 RV, plus additional errors concerned with the use of two additional research papers.

a. The mailing piece misrepresents the work of Spiotta (reference #6, a report to Bristol Laboratories) and a graph "adapted from Spiotta."

(1) The company seriously misleads by failing to tell the reader that the study represented by the graph was on only one patient. As evidence, see use of same graph in the enclosed October 1961 mailing piece which specified that this is the result of a study of a single case. What is more, there were only two patients in the Spiotta study who received serial additions of the ingredients of Salutensin in the order shown in the graph, namely Saluron, protoveratrine A, and then reserpine.

(2) The company fails to inform the reader that when all the ingredients were added each of the 7 patients in this phase of this study was finally receiving 200 mg. of hydroflumethlazide, 0.5 mg. of reserpine and 0.8 mg. of protoveratrine A per day (equivalent to 4 Salutensin tablets) and that not all of the patients were receiving the three components in the same order shown in the graph. The failure to disclose this is misleading because the headline in the promotional section of the mailing piece implies that the graphed results were obtained with "only one or two tablets a day."

(3) The company also fails to tell the reader that Spiotta studied additional patients who received only 2 of the 3 ingredients of Salutensin; that he found, for instance, results with hydroflumethiazide plus reserpine which were similar to those with Salutensin in some cases. Such information does not support the idea in the promotion that Salutensin is better than a combination of only two of its three components, and that protoveratrine A is needed for more successful antihypertensive therapy. It is apparent that the Spiotta study (and it is the only study in the NDA on the serial addition of each Salutensin component) involved an insufficient number of patients to warrant making *any* sound judgment regarding the comparative efficacy claim which the headline states: "instead of just thiazide-reserpine, use Salutensin."

b. The mailing piece presents the work of Thomas (reference #8, a report to Bristol Laboratories) and a graph purporting to show the effectiveness of Salutensin in longstanding hypertension of moderate severity. The reader is led to believe that all 40 patients received only Salutensin, and that the dose, as claimed in the headline of the promotion, was "one or two tablets per day" for all patients. On the contrary the approved package insert itself merely states the following about results with Salutensin in the Thomas study:

(1) "Thomas noted that in *many* patients it was possible to eliminate hydralazine which patients had been taking previously." (Emphasis added)

(2) "Statistical analysis of the data indicated that the supplementary dose of reserpine could be considerably reduced while they were on Salutensin in order to maintain satisfactory control of their hypertension." At least ten of the patients were taking supplementary doses of reserpine.

(3) "A few of the patients required the addition of other antihypertensive (reserpine, hydralazine, inversine, Singoserp, chlorothiazide) agents with Salutensin in order to maintain satisfactory control of their hypertension." The "few" patients referred to above numbered at least ten.

(4) "Some received as little as 1 tablet daily; others as much as 4 tablets daily, the dose being adjusted according to individual patient response as the study progressed." The headline in the mailing piece, however, invites the reader to believe that Thomas also found that the daily dose required to keep blood pressure down was "one or two tablets".

Examination of the Salutensin monograph appearing in the 1965 edition of the PDR reveals a third instance where labeling is not substantially the same as that which is set forth in the approved new drug application. In the same way as described above at page 8, paragraph 1 in relation to Mailing Piece "SH 3852 RV" this monograph fails to provide full disclosure concerning the drug's side effects, warnings and precautions.

II—Prostaphlin:

21 U.S.C. 352(f) (1) (Reg. 1.106(b)(4)).—Prostaphlin is a prescription drug and, as such, adequate directions for lay use cannot be written for it. It is quite obvious then that the labeling of the Prostaphlin here involved did not bear adequate directions for lay use as required by 21 U.S.C. 352(f)(1). Furthermore, the Prostaphlin was not exempt from 21 U.S.C. 352(f)(1) as provided by regulations 21 CFR 1.106(b) since it failed to comply with the conditions for exemption set forth in subparagraph 4(i) of such regulations. This condition requires that any labeling of a prescription drug shall contain adequate information for use including indications, effects, dosages, routes, methods and frequency and duration of administration and any relevant hazards, contraindications, side effects and precautions under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended. Further if the drug is subject to 21 U.S.C. 357, the labeling providing such information must be substantially the same as the labeling required as a condition for the certification of such drug (See regulations 21 CFR 146.2(b) and 146.4(a)(1)). In the case of Prostaphlin, examination of the monograph for such drug in the 1965 edition of the Physicians' Desk Reference, which is labeling for the drug as described in regulations 21 CFR 1.105(1), has disclosed that such labeling is not substantially the same as the labeling (package insert) which was submitted for purposes of obtaining certification. Examples of the omission of important items of information in the Prostaphlin monograph in the PDR which are contained in the package insert labeling submitted for purposes of certification are set forth below:

1. That safety for use of the drug in pregnancy has not been established.
2. That periodic assessment of organ system functions, including renal, hepatic and hematopoietic, should be made during long-term therapy with the drug.
3. A warning that anaphylactoid reactions to the drug have been encountered.
4. A warning that hazards of anaphylaxis to patients with a history of penicillin allergy must be balanced against the prognosis if the drug is withheld.

The Prostaphlin monograph in the 1965 edition of Physicians' Desk Reference also differs from the package insert labeling submitted for purposes of certification in that the monograph is false and misleading because of the following:

1. The monograph implies that the drug Prostaphlin is safe and effective when used in accordance with the information contained in the monograph, when in fact this monograph does not provide all the information required for safe and effective use of the drug because it fails to include the warnings referred to under the four points discussed in the preceding paragraph.
2. The monograph includes the statement "No anaphylactic reactions have been encountered" which statement is contrary to fact.
3. The monograph includes the statement "Reactions to this penicillin have been infrequent and mild in nature" which is misleading because of the phrase "mild in nature."

21 U.S.C. 352(1).—It is further alleged that Prostaphlin when introduced into interstate commerce was misbranded within the meaning of 21 U.S.C. 352(1) in that it was represented as a drug composed of a certifiable antibiotic, namely sodium oxacillin, and it was not from a batch with respect to which a certificate or release issued pursuant to Section 357 was in effect with respect to such drug since the certificate which was issued on February 4, 1965 for such batch had been obtained through misrepresentation and concealment of a material fact. The application for certification constituted a misrepresentation and was a concealment of a material fact in that it purported to be preceded or accompanied by specimens of all labeling to be used for such drug when in fact

it failed to include the monograph of said drug which appeared in the 1965 Edition of the Physicians' Desk Reference. (See 21 CFR 146.2(b) and 21 CFR 146.4(a)(1)).

EVIDENCE OF VIOLATIVE SHIPMENTS

On June 16, 1965, Food and Drug Inspector Joseph S. Slayton collected a sample of Salutensin from a lot of 72 60-tablet bottles which were held at McKesson and Robbins, Inc., Pittsburgh, Pennsylvania. A copy of an invoice and shipping records in the form of a motor express bill of Lading and/or freight bill showed that the lot had been received from the defendant's South Hackensack, New Jersey warehouse on or about 5/13/65. Inspector Slayton also obtained from Dr. James K. Spence of Pittsburgh, Pennsylvania a statement that he is a regular subscriber of the publication entitled "The American Journal of Cardiology." The doctor further identified pages 41 and 42 of the Salutensin advertisement in this publication bearing a November 1964 issue date.

On January 17, 1966, Food and Drug Inspector Alfred M. Levy obtained a statement from Donald J. Tierney, Production Manager of Fisher-Stevens, Inc. (Mailing Service for Bristol Laboratories) attesting to the fact that a total of 9,093 four page mailing pieces identified as SH 3852 RV and SH 3919 RV-2 and relating to Salutensin were mailed to physicians in Pennsylvania, on May 26, 1964, and July 15, 1964. Actual samples of these mailing pieces were also identified and furnished to the inspector.

On October 29, 1965 Food and Drug Inspector Joseph P. Brochetti collected a sample of Protaphlin from a lot of 10 48-capsule vials which were held at McKesson & Robbins Drug Division, 445 Fort Pitt Boulevard, Pittsburg, Pennsylvania. A copy of an invoice, the bill of lading, receiving record and dealer's statement showed that the lot had been received from the defendant's South Hackensack, New Jersey warehouse on or about September 12, 1965.

HEARING PURSUANT TO 21 U.S.C. 355

Pursuant to the Notice of Hearing regarding Salutensin dated August 9, 1965, Dr. Harold Frediani of Bristol Laboratories called the Food and Drug Administration's Buffalo District office on August 11, 1965 and was provided with details concerning the specific charges involving representations in the medical journal advertisement of November 1964 and in the labeling referred to as mailing pieces SH 3852 RV and SH 3919 RV-2.

The Hearing was originally scheduled for August 24, 1965 but was subsequently rescheduled at the request of the citee for September 7, 1965. The firm's answer was in the form of a 16 page letter dated September 3, 1965. The letter bore the signature of Hubert C. Peltier, M.D., Medical Director of Bristol Laboratories. This written answer denied all allegations. It maintained that the advertisement complained of complied with all pertinent requirements of the law. Likewise, the answer maintains that the mailing pieces involved contained adequate directions and information for the practitioner. The firm contended that the Salutensin advertisement in the November 1964 issue of the American Journal of Cardiology constituted an "alerting device" when read by the physician, and further referred the physician to the official package circular. The inference was that the advertisement "in its entirety" included package insert information not present in said advertisement. The firm likewise denied that the mailing pieces SH 3852 RV and SH 3919 RV-2 failed to contain full disclosure relative to side effects and warnings, etc. They contended the pertinent information given was all that a physician needed in order to use the drug; and that only unnecessary elaboration contained in the official package circular had been omitted. Throughout the written response, the firm contends and infers that many of the cautionary and warning statements, (although present in approved labeling), are superfluous and would not be needed by a physician, who would be aware of these omitted statements. The answer further indicated that the respondents would appreciate meeting with appropriate persons in the Washington headquarters of the Food and Drug Administration to discuss the matter with a view toward preventing such future differences.

Representatives of the firm met with Food and Drug Administration officials in Washington on October 11, 1965. The majority of the violations were discussed and the firm promised corrections in both future Salutensin advertisements and mailing pieces.

Pursuant to the Notice of Hearing regarding Prostaphlin dated November 4, 1965, and setting the Hearing date for November 17, 1965, the firm submitted an answer in the form of a four page letter dated November 16, 1965, signed by Hubert C. Peltier, M.D., Medical Director of Bristol Laboratories. The firm's answer, in essence, denied the charges made by the Government. However, it also included a somewhat corrected galley proposed for the 1966 Physicians' Desk Reference relative to the Prostaphlin monograph.

CONCLUSIONS

We believe that the factors which have been set forth in some detail above show that the labeling and advertisements used by this firm have not met the standards required by law. The omissions and deceptive statements involved were numerous and serious. Moreover, the required warnings were already well known to the company. As to Salutensin they were set down in the New Drug Application labeling and as to Prostaphlin they were included in the labeling submitted prior to antibiotic certification (package insert). In drug advertising the law does not provide for product touting or "puffing" when it entails a compromise in the requirement of full disclosure. The advertisement and mailing pieces involved in the Salutensin charge are replete with half-truths designed more to boost sales than to provide a physician with the information essential to the proper and safe prescription of that drug. As to Prostaphlin not only did the company fail to submit the Physicians' Desk Reference labeling as part of its request for batch certification as specifically required by regulations (21 CFR 146.2(b)) but the monograph which it did place in the Physicians' Desk Reference was at serious variance with the existing approved package insert. More oversight or carelessness cannot excuse the violations complained of here. The manufacturers of potent drugs, better than others, know the potential hazards of their products. Busy physicians should and must be able to rely on statements concerning a product without referring back to the original source to look for inconsistencies and contraindications. We believe the prosecution is fully warranted.

WITNESSES

The principal witnesses in this case will include the government inspectors who collected samples of the two drugs involved; witnesses to establish the interstate shipment of the drugs, the issuance of the PDR, mailing pieces and advertisement; medical officers from the Food and Drug Administration's Bureau of Medicine who will testify concerning the approved New Drug Application for Salutensin, the certification for this batch of Prostaphlin, the approved labeling and the serious nature of the alleged misbranding.

It is requested that if the form of Information is amended, that the United States Attorney furnish us with a copy thereof, and that we be kept advised of the progress and disposition of the case. Upon request, we shall render every further assistance.

Very truly yours,

WILLIAM W. GOODRICH,
Assistant General Counsel,
Food and Drug Division.

MARCH 26, 1969.

Re Bristol-Myers Co.—Alleged Violation of the Federal Food, Drug, and Cosmetic Act, F.D.C. No. 52397

MR. WILLIAM W. GOODRICH,
Assistant General Counsel, Food, Drug, and Environmental Health Division, Department of Health, Education, and Welfare, Washington, D.C.

DEAR MR. GOODRICH: We have carefully considered the request for prosecution of the above-mentioned company for alleged violations of the Federal Food, Drug, and Cosmetic Act stemming from its promotional activity in the field of advertising and labeling for the drugs Salutensin and Prostaphlin in 1965.

Since this matter was first referred to us the trial of the *Abbott* case, while unsuccessful, established a judicial precedent for the Government's contention that the monographs appearing in the Physicians Desk Reference are labeling. We understand that the Bristol-Myers Co. and the industry in general have accepted this determination and have been more careful to make certain that

the monographs closely correspond to the approved labeling. In addition, as a result of the Court's interpretation of the phrase "substantially the same" as used in the former regulation (21 C.F.R. 1.105) the agency has changed the regulations under which the labeling violation would be brought. This, of course, is also applicable in the case of the mailing piece, the use of which was claimed to violate the labeling regulations.

Thus, the institution of the criminal action requested would not serve any useful purpose in obtaining a judicial interpretation of the present labeling regulations or as to what constitutes labeling.

Any prosecutions based upon the advertisement of Salutensin in the medical publication for November, 1965, must be predicated upon the regulation which was in force at that time. This prosecution would necessarily involve certain contentions relative to the meaning of the statute and regulations with reference to practices which are not distinctly set out therein. Inasmuch as the agency is in the process of issuing new regulations which will clearly and in detail inform those subject thereto concerning what information is expected to be included and what conduct is prohibited, it is our opinion that the agencys interpretation of the statute can be best advanced by defending any judicial challenge to the issuance of the regulation, or if none is forthcoming, by bringing either a civil seizure or a criminal prosecution based on acts occurring after the regulations have become effective.

The institution of previous criminal proceedings has made known to the industry that this Department intends to make use of criminal sanctions for enforcement of the labeling and advertising provisions of the statute whenever it is necessary to do so to prevent the use use of improper promotional materials. Industry publications contain accounts of instances in which drug manufacturers have, after consultation with agency representatives, circularized the medical profession calling attention to improper advertisements or mailing pieces and correcting any misstatements therein.

Representatives of the subject company have stated that it has made an effort to comply with the regulations and intends to do so in the future. They have protested that a misunderstanding as to what practices constituted a violation was possible under the regulations then in force and that Bristol-Myers' violation was occasioned by such a mistake.

Accordingly, we do not believe that the suggested criminal prosecution is required to obtain judicial determination as to legal contentions of the agency or as a necessary aid to enforcement of the Act and regulations. Therefore, prosecution is declined.

While we stand ready to use any of the enforcement procedures prescribed by the statute to insure that prescription advertising fits the requirements of the statute and the regulations, candor requires us to observe that in those instances where we have secured criminal convictions for this type of violation, the penalties imposed by the Courts have not been such as to provide effective deterrents. On the other hand, the technique recently employed by the Commissioner of Food and Drugs, about which we have read in the trade media, appears to provide more assurance of future compliance on the part of those Companies subject to the regulations. It seems obvious that an ethical pharmaceutical company will regard the so-called Dear Doctor letter as a more opprobrious experience than any other available enforcement measure, particularly since it has not been the Commissioner's practice to recommend for prosecution the responsible individuals of the offending corporations. We urge that the Commissioner of Food and Drugs continue to utilize this technique which he has stated has proved very effective, while resorting to civil or criminal litigation only in respect to those recalcitrant offenders, if any there be, as to whom other measures have proved ineffective. If the Government can show that prosecution is resorted to only in such circumstances, the Courts may well adopt a different attitude in imposing sentence.

We are closing our file on this matter.

Sincerely,

WILL WILSON,
Assistant Attorney General,
Criminal Division.

By HAROLD P. SHAPIRO,
Chief, Administrative Regulations Section.

JANUARY 17, 1967.

In reply refer to F.D.C. No. 53053.
The Honorable ATTORNEY GENERAL,
Department of Justice,
Washington, D.C.

DEAR MR. ATTORNEY GENERAL: We request the institution of criminal proceedings under the Federal Food, Drug, and Cosmetic Act, against Rexar Pharmacal Corporation, Brooklyn, New York, Mr. Armin Rosner and Mr. Martin Benjamin.

The offenses complained of occurred during the period from about April 18, 1964, to about October 1, 1965, and involve the introduction into interstate commerce at Brooklyn, New York, for delivery to Teaneck, Fort Lee and Paramus, New Jersey, of Oby-Rex tablets and time disintegration capsules and Obetrol tablets.

There are transmitted herewith a suggested form of criminal information and the following exhibits:

(1) Copies of Notice of Hearing.

(2) Copies of bottle labels for Oby-Rex and Obetrol tablets.

(3) Copies of package insert labeling (the approved New Drug Application labeling) for Obetrol tablets.

(4) Copy of the advertisement for Obetrol tablets which appeared in *Modern Medicine* for September 13, 1965.

SECTIONS OF THE ACT INVOLVED

The Information charges four violations of 21 U.S.C. 331(d) in that the defendants caused the introduction into interstate commerce of new drugs, the Oby-Rex capsules and tablets, which was in violation of 21 U.S.C. 355(a), since no approval of an application filed pursuant to 21 U.S.C. 355(b) was effective with respect to the drugs.

The Information also alleges in one count that the Obetrol tablets were misbranded within the meaning of 21 U.S.C. 352(n) in that the defendants failed to include in the advertisement caused to be issued by them with respect to the drug in the September 13, 1965, issue of the *Modern Medicine*, a true statement of information in brief summary relating to side effects and contraindications and effectiveness of such drug as required by regulations 21 CFR 1.105(e) and (f)(2).

REASONS FOR INVESTIGATIONS

On July 24, 1959, the firm received an approved New Drug Application for a product known as Obetrol tablets in 10 and 20 milligram strengths. Obetrol consisted of a combination of four different amphetamine salts in equal strengths as follows: Methamphetamine Saccharate, Methamphetamine Hydrochloride, Amphetamine Sulfate, Dextro Amphetamine Sulfate.

"Obetrol" was the trade name used when the drug was sold to wholesalers, while "Oby-Rex" was the trade name used when the same drug was sold to doctors. The drug will be referred to as "Obetrol" in the letter in the interest of clarity.

In 1962, the Food and Drug Administration learned that the firm was distributing a 30 milligram tablet and capsule under the name of "Obetrol" without a supplemental New Drug Application. However, there was no evidence that the firm was shipping this drug in interstate commerce at that time. On February 6, 1963, Food and Drug Administration Inspector Ernest Schmalz inspected this firm and learned that it was still manufacturing the 30 milligram Obetrol capsules and tablets, but apparently not shipping the drug in interstate commerce. Mr. Armin Rosner, the President of the firm, was asked by the inspector about the 30 milligram dosage form and his reasons for not filing a New Drug Application or a supplemental New Drug Application for these products. Mr. Rosner replied that he was of the opinion that the New Drug Application for Obetrol allowed dosages up to 60 milligrams per day. He pointed out that the directions for use for the 30 milligram tablets provided that the daily dosage fell within this range. He, therefore, questioned the need for submitting a supplemental New Drug Application or a second New Drug Application for the 30 milligram dosage form. He was advised by Inspector Schmalz to discuss this matter with the Food and Drug Administration's New Drug Branch in Washington, D.C.

On August 3, 4 and 5, 1964, Food and Drug Administration Inspectors Carl E. Lorentzson and Charles Thorne inspected the firm and learned that it was still manufacturing the 30 milligram Obetrol tablet and capsule and shipping it in interstate commerce without an approved New Drug Application. As a follow-up to this inspection, the Food and Drug Administration collected samples of 30 milligram Obetrol time disintegration capsules and tablets in interstate commerce. (Counts I and II)

In the spring of 1964, the firm submitted a Supplemental New Drug Application. At that time, it came to the attention of the Bureau of Medicine of the Food and Drug Administration that the firm was advertising its 10 and 20 milligram Obetrol tablets with the use of false and misleading claims. Some of the objections raised by the Bureau of Medicine to the firm's advertising were as follows:

(1) It failed to list Obertol's side effects.

(2) It implied that Obetrol was unique in that it was safer and more effective than other amphetamines. This claim was unsupportable and illogical.

(3) It claimed that Obetrol was effective in "difficult cases," whereas, the two papers referred to in the advertisement did not demonstrate this fact. In addition, these two papers contained identical cases, were written by the same authors, but were published in two separate journals.

(4) It invited the misuse of the drug without proper regard for patient-safety by quoting, out of context, in such a way as to conceal the fact that some patients could not tolerate the drug at all, and others found it necessary to reduce the dosage to avoid dangerous side effects.

(5) It tampered with a direct quote through the insertion of a phrase, a wrongful act aggravated: (a) by the fact that there was no information in the author's article justifying the idea suggested in the inserted phrase; and (b) by the fact that the tampering invited a dangerous over-confidence in the use of Obetrol in cardiovascular patients in whom the drug was contraindicated.

The quote from the author's article reads as follows, with the words the defendants inserted being in brackets: "In the cooperative patient [Obetrol] was markedly beneficial in producing the desirable weight loss with minimal side effects, even in [the case of a high percentage of patients] with cardiovascular and other chronic ailments which [normally] make use of other amphetaamines undesirable because of side effects."

On August 4, 1964, Mr. Armin Rosner and his attorney met with representatives of the Food and Drug Administration and were advised to discontinue their current advertising campaign with respect to Obetrol tablets. The firm then advised the representatives of the Food and Drug Administration that it manufactured and sold a 30 milligram Obetrol tablet and capsule without an approved New Drug Application, since it was of the opinion that the submission of a New Drug Application was not necessary, as it was selling this drug directly to physicians.

In a letter dated August 12, 1964, from Rexar Pharmacal Corporation to the Food and Drug Administration, the firm promised to discontinue all advertising of the Obetrol 10 and 20 mg. tablets and to discontinue the manufacture of Obetrol tablets and capsules in excess of 20 milligrams. The firm then proposed a revised labeling as part of its supplemental New Drug Application for Obetrol tablets. The final labeling for the drug was approved by the Food and Drug Administration on July 13, 1965.

Shortly after the labeling was approved, the Food and Drug Administration learned that the firm had once more reinstituted an advertising and promotional campaign for Obetrol. The firm placed an advertisement in the September 13, 1965, issue of *Modern Medicine*, which did not state in brief summary, or at all, those precautions as set forth in the approved New Drug Application labeling for the drug, which were pertinent with respect to the use recommended or suggested in the advertisement as required by the regulations 21 CFR 1.105(e) and (f)(2) in that the brief summary failed to state that the drug should be used with caution in individuals with anoxeria, insomnia, vasomotor instability, asthenia, psychopathic personality, a history of homicidal or suicidal tendencies, and individuals who are known to be hyperactive to sympathomimetic agents or emotionally unstable individuals who are known to be susceptible to drug abuse; and that certain monoamine oxidase inhibitors may potentiate the action of Obetrol. Consequently, the Food and Drug Administration collected a sample of Obetrol (Count V).

The defendants may claim that since the advertisement in *Modern Medicine* contained a brief summary of side effects and contraindications, as set forth

in the approved New Drug Application labeling, they have not violated Section 502(n) of the Act, nor regulations 21 CFR 1.105(e) and (f), as these sections and regulations only require a brief summary of side effects and contraindications as set forth in the approved New Drug Application labeling, no mention being made of precautions.

We believe that "side effects" and "contraindications" certainly include "precautions" as this word is used in the approved New Drug Application labeling. Congress clearly intended that prescription drug manufacturers should provide physicians with adequate warnings in prescription drug advertisements of those conditions in which use of the drug entailed a high degree of risk. It is pure sophistry to contend that Congress wanted physicians to be warned of side effects and contraindications as set forth in the approved New Drug Application labeling, but not to be warned of the "precautions" as set forth in the approved New Drug Application labeling.

On September 29, 1965, Food and Drug Administration Inspector Paul T. Wiener inspected this firm and learned that it was still manufacturing and shipping in interstate commerce 30 mg. Obetrol tablets without an effective New Drug Application. As a follow-up to this inspection, the Food and Drug Administration collected two samples of Obetrol 30 mg. tablets in interstate commerce because the article was a new drug without an approved New Drug Application (Counts III and IV).

HISTORY OF FIRM AND INDIVIDUALS

This firm first came to the attention of the Food and Drug Administration in early 1953 when the Connecticut State Division of Drugs, Devices, and Cosmetics referred a sample of dextro-amphetamine sulfate to the Food and Drug Administration's office because the label declared a fictitious name and address of a manufacturer. The manufacturer and shipper were believed to have actually been Rexar Pharmacal Corp. As a result of this complaint, an initial inspection of the firm was made on March 11, 1953, which disclosed that the firm was operating with poor manufacturing control conditions. The original sample which bore the fictitious name and address of the manufacturer was assayed and found to contain only 72% of labeled amount of dextro-amphetamine sulfate. However, the sample was placed in permanent abeyance because it could not be definitely ascertained that the subject firm was the manufacturer and distributor of these amphetamine tablets.

The firm was again inspected on December 15, 1953, at which time, according to Mr. Armin Rosner, the firm was doing a minimal business. The firm was not then shipping its drugs in interstate commerce.

The firm was inspected once more on February 15, 1955, at which time it was learned that the firm was manufacturing Obetrol, a new drug, without an effective New Drug Application and shipping the drug while using false and misleading claims. As a follow-up to this inspection, a sample was collected which resulted in a Hearing on September 28, 1956. The sample was placed in permanent abeyance, however, because the firm agreed: (1) to revise its labeling in an effort to bring the drug in compliance with the law, and (2) to submit a New Drug Application for the 10 and 20 mg. Obetrol tablets.

The firm was inspected on July 25, 1955, at which time it was learned that the firm was shipping another new drug, namely, Obertina tablets, a combination of amphetamine and rauwolfia serpentina, without an effective New Drug Application. However, the Food and Drug Administration could not obtain a sample of the product in interstate commerce and no action was brought.

A follow-up inspection, made on July 8, 1958, showed that the firm was marking time while its New Drug Application for Obetrol was under study by the Food and Drug Administration.

The firm was again issued a Notice of Hearing in early 1963 because it had shipped a new drug consisting of thyroid and 30 mg. of amphetamine salts without an effective New Drug Application. At the time of the Hearing, the respondent stated that a New Drug Application was unnecessary as the drug was shipped under what the firm termed a physician-pharmacist relationship. The firm had made this drug to order for one physician. The number was placed in permanent abeyance. It was its position that Rexar Pharmacal Corp. was simply asked to fill a prescription for the physician. No further action was taken because the firm agreed to discontinue the interstate distribution of this product.

On February 6, 1963, the firm was again inspected and the Food and Drug Administration learned that the firm was distributing Obetrol tablets in violation of its New Drug Application. A seizure was made of this drug in Los Angeles, California.

EVIDENCE OF VIOLATIVE SHIPMENT

Counts I and II

This sample was collected on August 8, 1964, from J. Raymond McSpirit D.O., 703 Cedar Lane, Teaneck, New Jersey, by Inspector Frederick T. Merola. The sample was identified by Dr. McSpirit, who furnished the Inspector with an invoice showing that the drugs were shipped by Rexar Pharmacal Corp. from Brooklyn, New York on or about April 18, 1964.

Counts III and IV

This sample was collected on October 5, 1965, from Daniel Reider, D.O., 2361 Lemoine Avenue, Fort Lee, New Jersey, by Inspector Paul T. Wiener. The sample was identified by Dr. Reider, who furnished the Inspector with an invoice showing that the drugs were shipped by Rexar Pharmacal Corp. from Brooklyn, New York, on or about March 1, 1965.

Count V

This sample was collected on December 15, 1965, from D. Katzman & Co., 670 Winters Avenue, Paramus, New Jersey, by Inspector Alfred M. Levy. The sample was identified by Mr. Stanley Szewczyck, a buyer for the firm, who furnished the Inspector with an invoice showing that the drug had been shipped by Rexar Pharmacal Corp. from Brooklyn, New York, on or about October 1, 1965. On December 29, 1965, Inspector Levy obtained from Richard P. Keating, M.D., 130 Prospect Street, Ridgewood, New Jersey, the September 13, 1965, issue of *Modern Medicine*, together with an appropriate affidavit signed by Dr. Keating.

RESPONSIBILITY OF INDIVIDUALS

Both Mr. Armin Rosner, President, and Mr. Martin Benjamin, Vice President, share equally the responsibility for the conduct of the firm. During the inspection of February 6, 1963, the Inspector observed that both men were familiar with the manufacturing and control procedures. They told the inspector they shared equally in the responsibility for making major decisions in the firm's operations. During the inspection of August 3, 4 and 5, 1964, the Inspectors obtained information and specimens of the advertisements of Obetrol tablets from Mr. Martin Benjamin. At that time, Mr. Armin Rosner told the inspectors that he considered the responsibility for operations of the firm, including labeling, shipping and sanitation, to be a joint one between himself and Mr. Benjamin. Both men, the Inspector noted, knew exactly what was going on in the operation of this business.

During the inspection of September 29, 1965, Mr. Benjamin told the Inspector that Mr. Rosner was in charge of plant sanitation, shipping and manufacturing operations and that Mr. Benjamin was active in sales and promotion.

In the last three to four years, both Mr. Rosner and Mr. Benjamin have dealt with the Inspectors either singly or together during each of the inspections made by the Food and Drug Administration. The firm is small enough so that each of the two men was aware of what was going on in the firm. In addition, they jointly set company policy and were equally responsible for the labeling and the advertising for the drugs which were shipped in interstate commerce.

HEARING HELD PURSUANT TO 21 U.S.C. 335

A Notice of Hearing was issued to Rexar Pharmacal Corp., Mr. Arwin Rosner and Mr. Martin Benjamin on January 10, 1966, charging the shipment in interstate commerce of a New Drug, the 30 mg. dosage form of Obetrol, without an approved New Drug Application. It was also alleged that the firm had misbranded its Obetrol 10 mg. tablets because of medical journal advertising which did not state in brief summary, or at all, certain side effects and contraindications as set forth in its approved New Drug Application labeling for the drug. Mr. Rosner and Mr. Benjamin, together with their attorney and consultants, appeared at the Hearing.

The respondents first addressed themselves to the charge concerning the omission of a precautionary statement in the advertising for the drug, Obetrol. They claimed that they were guided by a press release issued by the Food and Drug

Administration on November 23, 1964, pertaining to the information required in a brief summary. They also stated that they were guided by other firms' advertising for similar drug products. In addition, they felt that the context of the advertisements was geared for physicians, and since the doctors themselves received other material, such as brochures, the doctors undoubtedly would have some realization of the precautionary guides to be observed. However, they admitted that they were wrong in omitting the precautionary statements, and they assured the Food and Drug Admiinstration that this error had been corrected in the current advertising for the drug.

The firm knew full well that the gravamen of the regulations was pertaining to prescription drug advertising. It had been warned in 1964 that its drug advertising for this product was false and misleading. It had discussed with the Food and Drug Administration the advertising drug regulations and how to correct its advertising. Despite this information, the firm blatently advertised this drug in the summer of 1965 without giving full information as required by the regulations. The precautionary statements, which the firm omitted, contained the most important information about the cautions to be observed in patients with anorexia, insomnia, vasomotor instability, asthenia, psychopathic personality, a history of homicidal or suicidal tendencies, and individuals who are known to be hyperactive to sympathomimetic agents or emotionally unstable individuals who are known to be susceptible to drug abuse; and that certain monoamine oxidase inhibitors may potentiate the action of Obetrol.

With respect to the interstate shipments of the Obetrol 30 mg. tablets and capsules, the firm stated that this drug was sold by the firm since 1952. Hence, the firm was under the impression that the drug fell within the scope of the "grandfather clause" and a New Drug Application was not necessary.

Unfortunately for the defendants, the "grandfather clause" (Pub. L. 87-781, Section 107) requires that the drug be generally recognized, as of October 9, 1962, as safe when used for the purposes intended. This drug was not so recognized on that date.

The second point the firm made at this Hearing was that the drugs were sold directly to physicians and not through regular commercial channels. This, it said, was an ordinary "Physician-Pharmacist" relationship, whereby the firm was simply filling a prescription for the physician. The defense fails to explain how an order involving some 3,000 tablets sold to one physician and a 1,000 tablet order to a second physician is the same as prescribing for an individual patient as is usually done in the physician's daily practice of medicine. Another objection to the defendant's defense is that, when there is a violation of 21 U.S.C. 355(a), there is no exemption for any so-called "Physician-Pharmacist" relationship. As you recall, the first four counts charge a violation of 21 U.S.C. 355(a). The firm had been previously advised that this conception of theirs was wrong during the Hearing held in early 1963.

The third point the firm made was that the 30 mg. tablets came within the limits of the 60 mg. daily dosage requirements under their New Drug Application for the firm's 10 and 20 mg. Obetrol tablets. This argument had no merit since the New Drug Application provided for the marketing of a specific formulation of the drug with specific labeling. The formulation and labeling for these 30 mg. preparations differed from that provided for by the New Drug Application, hence, these preparations were not covered by the New Drug Application.

Lastly, the respondents stated that they were currently preparing to submit a New Drug Application for their 30 mg. Obetrol tablets and capsules. This Application is still pending. The firm was well aware of our position with respect to the status of this drug. It was advised in August, 1964, that the Food and Drug Administration considered these preparations to be New Drugs without an effective New Drug Application and was told that the Food and Drug Administration could not condone the marketing of this drug in interstate commerce without an approved New Drug Application. Yet, the firm chose to continue the sale of this drug without an approved New Drug Application. It is noteworthy that, at the time of the Hearing, the firm indicated, that it had ceased distributing this drug in interstate commerce, but that it was still selling this drug in intrastate commerce.

CONCLUSIONS

Warnings at Administrative Hearings and at meetings with the Bureau of Medicine of the Food and Drug Administration have gone unheeded by this

firm. It had been advised as far back as 1958 that its 30 mg. Obetrol tablets and capsules were New Drugs. Despite this warning, the firm still failed to file a New Drug Application for these drugs and continued to ship them in interstate commerce without an approved New Drug Application. Similarly, the firm was advised in early 1964 that its advertising for its Obetrol 10 and 20 mg. tablets was false and misleading and that it could only advertise the drugs through the use of claims set forth in the labeling approved in the firm's New Drug Application. While it is true the firm discontinued advertising its 10 and 20 mg. Obetrol tablets until the new labeling for these drugs was approved in the summer of 1965, the firm started to illegally advertise again as soon as the final printed labeling had been approved. This time the firm omitted the precautionary statements which relate to the side effects, contraindications, and effectiveness required to be fairly presented in the advertising by the regulations under the drug advertising section of the law. It is our opinion that prosecution of the firm and the two responsible individuals is fully warranted.

WITNESSES

The principal witnesses in this case will be the Government inspectors who collected the samples; cooperating physicians who subscribe to *Modern Medicine* and medical officers of the Food and Drug Administration's Bureau of Medicine who can testify as to the approved New-Drug applications, approved labeling, and the serious nature of the alleged medical journal advertising misbranding.

It is requested that, if the Information is amended, the United States Attorney furnish us with a copy thereof; also, that the United States Attorney keep us advised of the progress of the case and its disposition. The New York District of the Food and Drug Administration will arrange for the presence of the necessary witnesses and assist in the presentation of the case. Upon request, we shall render such further assistance as may be possible.

Very truly yours,

WILLIAM W. GOODRICH,
Assistant General Counsel,
Food and Drug Division.

UNITED STATES DEPARTMENT OF JUSTICE,
Washington, D.C., April 24, 1967.

Re Rexar Pharmacal Corp., Armin Rosner, and Martin Benjamin, FDC No. 53053, Federal Food, Drug, and Cosmetic Act.

DEAR MR. GOODRICH: This is in reply to your letter to the Attorney General of January 17, 1967, in which you request the institution of criminal proceedings against the above-captioned subjects for violations of the Federal Food, Drug, and Cosmetic Act committed between April, 1964, and October, 1965.

We have carefully reviewed the statements set out in your letter concerning the subjects' activities relative to the sale of certain drug products.

As to the fifth count, we are not disposed toward the conclusion expressed in your letter that the words of the statute, also used in your regulations, requiring a statement of contraindications, side effects, and effectiveness in prescription drug advertisements are so clearly inclusive of "precautions" as to give the subjects "fair warning" that such items must be included. We have observed that in the advertisement in *Modern Medicine* in September, 1965, the subjects included, under the statutory headings, the full and exact language found under those headings in the labeling approved by the Food and Drug Administration. There is nothing in the Act or the regulations to indicate that the words therein have a larger meaning than that of the approved labeling. Accordingly, we are of the opinion that the advertisement to which reference was made in your letter is not violative of the Act. Moreover, we do not believe that the factual situation here is such that the Government would be able to prevail in the event the theory suggested in your letter were to be tried out in a criminal prosecution of Rexar and its officers. Therefore, prosecution is declined as to the charges set out in Count V of your suggested information.

Inasmuch as the violations of April 18, 1964, and March 1, 1965, were not reported to us for criminal prosecution until after the appearance of the advertisement in *Modern Medicine* in September, 1965, we are uncertain as to whether you are of the opinion that prosecution is merited on the basis of those acts

alone. Since your letter leaves the impression (p. 9) that the subjects have filed a supplemental new drug application covering the 30 mg dosage form for "Obetrol" and you do not indicate whether or not the application has been rejected, it would appear that in this respect compliance with the Act may be deemed to have been achieved.

Therefore, we are withholding further action with regard to the violations of April 18, 1964, and March 1, 1965, in order that you may inform us as to whether you believe prosecution for these violations should be instituted. In view of the factual situations outlined in your letter we are particularly interested in being informed as to the status of any supplemental application for the 30 mg dosage form. You will undoubtedly appreciate the force of an argument to a jury that physicians could have prescribed two 30 mg doses per day which would have been within the allowable lifitation of the approved labeling and which would have been available to patients by taking one 20 mg and one 10 mg tablet.

If there is any sound medical reason why such dosage should not be prescribed and thus why 30 mg tablets should not be available to physicians, we would be able to counteract any such defense with some force. Whether or not such reason exists is therefore a factor to which we would attach considerable importance in the event prosecution is requested as to the foregoing violations.

We also believe that it would be helpful to know whether the subjects in any way solicited the sale of the 30 mg tablets on April 18, 1964, and March 1, 1965, to Doctors McSpirit and Reider respectively, or whether such sales were solely as a result of unsolicited orders by the purchasers.

Sincerely,

FRED M. VINSON, Jr.,
Assistant Attorney General,
Criminal Division.
By HAROLD P. SHAPIRO,
Chief, Administrative Regulations Section.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
September 26, 1967.

Attention Harold P. Shapiro, Chief, Administrative Regulations Section.
Re Rexar Pharmacal Corp., Armin Rosner, and Martin Benjamin. Your ref: FMV:JWK:mlh, 21-52-246, F.D.C. No. 53053.

Hon. FRED M. VINSON, Jr.,
Assistant Attorney General, Criminal Division, Department of Justice, Washington, D.C.

DEAR MR. VINSON: We have considered with the Food and Drug Administration the questions that you raised concerning this case.

The four counts which allege violations of 21 U.S.C. 331(d) are strong counts involving the distribution of unapproved new drugs, and would by themselves, support criminal action.

The firm did submit a supplemental new drug application for Oby-Rex 30 mg., but it was incomplete and the firm has been advised of this. Therefore, compliance has not been achieved. Moreover, the firm was advised in 1964 both to discontinue their violative advertising and that a 30 mg. tablet would require a new drug application.

It is irrelevant that a physician could have prescribed a 20 mg. and a 10 mg. tablet, thereby giving his patient a total of 30 mg. at each dose. This does not make it legal for the firm to market a 30 mg. dose without complying with the new drug requirements. Had a doctor so prescribed, he would have exceeded the limits of the safety approval in the new drug application. While he may, in his discretion, prescribe an excessive dose for his own patient, he does so at the risk of civil liability for exceeding the dosage that has been proved safe, as required by law. The fact is that the consensus of medical opinion holds that the dosage of 30 mg. per tablet is not generally recognized as safe. To say that a person can take 20 5-grain aspirins at one time is not to say that it is permissible to make a 100-grain aspirin tablet.

The Administration's file does not reflect that the firm has detail men or uses other means for the direct solicitation of orders from physicians.

In regard to the count based on the advertisement in *Modern Medicine*, September, 1965, we would ask you to reconsider your decision not to prosecute with the following considerations.

We have previously written you our views as to the legal necessity for including in the brief summary, information from the package insert titled there "warnings" and "precautions". [United States v. Wyeth Laboratories, F.D.C. 52673 Your ref: FMV:JNK:mfs. 21-62-326 22A-48-20] The law requires that every ad for a prescription drug shall present in brief summary form "such other information * * * relating to side effects, contraindications, and effectiveness as shall be prescribed in regulations."

The regulations require that this summary shall fairly show the effectiveness of the drug in the conditions for which it is recommended, * * * together with those side effects and contraindications that are pertinent with respect to the uses suggested in the advertisement and any other use or uses for which the dosage form advertised is commonly prescribed. When the drug is an approved new drug this information shall be the information from the approved new drug application.

Here, the information omitted, though headed precautions in the approved labeling, was information relating to side effects and contraindications. It warned against use of the drug by persons with anorexia, insomnia, vasomotor instability and other conditions. This was to tell the physician that such persons might experience serious side effects—so serious that the drug should be avoided. While the drug may not be completely contraindicated for all persons with these symptoms, it is contraindicated in some, and in others, side effects are to be expected.

So literally this information was related and pertinent to side effects and contraindications in the medical sense.

Far more important, however, is the fact that Congress used "side effects" and "contraindications" in 502(n) to cover the relevant hazards—whether so denominated in the labeling so-called precautions or warnings.

The legislative history on this point clearly shows that Congress intended the physician to be fully informed by those ads, since they recognized that the majority of doctors learn about drugs from such promotions. This has been discussed in greater detail in our previous letter. For example, the provision, that ads could be exempted from all of the requirements of informing the physician, if they included a statement that full information could be obtained on request, was rejected on the floor of the House. Cong. Rec. House 87th. Cong., 2d Sess., September 27, 1962, pp. 19928-9. The information to be supplied would be the full disclosure inserts which were required even then to include "precautions". The sponsor of this amendment, Representative Blatnik, specifically stated that "There is ample evidence to demonstrate that because of time limitations physicians rely on drug advertisements a great deal in deciding which they should prescribe for their patients. It is incumbent upon us to assure that no false or misleading information is inadvertently relied upon.", p. 19922, and then, "I want to see this bill so drawn as to make sure that doctors get all available information * * *" [in the advertisement itself], p. 19923. To leave a doctor with the impression that no special consideration or care need be given to a patient with anorexia, etc. is certainly misleading.

President Kennedy's proposed amendment on advertising to the Senate Bill was offered on the ground that "Such advertisements should be required to make fair disclosure to physicians of the information (good or bad) needed to permit them to do a better job of selecting drugs for use in their practice". Letter from President Kennedy to Senator Eastland, August 4, 1962, reported Cong. Rec. Senate, August 6, 1962, p. 14682. This would, in our opinion, include precautions.

We think that a reading of the Legislative History on this matter leaves no doubt that the information lacking in this ad was of the sort that Congress intended be presented to the physician.

If we may be of any further assistance, please do not hesitate to call upon us.

Sincerely yours,

WILLIAM W. GOODRICH,
Assistant General Counsel,
Food and Drug Division.

OCTOBER 25, 1967.

Re Rexar Pharmacal Corp., FDC No. 53053.
MR. WILLIAM W. GOODRICH,
Assistant General Counsel, Department of Health, Education, and Welfare, Washington, D.C.

DEAR MR. GOODRICH: This is in response to your letter of September 28, 1967, in which you answered certain questions which we raised in our letter to you dated April 24, 1967. The views you express concerning the subject's advertisement of the drug Oby-Rex in *Modern Medicine* for September, 1965, have been carefully considered. However, we have observed that, although the statute and the regulations pertaining to advertising refer only to "side effects" and "contraindications", other regulations pertaining to the labeling of prescription drugs refer to "relevant hazards, contraindications, side effects, and precautions" (for example, see: 21 C.F.R. Section 1.106(b)(3)(i); 1.106(b)(4)(i); 130.4(c); 130.9(d)(1); 130.11(a)(1) and (3)). Thus, where the agency has desired to require inclusion of information in the labeling of a prescription drug of "hazards" or "precautions", it has done so by using those specific words even though in the same sentence it has required the inclusion of "side effects" and "contraindications." Accordingly, it appears that the agency has recognized that each of these words has a separate definite meaning and we could not sustain a contention that "precautions" are included by implication in the statutory language, particularly in an instance in which the labeling of the drug as approved by the agency distinguished between what constitutes "side effects and contraindications" and "precautions."

Therefore, prosecution on the basis of the failure of the subjects to include in the advertisement a statement of the "precautions" is declined.

Insofar as the counts pertaining to the shipment, on April 18, 1964, and March 1, 1965, to Doctors McSpirit and Reider, according to their request, of 30 mg strength tablets of Oby-Rex and Oby-Rex M tablets are concerned, we are not persuaded that such drastic action as criminal prosecution is required, or that if it were instituted a successful result could be obtained.

The offenses took place between two and one half and three and one half years ago, but were not reported until January of this year. Despite your statement that compliance has not been achieved, no additional violations have been reported and the subjects have filed a supplemental new drug application requesting approval for the 30 mg dosage form. Although this application has been characterized as "incomplete" it has not been withdrawn nor has the agency taken any steps looking toward a refusal to approve it. Apparently the subjects are attempting to complete the application. Thus, despite your statement as to the consensus of medical opinion, the record before the agency is such as to leave open the question as to whether such dosage form is proper.

In addition, the facts that under the approved labeling a dosage totaling 60 mg per day may eventually be reached in the administration of this drug and that the dosage form of the shipment was specifically ordered by licensed physicians who are legally entitled, and ethically required, to prescribe for their patients the dosage dictated by their own judgment based upon a knowledge of their patients' requirements will tend to weaken any criminal prosecution.

Accordingly, it is our view that the time which has elapsed since the commission of the violation and the factual situation make this an unattractive case for criminal action. Moreover, since the subjects have not sold this dosage indiscriminately in interstate commerce and have filed a supplemental application covering its use, it would seem prosecution is not necessary to enforce compliance with the requirement of the law.

Thus, prosecution is declined.

Sincerely,

FRED M. VINSON, Jr.,
Assistant Attorney General,
Criminal Division.
By HAROLD P. SHAPIRO,
Chief, Administrative Regulations Section.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
April 18, 1968.

Attention Harold P. Shapiro, Chief, Administrative Regulations Section.
Re Rexar Pharmacal Corp., Your Ref. FMV:JWK:adj 21-52-246, FDC No. 53053.

Hon. FRED M. VINSON, Jr.,
Assistant Attorney General, Criminal Division, U.S. Department of Justice, Washington, D.C.

DEAR SIR: You will recall that Mr. Barrett and I met with Mr. Shapiro and Mr. Murphy last November to discuss your reasons for declining prosecution, set forth in your letter of October 25, 1967.

We went over the file together and we pointed out that the new drug charge was a serious one because (1) the product was labeled with no warning information at all (no package insert was included) and with dose recommendation of "one table once to twice daily", (2) the strength of this tablet (30 mg.) which contains methamphetamine (speed) along with amphetamine makes it a dangerous product, (3) our medical advisors supplied a memorandum describing adverse reactions to 30 mg. doses of amphetamine, and (4) the two sales involved were not isolated transactions.

We asked our New York Office for further information. They have sent us an inspection report covering an inspection in September 1967 and a list of interstate shipments of this product made in June 1965 (the month the violation occurred). There were four additional shipments made that month, two to consignees in Ohio, one to a purchaser in Massachusetts and one to Long Beach, California. Each shipment involved a bottle or bottles of 100 tablets or capsules.

Our letter of September 28, 1967, said that the firm does not have detailmen. The file shows that Mr. Benjamin personally delivered one shipment as a salesman.

You asked whether the firm had in fact discontinued the 30 mg. dosage. The 1967 report shows that the firm claims to have discontinued interstate shipments but continues to do about $20,000 per year in intrastate business in products without approved new drug applications, including Oby Rex in a 30 mg., Timed Disintegration Capsule and Tablet form. The firm was also using a "Dear Doctor" promotional letter with physician samples to elevate mood and and help relieve despondency, claims not approved in the new drug labeling, for those products and not included in the prescribing information.

It seems, therefore, that the firm despite several warnings has not yet decided to comply with the new drug requirements of the law. The proposed defendants seem to have little concern for patient safety or little appreciation of the hazards in the use of high doses of amphetamines.

As to the advertising charge, we think there can be no doubt whatever that the information the Company headed "precautions" in its labeling was information "related to side effects and contraindications". Congress used different language in Section 502(n), than the Agency used in its full disclosure labeling regulations promulgated several years before, but the intent of the Congress was plain, as we have shown in our discussion of these advertising cases with your people.

We simply cannot agree that any material now included in product brochures approved over the past 28 years in new drug clearances that is headed "precautions" or "warnings", or indeed anything other than material headed "side effects" or "contraindications", is not information *related* to "side effects" and "contraindications" as those terms were used in the 1962 Drug Amendments. Not only is this directly contrary to the Congressional intent and to the plain statutory language, it is untrue as a factual matter. In this case, the precautionary information left out of the ad was the most important information needed for safe use of the drug.

Your declination of the new drug charge was based on your appraisal of the likelihood of success, the drastic nature of the proposed action, the time lag between the violations and reporting them to you, your understanding of the "incomplete status" of the NDA, and on the startling statement that a physician is ethically and legally bound to treat patients with drug dosages beyond the limits of safety proven through the new drug procedures.

This action is not drastic when one considers that the drug involved is a potent amphetamine mixture, with well recognized hazards, which despite some years of clinical use in medicine has not been shown or recognized to be safe in the 30 mg. dosage. To place such an unproved dosage on the market in utter disregard for the new drug procedure is a substantial violation of law and a distinct disservice to physicians who prescribe and patients who are expected

to use prescription drugs. The incomplete application was rejected by the incomplete letter. Our regulations, upheld on this point by the Sixth Circuit in the Turkel case, call for filing over protest if the Company wishes to pursue its application. This Company has not done so and its application is a closed one.

Exceeding approved dosage of drugs is one of the surest ways to patient injury. Physicians have neither the legal nor the ethical right to experiment with their patients with excessive dosages without the patients informed consent, and when drugs of interstate origin are used, without compliance with the IWD regulations.

Very truly yours,

WILLIAM W. GOODRICH,
Assistant General Counsel,
Food and Drug Division.

MAY 29, 1968.

Re Rexar Pharmacal Corp., FDC No. 53053.
Mr. WILLIAM W. GOODRICH,
Assistant General Counsel,
Department of Health, Education, and Welfare,
Washington, D.C.

DEAR MR. GOODRICH: This is to acknowledge receipt of your letter of April 18, 1968, requesting us to reconsider our decision to decline prosecution in this matter.

Your comments relative to the alleged violation of the advertising provisions of the Federal Food, Drug, and Cosmetic Act appear to be the same as those made in at least one other similar matter. (See Syntex Laboratories, Inc., FDC No. 53222.) Our views regarding the narrow issue presented by similar facts were fully set forth in our letters to you pertaining to that matter and in our letter of October 25, 1967, concerning the present submission. We adhere to them and to our decision not to prosecute this matter insofar as the advertisement is concerned.

Neither does the information contained in your letter warrant any change in our decision not to prosecute on the basis of the shipments to Dr. McSpirit in April 1964, and Dr. Reider in March of 1965. Despite the statement that there were four additional shipments in June 1965, no evidence has been submitted proving that the sales were to persons other than duly qualified physicians who ordered the larger dosage form for the purpose of dispensing them to bona fide patients being treated by them. The sales of the drug in New York State do not constitute violations of the Federal law and cannot be construed as exhibiting an intent to violate the Federal Food, Drug, and Cosmetic Act.

Accordingly, we are still of the opinion that the age of the alleged violations and the factual situation present a very poor basis for criminal prosecution. The facts are such as to raise grave doubts as to whether they constitute a violation in the legal sense. Moreover, it is our belief that the circumstances upon which the Government would be compelled to rely are so unappealing to a judge and a jury as to render a conviction highly unlikely.

We desire to correct the statement attributed to us in your letter that, "a physician is ethically and legally bound to treat patients wih drug dosages beyond the limits of safety proven through new drug procedures." That is *not* our position. The correct statement of our position, to which we adhere, appears in the next to the last paragraph of our letter of October 25, 1967.

For the reasons indicated above, we continue to be of the view that prosecution of this case is not feasible. We are therefore closing our file.

Sincerely,

FRED M. VINSON, Jr.,
Assistant Attorney General,
Criminal Division.
By HAROLD P. SHAPIRO,
Chief, Administrative Regulations Section.

MARCH 16, 1967.

In reply refer to F.D.C. No. 53222.
The Honorable ATTORNEY GENERAL,
Department of Justice, Washington, D.C.

DEAR MR. ATTORNEY GENERAL: We request the institution of criminal proceedings in the District of New Jersey, under the Federal Food, Drug, and

Cosmetic Act, against Syntex Laboratories, Inc., 1401 Hillview Drive, Palo Alto, California, and 45 Walnut Avenue, Clark, New Jersey. The offenses complained of occurred on or about September 29, 1965, November 18, 1965, and February 18, 1966, and involve the introduction into interstate commerce at Clark, New Jersey, for delivery to Berkeley, California, of quantities of Norinyl, a prescription drug.

There are transmitted herewith a suggested form of criminal Information and the following exhibits:

A. Copy of Notice of Hearing.
B. Carton and bottle labels.
C. Package insert (approved new drug application labeling).
D. Copy of monograph in 1965 Edition of Physicians' Desk Reference.
E. Copy of advertisements in the November 1, 1965, November 15, 1965, and February 1, 1966, Editions of The American Journal of Obstetrics and Gynecology; the November, 1965, and February, 1966, Editions of Obstetrics and Gynecology; and the February 14, 1966, Edition of Modern Medicine.

SECTIONS OF ACT INVOLVED

The Information charges violation of 21 U.S.C. 331(a) in that the defendant caused the introduction into interstate commerce of quantities of Norinyl which were misbranded as hereinafter described.

Count I.—The drug was misbranded within the meaning of 21 U.S.C. 352(f)-(1) in that its labeling failed to bear adequate directions for use and it was not exempt from such requirement since its labeling, a monograph in the 1965 Edition of the Physicians' Desk Reference, failed to comply with the requirements of regulations 21 CFR 1.106(b)(4)(i).

Counts II and III.—The drug was misbranded within the meaning of 21 U.S.C. 352(n) in that the defendant failed to include in advertisements caused to be issued by it in the (Count II) November 1 and 15, 1965, Edition of The American Journal of Obstetrics and Gynecology and the November, 1965, Edition of Obstetrics and Gynecology, and in the (Count III) February 1, 1966, Edition of The American Journal of Obstetrics and Gynecology, the February, 1966, Edition of Obstetrics and Gynecology, and in the February 14, 1966, Edition of Modern Medicine, a true statement of information in brief summary relating to the side effects and contraindications of the drug as required by regulations 21 CFR 1.105(e) and (f).

BACKGROUND INFORMATION

"Norinyl" is a registered trade name used by the defendant for a drug composed of 2 mg. of Norethindrone and 0.1 mg. of Mestranol. At the time of the alleged violations, Norinyl was commonly prescribed as an oral contraceptive.

Syntex submitted to the Food and Drug Administration a new drug application for Norinyl which was approved on March 5, 1964. At this time, the Commissioner of the Food and Drug Administration sent a letter to Syntex Laboratories, Inc., in which he said that the claims made in the labeling were limited by the representations made in the new drug application. The Commissioner also said that the approval of the new drug application in no way relieved Syntex Laboratories from complying with all of the provisions of the Federal Food, Drug, and Cosmetic Act.

The 1965 edition of the Physicians' Desk Reference, published by Medical Economics, Inc., bore a monograph for Norinyl which appeared on pages 962 and 963. The Physicians' Desk Reference is published annually in cooperation with the subscribing manufacturers. The purpose of the Physicians' Desk Reference is to make available to physicians information on major pharmaceutical specialties. Information appearing in the Physicians' Desk Reference is solely that furnished by the manufacturers. This is explained by the foreward in the 19th Edition which contains the following statement: "The function of the publisher is the compilation, organization, and distribution of the information. Each product description has been prepared by the manufacturer, and edited and approved by the manufacturer's Medical Department, Medical Director, or Medical Consultant."

EVIDENCE OF MISBRANDING

Count I.—The drug, Norinyl, which is a prescription drug and which is a new drug subject to 21 U.S.C. 355, was not exempt from the requirements of 21 U.S.C. 352(f)(1) that adequate directions for use appear in its labeling since

it failed to comply with the condition for exemption set forth in the regulations 21 CFR 1.106(b)(4). Such condition requires that, in case of a drug subject to 21 U.S.C. 355, the labeling be substantially the same as the labeling authorized by the approved new drug application for such drug. This was not true with respect to Norinyl because its labeling, the 1965 Edition of the Physicians' Drug Reference, failed to include the following information which was in the new drug application labeling:

(1) A statement concerning the length of experience with the drug, and that although no deleterious effect of the drug on pituitary, ovarian, adrenal or uterine function has been noted, the long-range effect on these and other organs must await more prolonged observation.

(2) The information regarding the possibility of pregnancy if the treatment schedule is not adhered to; and that, if the regular menses fail to appear and the treatment schedule has not been adhered to, or, if the patient misses two regular menstrual periods, the possibility of pregnancy should be resolved before resuming Norinyl. If pregnancy is established, Norinyl should be discontinued during the period of gestation, on the basis that virilization of the female fetus has been reported with oral use of progestational agents or estrogen.

(3) The important information regarding the possible causal relationship between progestational agents and intravascular clotting. In addition, the Physicians' Desk Reference labeling contained the statement "it provides maximum protection against unplanned pregnancy and minimizes undesirable side effects resulting in fewer patient dropouts" which statement was not supported by the approved new drug application labeling.

Counts II and III.—In regard to the advertisements upon which the misbranding charges are based, examination has shown that they omitted certain information which was in the new drug application labeling and that they included certain information which was not in such labeling. The nature of such information is alleged in the criminal Information. Because of such omission and of such inclusion, the advertisements failed to include true statements relating to the side effects and contraindications of Norinyl as required by regulations.

EVIDENCE OF VIOLATIVE SHIPMENTS

Count I.—A sample of two 100-tablet bottles of Norinyl was taken at random from a lot of ten such bottles in the shelf stock of the Permanente Services Pharmacy, South San Francisco, California, by Food and Drug Inspector Frank W. Scholl. The lot was identified by Donald E. Murray, Manager and Pharmacist in Charge of the Dapite Division of Permanente Services, Inc., Berkeley, California, who said that the lot had been received from Syntex Laboratories, Inc., Clark, New Jersey, on October 8, 1965, and subsequently shipped to the above-mentioned pharmacy. Mr. Murray supplied the Inspector with supporting documents.

Count II.—No physical sample was obtained. However, Donald E. Murray of the Dapite Division of Permanente Services said that his firm had received 36 twenty-tablet packages and 48 100-tablet bottles of Norinyl from Syntex Laboratories, Inc., Clark, New Jersey, on November 26, 1965. Mr. Murray supplied Inspector Frank D. Korun with supporting documents relating to the shipment. Mr. Richard Wickel, Assistant Administrator for the Samuel Merritt Hospital, Oakland, California, provided Inspector Korun with copies of advertisements for Norinyl which appeared in the November 1, 1965, and November 15, 1965, Editions of The American Journal of Obstetrics and Gynecology, and the November, 1965, Edition of Obstetrics and Gynecology.

Count III.—A sample of three 100-tablet bottles was taken by Food and Drug Inspector Frank Korun at random from a lot of 48 such bottles at the Dapite Division of Permanente Services, Inc., Berkeley, California. The lot was identified by Mr. Donald Murray, who said that the firm received the lot from Syntex Laboratories, Inc., Clark, New Jersey, on February 28, 1966. Copies of documents relating to the shipment were provided by Mrs. Florence Burns, an employee of Dapite. Mr. Richard Wickel, Assistant Administrator for the Samuel Merritt Hospital, Oakland, California, provided Inspector Korun with copies of advertisements for Norinyl which appeared in the February 14, 1966, Edition of Modern Medicine, the February, 1966, Edition of Obstetrics and

Gynecology, and the February 1, 1966, Edition of The American Journal of Obstetrics and Gynecology.

The headquarters of Syntex Laboratories, Inc., are presently located in Palo Alto, California, but manufacturing at the time of the alleged violations was carried out elsewhere. The drug in question was manufactured by Syntex Laboratories employees' using equipment located on the premises of Warner-Chilcott Laboratories, Inc., Morris Plains, New Jersey. This manufacturing operation was under the control of Syntex Laboratories, Inc. The shipments of the drug were made by the Syntex Laboratories Branch in Clark, New Jersey.

HEARING HELD PURSUANT TO 21 U.S.C. 335

A Notice of Hearing issued pursuant to 21 U.S.C. 335 on April 8, 1966, addressed to Syntex Laboratories, Inc., 1401 Hillview Drive, Palo Alto, California.

A personal response was made by Mr. Vincent Kleinfeld, Attorney for the firm, on April 21, 1966. Mr. Kleinfeld did not question the interstate nature of the shipments and did not deny that the Physicians' Desk Reference was accompanying labeling as is charged in Count I. Neither did he deny the firm's responsibility for the shipments, for the placing of the monograph in the Physicians' Desk Reference, nor for the placement of the advertisements in question in the November issues of the various medical journals.

Mr. Kleinfeld said that the firm had no intention of deliberately omitting information from the Physicians' Desk Reference or from medical journal advertising that they believe would have been desired by the Food and Drug Administration. He said that honest men can differ in opinions as to what is required under the regulations and that Syntex's doctors had believed their medical journal advertising and the monograph in the Physicians' Desk Reference were in full compliance with the law. Mr. Kleinfeld stated that he himself did not realize the full extent of the information desired by the Food and Drug Administration to appear in these publications.

Mr. Kleinfeld said he was helping the firm to set up the procedure for the development of advertising and labeling that will assure full compliance with the requirements of the Food and Drug Admiinstration. He had prepared and submitted to the Food and Drug Administration a new proposed monograph for the Physicians' Desk Reference to be published in the next quarterly supplement after it is approved by the Food and Drug Administration. He had also prepared a statement for use in medical journal advertising as soon as he obtained approval from the Food and Drug Administration. He stated that he was of the opinion that these proposals would meet all the points raised in the Notice of Hearing but that they would be changed if they were still not satisfactory to the Food and Drug Administration.

On June 21, 1966, Mr. Kleinfeld, and other representatives of Syntex Laboratories, Inc., met with representatives of the Food and Drug Administration in Washington, D.C. A proposed monograph for the Physicians' Desk Reference was submitted and discussed as was proposed material for journal advertising. The firm indicated an intention to comply with the recommendations and requirements of the Food and Drug Administration.

SEIZURES

No seizures were made of the shipments which are the subject of the proposed Information.

CONCLUSIONS

We have considered the representations which were made on behalf of the firm at the above hearing. However, we cannot ignore the facts which show that Syntex Laboratories, Inc., has had an extensive experience in the development of new drugs and their subsequent distribution in accordance with the new drug regulations; and that such firm was fully aware of the regulations which required that the contraindications and side effects set forth in the approved new drug application labeling be presented in the Physicians' Desk Reference monograph and in the medical journal advertisements.

In these circumstances and in the interest of protecting the health of the consuming public, it is our opinion that criminal prosecution is necessary to impress upon Syntex Laboratories, Inc., its responsibility for compliance with the law, and to deter other firms from similar violations of the law.

WITNESSES

The principal witness in this case will be the Government Inspectors who collected the samples and made the inspections, the Government Analyst who analyzed the samples, witnesses to establish the interstate origin of the samples and the issuance of the advertisements, and medical officers of the Food and Drug Administration's Bureau of Medicine who can testify as to the approved new drug application, the approved labeling, and the serious nature of the alleged medical journal advertising misbranding.

It is requested that, if the form of Information is amended, the United States Attorney furnish us with a copy thereof; also, that he keeps us advised as to the progress of the case and its disposition.

The New York District Office of the Food and Drug Administration, located at 850 Third Avenue (at 30th Street), Brooklyn, New York 11232, Telephone: 788-1300, will arrange for the presence of the necessary witnesses and assist in the presentation of the case. Upon request, we will render such further assistance as may be possible.

Very truly yours,

WILLIAM W. GOODRICH,
Assistant General Counsel,
Food and Drug Division.

APRIL 22, 1968.

Re Syntex Laboratories, Inc., F.D.C. No. 53222, Federal Food, Drug, and Cosmetic Act

MR. WILLIAM W. GOODRICH,
Assistant General Counsel, Department of Health, Education, and Welfare, Washington, D.C.

DEAR MR. GOODRICH: In view of the expressions contained in your letter of March 1, 1968, we have re-examined our previous determination relative to prosecution of this matter. The reasons set out in your letter tend only to reinforce our opinion that this matter does not present a case for prosecution and is not a proper setting in which to attempt to sustain a judicial interpretation of the regulations issued pursuant to Section 352(n) of the Act.

We believe that any attempt to secure a judicial interpretation which will enlarge the meaning of the statutory terms on the basis of the meaning of the word "relating" as suggested by you would be frustrated by the factual situation. The difficulty inherent in any such attempt is that the labeling which was approved by the Food and Drug Administration contains the same words as are found in the statute and regulations, i.e., "side effects" and "contraindications." Under each heading, the specific items or conditions are listed. Many of the conditions which you now contend are side effects or contraindications are not listed under those headings in the labeling but are set out under other headings in the labeling. In a criminal prosecution, such a factual situation creates an impossible barrier to success. In all likelihood, the only result would be to obtain a judicial expression contrary to your desire. In passing, we consider the possibility that the court might find an analogy between the present situation and that of *Haynes* v. *United States*, —— U.S. ——, decided January 29, 1968, wherein the Supreme Court commented that "so much could not be derived from so little."

Moreover, the argument presented relative to the meanings of certain language used in the advertisement as compared to that of the labeling presents so fine and tenuous a distinction as to render conviction most unlikely. In other instances, the suggested violation appears to consist of a failure to furnish information which does not appear in the approved labeling.

Specifically, the argument that the statement in the advertisement that the drug is contraindicated in pregnancy is not satisfactory because the doctor should have been told to discontinue the drug "at the earliest possible sign of pregnancy" is untenable. Obviously, the physician is not going to use the drug to prevent pregnancy if the patient is pregnant. Neither would it seem logical to expect that a physician would continue its use after the patient became pregnant. Moreover, under the circumstances, any physician would be aware that contraindications of the drug in pregnancy can only mean that it should be discontinued if the patient becomes pregnant.

As to the necessity for discontinuance at the earliest possible sign, it will be observed that the approved labeling under the heading of "side effects" notes that symptoms "resembling early pregnancy" as well as changes in the men-

strual cycle, including occasional inter-menstrual bleeding and spotting and sometimes with the period being missed entirely, may occur. Thus, the approved labeling certainly indicates that some of the "earliest possible" signs of pregnancy may be false ones which do not justify discontinuance of the medication. Accordingly, a warning to the physician to discontinue the drug at the "earliest possible" signs of the condition the drug is meant to prevent is not consistent with the approved labeling.

Under these circumstances, we see no justification for any attempt to predicate a criminal prosecution in the factual situation above described.

Your letter states that "contraindication for psychic depression in the approved labeling is directed to patients with a history of psychic depression and not just to those with presently observable psychic depression." However, the language used in the labeling approved by the Food and Drug Administration is not that clear or unambiguous. The labeling stated under "contraindications" that "patients with a history of psychic depression should be carefully observed, and the drug is discontinued if depression recurs to a marked degree." The advertisement stated that the drug was contraindicated in "severe depression."

Thus, the labeling does not say the drug should not be used in patients with a history of psychic depression or even that it must be discontinued if that condition should appear. Its use is contraindicated only if the condition reappears to a marked degree. The advertising statement contraindicating the drug in the event of severe depression, therefore, does not significantly differ from that of the labeling. Its terseness is not a vice, indeed, a "brief summary" not a verbatim quote of the labeling is all that the Act requires.

It will be observed that it is also arguable that the flat contraindication of the advertisement may be considered to be more restrictive than the permissive and rather ambiguous wording of the labeling.

While the labeling of the drug might well have included under the heading "side effects" a warning about the blood clotting possibilities of the drug, the fact is that it did not. The Food and Drug Administration approved labeling which treated it in another fashion, and many courts and juries would consider it manifestly unfair for the Government to attempt to impose criminal sanctions for the failure of the subject to set this condition out as a side effect without having first been advised of the necessity so to do.

Additionally, the agency's position is considerably weakened by the fact that in the labeling the coupling of the reference to blood clotting with the favorable comment of the Ad Hoc Advisory Committee has the effect of minimizing the potential threat to the patient. This circumstance would also tend to diminish the seriousness of the failure to list the condition as a "side effect."

Much of the same objection applies to the contention relative to the failure to set forth as a side effect a statement found in the labeling under a different heading relative to the effect of estrogens on calcium and phosphorus. In addition to the questionable fairness of a prosecution in these circumstances, the labeling statement does not refer to a definite knowledge that the drug has a deleterious effect on calcium and phosphorus metabolism but only to a general medical learning that estrogens are known to have such an influence. The complaint, therefore, seems to relate to a failure to list as a side effect of the drug a matter of medical learning which is applicable to estrogens. Thus, the information does not seem to relate to a side effect of the drug advertised, and for that reason a prosecution based upon this omission is not sound.

Nor do we believe that the failure of the advertisement to include the specific details relative to the length of experience with the drug forms a basis for criminal action. Such information was not required as a part of the statement in the labeling concerning side effects, and the advertisement did, by inference at least, inform the physician that "prolonged observations" had not taken place.

That portion of the advertisement which speaks of the low incidence of side effects does not appear to constitute a violation of the statute. In our view, the advertisement does not falsely represent the incidence of side effects which attends the use of the drug. Although we think it is at least debatable whether the advertisement claims a superiority over other products in connection with the incidence of side effects, such statements are within the area of allowable promotion of the drug. The statute is, in our opinion, oriented toward requiring truthfulness in the area pertaining to safety and effectiveness. We do not read the legislative history as indicating that the statute is designed to prevent the usual effort to convince consumers that the advertiser's product is superior to other almost identical products so long as the factual statements are true.

Your letter leads us to the conclusion that you do not contend that the advertisement for Norinyl claimed any use not included in the approved labeling but only that it did not set forth all the side effects with the specificity which the agency finds desirable. Your letter also states that it is your position that advertisements of new drugs subject to prescription use for which applications were approved after October 10, 1962, cannot contain any statement that is not in the approved New Drug Application.

We have observed that had the advertisement set forth as "side effects" some of the statements which you contend should have been there included such act would be a direct violation of the position stated above because the statements of the conditions allegedly omitted are *not* found under that heading in the approved labeling. Your contentions, therefore, seem to be diametrically opposed to your argument as to the necessity that the advertisement conform to the labeling.

Although we are declining prosecution based upon the alleged violations of the advertising provision of the Act, we do not have the same reservations concerning the violation alleged in Count I of the suggested form of information which relates to the use of improper labeling in the monograph in the *Physicians' Desk Reference.*

We are engaged in the process of redrafting that Count in accordance with the ideas expressed in our last communication. A copy of our communication to the United States Attorney will be forwarded to you when it is mailed.

Sincerely,

FRED M. VINSON, Jr.,
Assistant Attorney General,
Criminal Division.
By HAROLD P. SHAPIRO,
Chief, Administrative Regulations Section.

UNITED STATES DEPARTMENT OF JUSTICE,
UNITED STATES ATTORNEY,
FOR THE DISTRICT OF NEW JERSEY,
Newark, N.J., May 21, 1968.

Attention Harold P. Shapiro, Chief, Administrative Regulations Section.
Re Syntex Laboratories, Inc., FDC No. 53222, Federal Food, Drug, and Cosmetic Act. Your Ref.: FMV:JWK:mc, 21-48-353.

DEPARTMENT OF JUSTICE,
Washington, D.C.

DEAR MR. SHAPIRO: We have reviewed the file in the above-referenced matter and have concluded that the case lacks prosecutive merit.

We recognize that discrepancies between the monograph and the approved labeling do exist. However, the regulations themselves require only that the labeling be "substantially" the same as the labeling authorized by the approved new drug application. The word "substantially" certainly gave the company some license to synopsize the information contained in the approved new drug application. A reasonable doubt exists in our minds as to whether the labeling in the monograph is substantially different from the labeling in the approved new drug application, and we believe that a lay jury would also harbor such a doubt.

Moreover, the discrepancies between the monograph and the approved labeling do not appear to have been the result of a purposeful evasion of the regulatory requirements of the Administration but of an honest difference of opinion as to what was required under the regulations. In fact, at the hearing held on April 8, 1966, the firm offered to obviate all future difficulties by submitting sample advertising and monographs to the Food and Drug Administration before publication.

In closing, we note that the offense complained of occurred in September, 1965, almost three years ago. No indications of violations of the Food and Drug law subsequent to that date are reported. Prosecution at this rather late date would not be in the best interests of the Federal Government.

Very truly yours,

DAVID M. SATZ, Jr.,
U.S. Attorney.
By MARLENE GROSS,
Assistant U.S. Attorney.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
May 28, 1968.

Attention Fred M. Vinson, Jr., Assistant Attorney General.
Re Syntex Laboratories, Inc. Your ref: FMV:JWK:mch 21-48-353, FDC No. 53222.

Hon. RAMSEY CLARK,
Attorney General,
Department of Justice,
Washington, D.C.

DEAR SIR: This is with reference to your letter of April 22, 1968, and the United States Attorney's letter of May 21, 1968, declining prosecution on both the advertising and the labeling violations we have reported to you.

The United States Attorney declines for the reasons that (1) there is a reasonable doubt whether the labeling (FDA monograph) is substantially different from the approved labeling, (2) the violations appear to be the result of honest differences of opinion as to what is required, and (3) the offense is almost three years old and ther eare no indications of violations since 1965.

(1) There can be no reasonable doubt that the PDR differed from the approved labeling in a substantial way. It was too brief, it was promotionally slanted, and it omitted important information for safe prescribing.

(a) A comparison of the approved labeling and the PDR monograph plainly shows that some of the most vital safety information was omitted from the monography. A copy of the 1965 omnograph is enclosed. It exaggerates the effectiveness of the drug, and it minimizes the side effects, precautions and contraindications. We simply cannot understand how it can be said that this abbreviated material, and particularly the seven lines devoted to side effects, can possibly be said to be substantially the same as the approved directions for safe use of this drug. The substance of the monograph and the substance of the approved labeling are not the same.

Fundamentally, what the Company did was to present a reassuring write-up for the physician's desk which omitted the most important information he needed to have to prescribe this drug for his patients with safety. As the criminal information which your office drafted shows, the physician was not alerted to the possibility of effects on the fetus if a pregnant woman should take the drug not knowing she was pregnant, he was not alerted to the limited experience with the drug and its possible long range effects upon a variety of organ and endocrine systems, including pituitary, ovarian, adrenal, uterine, liver, and thyroid, he was not alerted to the possibility of intravascular clotting (a risk now known to be even more serious than in 1965), he was not warned about effects on patients with any condition involving calcium or phosphorus metabolism, and he was not told to use the drug with care in any patient who had a history of psychic depression.

We feel confident that we can prove by acceptable medical evidence that the prescribing information in PDR-1965 was *not* substantially the same as the approved labeling, as the regulations require. And we are equally confident that we can prove the omissions and changes were significant from the standpoint of patient safety. Our Advisory Committee on Obstetrics and Gynecology, quoted in the Company's labeling, said that the physician must decide for his patient whether to accept the risk involved in the use of oral contraceptives, small though it may be, but that he "can do this wisely only when there is presented to him dispassionate scientific knowledge of the available data." The PDR monograph did not serve this purpose, and the violative ads we will discuss later compounded the hazard.

(2) There was no basis for considering this violation a result of an honest difference of opinion as to what is required. The applicable regulations had been in effect since 1961, and the Company's performance shows that it did not comply with what was clearly required—it did not present substantially the same information in PDR as in the approved labeling. It had the labeling at hand and it chose to omit some of the information from the PDR monograph.

(3) Syntex has not been in compliance since 1965. The ad charges you eliminated would have shown the United States Attorney that the same failures to inform continued after that date. And within the past few months, on January 22, 1968, we required the Company to mail a letter to all physicians in the United States calling attention to its failure to include in its then current ads appropriate warnings about use of the drug in psychic depression and about the possibility of thromboembolic episodes. A copy of the letter is enclosed.

Turning to the reasons given in your letter of April 22, 1968, for declining to prosecute the advertising violations, we must reiterate what we have frequently said to your representatives, that the brief summary is required to disclose true information related to side effects, contraindications, and effectiveness as specified in our regulations, not merely the information headed "side effects" and "contraindications" in the approved labeling.

We are confident that any qualified expert would regard the information about clotting, calcium and phosphorus metabolism, effect on organ and endocrine functions, etc., as information related to "side effects" and "contraindication" as those terms were used in the 1962 Drug Amendments. The fact that the information in certain instances was headed "Thyroid Gland", etc., does not make it less information related to side effects than the material in the labeling under the heading "Side Effects." A mere reading of the package insert establishes this.

While criminal prosecutions do sometimes involve strict interpretations of regulations, there is "no canon against using common sense" in applying a criminal law.

As to the point you make that our understandings of what was said in the advertising are based upon tenuous constructions, we think we should have an opportunity to present these points to a court or jury with an explanation of their important medical significance.

Surely a jury would understand the need to warn a physician, and through him the patient, that a missed dose or a miscalculation in taking the oral contraceptive drug may result in pregnancy, and that if that occurs there is danger to the unborn child from continuing to take the drug. Telling the physician that the drug is contraindicated in pregnancy does not tell him what he really needs to know for his patient's safety in bearing a child. It is the need to alert the user to the hazard to the unborn child which may result from a missed dose or a miscalculation that calls for this early pregnancy warning.

On psychic depression, we have noted above that as late as January 1968, Syntex was still not properly presenting the message about this hazard to the profession. A corrective letter was necessary. What is missing in the ads is the warning that any patient with a history of psychic depression should be carefully observed (this means the patient should be followed much more closely than the routine patient) if a decision is made by the physician to prescribe the oral contraceptive. A statement that the drug is contraindicated in "severe depression" does not adequately advise the physician of the risk he runs with a patient who has had depression in the past but now has it under control.

Blood clotting has been a problem with these drugs for a long time. When these ads ran, the labeling was required to say that such episodes had occurred, that a causal relationship had not been established, and that the problem was under investigation. The ad said nothing about this. Instead, it said the drug was contraindicated in thrombophlebitis and pulmonary embolism (current or past). This is quite different from telling the physician that the cause and effect relationship of the oral contraceptive drugs to these serous complications, particularly in the older age groups, was then under scientific investigation.

As you know, this problem has caused a progressive strengthening of the warning as more experience has been gained.

Finally, we must express our disagreement with the idea that a drug company can use a literally true statement to convince prescribers that its products are superior to other identical products. A half-truth is still sometimes a great lie. Promotional practices with this class of products have been characterized by the use of such half-truths to gain marketing advantages. We have had to require several companies to discontinue such ads and to send letters of correction to the profession. For from being harmless puffing—which in any event is not tolerated in prescription drug advertisements—this kind of promotion affirmatively misrepresents both the effectiveness and the safety of the oral contraceptives.

We have written you at this length because of the serious consequences to the profession and to patients of improper prescription drug advertising.

Six million women are considered to be on oral contraceptive drugs at this time in the United States. Their safe use depends upon proper promotion of the drugs to the profession. Syntex has seriously failed in the instances cited in our recommended prosecution case.

Yours very truly,

WILLIAM W. GOODRICH,
Assistant General Counsel,
Food and Drug Division.

MAY 27, 1968.

Hon. RAMSEY CLARK,
Attorney General,
Department of Justice,
Washington, D.C.

Attention Fred M. Vinson, Jr., Assistant Attorney General.
Re Syntex Laboratories, Inc., Your ref: PNV:JWK:mch 21-48-353, ?? No. 53222.

DEAR SIR: This is with reference to your letter of April 22, 1968, and the United States Attorney's letter of May 21, 1968, declining prosecution on both the advertising and the labeling violations we have reported to you.

The United States Attorney declines for the reasons that (1) there is a reasonable doubt whether the lableing (??? monograph) is substantially different from the approved labeling, (2) the violations appear to be the result of honest differences of opinion as to what is required, and (3) the offense is almost three years old and there are no indications of violations since 1965.

(1) There can be no reasonable doubt that the ??? differed from the approved labeling in a substantial way. It was too brief, it was promotionally slanted, and it omitted important information for safe prescribing.

(a) A comparison of the approved labeling and the PBR monograph plainly shows that some of the most vital safety information was omitted from the monograph. A copy of the 1965 monograph is enclosed. It exaggerates the effectiveness of the drug, and it minimizes the side effects, precautions and contraindications. We simply cannot understand how it can be said that this abbreviated material, and particularly the lines devoted to side effects, can possibly be said to be substantially the same as the approved directions for safe use of this drug. The substance of the monograph and the substance of the approved labeling are not the same.

Fundamentally, what the Company did was to present a reassuring write-up for the physician's desk which omitted the most important information he needed to have to prescribe this drug for his patients with safety. As the criminal information which your office drafted shows, the physician was not alerted to the possibility of effects on the fetus if a pregnant woman should take the drug not knowing she was pregnant, he was not alerted to the limited experience with the drug and its possible long range effects upon a variety of organ and endocrine systems, including pituitary, ovarian, adrenal, uterine, liver, and thyroid, he was not alerted to the possibility of intravascular clotting (a risk now known to be even more serious than in 1965), he was not warned about effects on patients with any condition involving calcium or phosphorus metabolism, and he was not told to use the drug with care in any patient who had a history of psychic depression.

We feel confident that we can prove by acceptable medical evidence that the prescribing information in PDR-1965 was not substantially the same as the approved labeling, as the regulations require. And we are equally confident that we can prove the omissions and changes mor significant from the standpoint of patient safety. Our Advisory Committee on Obstetrics and Gynecology, quoted in the Company's labeling, said that the physician must decide for his patient whether to accept the risk involved in the use of oral contraceptives, small though it may be, but that he "can do this wisely only when there is presented to him dispassionate scientific knowledge of the available data." The PDR monograph did not serve this purpose, and the violative ads we will discuss later compounded the hazard.

(2) There was no basis for considering this violation a result of an honest difference of opinion as to what is required. The applicable regulations had been in effect since 1961, and the Company's performance shows that it did not comply with what was clearly required—it did not present substantially the same information in PDR as in the approved labeling. It had the labeling at hand and it chose to omit some of the information from the PDR monograph.

(3) Syntex has not been in compliance since 1965. The ad charges you eliminated would have shown the United States Attorney that the same failures to inform continued after that date. And within the past few months, on January 22, 1968, we required the Company to mail a letter to all physicians in the United States calling attention to its failure to include in its then current ads appropriate warnings about use of the drug in psychic depression and about the possibility of thromboenbolic episodes. A copy of the letter is enclosed.

Turning to the reasons given in your letter of April 22, 1968, for declining to prosecute the advertising violations, we must reiterate what we have frequently said to your representatives, that the brief summary is required to disclose true information related to side effects, contraindications, and effectiveness as specified in our regulations, not merely the information headed "side effects" and "contraindications" in the approved labeling.

We are confident that any qualified expert would regard the information about clotting, calcium and phosphorus metabolism, effect on organ and endocrine functions, etc., as information related to "side effects" and "contraindications" as those terms were used in the 1962 Drug Amendments. The fact that the information in certain instances was headed "Thyroid Gland", etc., does not make it less information related to side effects than the material in the labeling under the heading "Side Effects." A mere reading of the package insert establishes this.

While criminal prosecutions do sometimes involve strict interpretations of regulations, there is "no canon against using common sense" in applying a criminal law.

As to the point you make that our understandings of what was said in the advertising are based upon tenuous constructions, we think we should have an opportunity to present these points to a court or jury with an explanation of their important medical significance.

Surely a jury would understand the need to warn a physician, and through him the patient, that a missed dose or a miscalculation in taking the oral contraceptive drug may result in pregnancy, and that if that occurs there is danger to the unborn child from continuing to take the drug. Telling the physician that the drug is contraindicated in pregnancy does not tell him what he really needs to know for his patient's safety in bearing a child. It is the need to alert the user to the hazard to the unborn child which may result from a missed dose or a miscalculation that calls for this early pregnancy warning.

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Blood clotting has been a problem with these drugs for a long time. When these ads ran, the labeling was required to say that such episodes had occurred, that a causal relationship had not been established, and that the problem was under investigation. The ad said nothing about this. Instead, it said the drug was contraindicated in thrombophlebitis, and pulmonary embolism (current or past). This is quite different from telling the physician that the cause and effect relationship of the oral contraceptive drugs to these serious complications, particularly in the older age groups, was then under scientific investigation.

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Finally, we must express our disagreement with the idea that a drug company can use a literally true statement to convince prescribers that its products are superior to other identical products. A half-truth is still sometimes a great lie. Promotional practices with this class of products have been characterized by the use of such half-truths to gain marketing advantages. We have had to require several companies to discontinue such ads and to send letters of correction to the profession. Far from being harmless puffing—which in any event is not tolerated in prescription drug advertisements—this kind of promotion affirmatively misrepresents both the effectiveness and the safety of the oral contraceptives.

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the drugs to the profession. Syntex has seriously failed in the instances cited in our recommended prosecution case.

Yours very truly,

WILLIAM W. GOODRICH,
Assistant General Counsel,
Food and Drug Division.

SEPTEMBER 20, 1968.

Re Syntex Laboratories, Inc., F.D.C. No. 53222—Federal Food, Drug, and Cosmetic Act.

Mr. WILLIAM W. GOODRICH,
Assistant General Counsel,
Department of Health, Education, and Welfare,
Washington, D.C.

DEAR MR. GOODRICH: Enclosed is a copy of our letter of even date to the United States Attorney at Newark, New Jersey, requesting that his office reconsider the above matter in light of your letter of May 21, 1968. Your attention is invited to our suggestion on page two that the United States Attorney interview the Food and Drug Administration experts who would be called as witnesses and review the expected testimony of non-Government experts who may also be called. We believe that such action is necessary to ascertain whether or not the differences between the P.D.R. and the approved labeling are substantial.

It is suggested that you arrange with the United States Attorney for him to interview the Food and Drug Administration experts and furnish him with a statement of the testimony which may be expected from any other experts who will appear for the Government.

Sincerely.

FRED M. VINSON, Jr.,
Assistant Attorney General,
Criminal Division.

By HAROLD P. SHAPIRO,
Chief, Administrative Regulations Section.

SEPTEMBER 20, 1968.

Re Seyntex Laboratories, Inc., F.D.C. No. 53222—Federal Food, Drug, and Cosmetic Act.

Mr. DAVID M. SATZ, Jr.,
U.S. Attorney,
Newark, N.J.

DEAR MR. SATZ: After receiving your letter of May 21, 1968, recommending that the above-captioned matter be closed without prosecution, we received a letter from Mr. Goodrich, Assistant General Counsel, Food and Drug Division, taking exception to your conclusions and requesting a further consideration. In view of the strong differences of opinion held by Mr. Goodrich, your office, and ourselves, we suggested that a meeting be arranged whereby all parties could discuss their views.

However, our efforts to arrange such a meeting have been to no avail, and since the matter is growing stale, we believe it is appropriate to forward a copy of Mr. Goodrich's letter. We understand that Mr. Goodrich's assistant, Mr. Gottlieb, has previously shown Miss Gross a rough draft of this letter so that she is familiar with its contents.

You will observe that Mr. Goodrich not only disagrees with your conclusion, that the alleged violations of the Act which relate to the monograph on the drug Syntex, which appeared in the *Physicians' Desk Reference* for 1965, do not justify criminal prosecution, but also with our decision that the alleged violations of the advertising provisions of the Act do not provide a basis for prosecution. Insofar as our decision on the latter problem is concerned, the views set forth in Mr. Goodrich's letter have long been known to us and were thoroughly considered at the time we reached our conclusion. They, therefore, are not, in our view, so persuasive as to result in a change of our views.

We have noted that Mr. Goodrich strongly disagrees with your analysis of the discrepancies between the monograph and the approved labeling. In view of the decision of Judge Lepold in the *Abbott* case, we think that your point may be well taken but the question is impossible to evaluate in the absence of expected testimony. It would appear that the nature of these differences is a matter that could best be decided after discussion with medical experts of the Food and Drug Administration, who would be called at witnesses, as well as a combination of the statements of any outside experts who would be expected to testify on behalf of the Government. It is, therefore, suggested that you should interview the appropriate Food and Drug Administration experts and examine the statements of expected witnesses before making a final decision.

While it appears that the subject has seen the error of its ways and has voluntarily complied with the desires of the Agency both with respect to its P.D.R. labeling and advertising practices, we believe you should balance these factors with the Agency's opinion as to the seriousness of the offense and the necessity for criminal action. We suggest that the Court's attitude toward this kind of an offense may be ascertained at the time it imposes sentence in the *Ciba* matter, which, we understand, is expected to take place shortly and may be considered by you in evaluating this matter.

Accordingly, your reconsideration of this matter in the light of Mr. Goodrich's comments will be appreciated. We trust that you will advise us in your final decision.

Sincerely,

FRED M. VINSON, Jr.,
Assistant Attorney General,
Criminal Division.

By HAROLD P. SHAPIRO,
Chief, Administrative Regulations Section.

UNITED STATES DEPARTMENT OF JUSTICE,
UNITED STATES ATTORNEY,
FOR THE DISTRICT OF NEW JERSEY,
Newark, N.J., October 30, 1968.

Attention Harold P. Shapiro, Chief, Administrative Regulations Section.
Re Syntex Laboratories, Inc., F.D.C. No. 53222—Federal Food, Drug and Cosmetic Act. Your Ref: FMV:JWK:mc, 21-48-353.

DEPARTMENT OF JUSTICE,
Washington, D.C.

DEAR MR. SHAPIRO: At your suggestion we have again reconsidered our file in the above-referenced matter and have again concluded that the case lacks prosecutive merit for substantially the reasons set forth in our letter dated May 21, 1968.

We do not believe that interviews with medical personnel concerning the discrepancies between the monograph and approved labeling would affect our opinion regarding the prosecutive merits of this action. The regulations themselves give the company some license to synopsize the material of the approved labeling in the monograph. Even if medical personnel could convince us that there were substantial differences and that we could in fact carry our burden of proof, we feel that prosecution of this offense that occurred over three years ago would not be in the best interests of the Federal Government, especially in light of the fact that revised and current monographs do comply with the regulations.

On October 25, 1968, the Ciba Pharmaceutical Company was fined $200.00 on each count of a two count Information charging violations similar to those here. In view of the time expended on this case by this office and by the Food and Drug Administration, we found this result most discouraging. In view of the factors outlined above and in our previous correspondence, we doubt that we could achieve a more staisfactory result in this matter.

Very truly yours,

DAVID M. SATZ, Jr.,
U.S. Attorney.
By MARLENE GROSS,
Assistant U.S. Attorney.

UNITED STATES DEPARTMENT OF JUSTICE,
Washington, D.C., March 25, 1969.

Re Syntex Laboratories, Inc., F.D.C. No. 53222—Federal Food, Drug, and Cosmetic Act. Your Ref: MG:ch 748447.

Mr. WILLIAM W. GOODRICH,
Assistant General Counsel, Food, Drug, and Environmental Health Division, Department of Health, Education, and Welfare, Washington, D.C.

DEAR MR. GOODRICH: We note that you have been furnished with a copy of the United States Attorney's letter to us declining prosecution in the above matter. We have carefully considered whether this office should persevere in its effort to persuade the United States Attorney to agree to prosecution of the above-captioned matter. Mr. Satz has filed criminal informations in two similar cases on previous occasions and is, therefore, familiar with such prosecutions and sympathetic to the enforcement efforts of the Food and Drug Administration. It has been noted that in the *Abbott* case the court seemed to feel that some editorializing was permissible under the regulations then in effect, and in the *Ciba* and *Armour* cases very small fines were imposed upon the defendants for violations similar to those reported in the instant matter. Also we have observed that new and more comprehensive regulations are about to be adopted in the field of advertising and that the industry seems to have accepted the ruling of the *Abbott* case that the Physician's Desk Reference constitutes labeling.

For the above reasons, we do not believe that any useful purpose will be served by directing the United States Attorney to institute a prosecution which is contrary to his best judgment. Prosecution is, therefore, declined.

Sincerely,

WILL WILSON,
Assistant Attorney General,
Criminal Division.
By HAROLD P. SHAPIRO,
Chief, Administrative Regulations Section.

UNITED STATES DEPARTMENT OF JUSTICE,
UNITED STATES ATTORNEY,
FOR THE DISTRICT OF NEW JERSEY,
Newark, N.J., March 28, 1969.

Attention Alvin L. Gottlieb.

Re Syntex Laboratories, Inc., Federal Food, Drug, and Cosmetic Act. Your Ref: 53222.

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
Office of the General Counsel,
Washington, D.C.

DEAR MR. GOTTLIEB: In view of the fact that prosecution has been declined in the above-captioned matter, we are returning herewith all exhibits furnished to this office.

Please be advised that we are closing our file in this matter.

Very truly yours,

DAVID M. SATZ, Jr.,
U.S. Attorney.
By MARLENE GROSS,
Assistant U.S. Attorney.

MAY 25, 1967.

In Reply Refer to F.D.C. No. 53548.

Hon. RAMSEY CLARK,
Attorney General,
Department of Justice,
Washington, D.C.

DEAR MR. CLARK: We request the institution of criminal proceedings under the Federal Food, Drug, and Cosmetic Act, against Warner-Lambert Pharmaceutical Company, a corporation trading as Warner-Chilcott Laboratories, at Morris Plains, New Jersey.

The offenses complained of occurred during the period from about February 4, 1966, to about April 22, 1966, and involved the introduction into interstate

commerce at Morris Plains, New Jersey, for delivery to Glendale, New York, and New York, New York, quantities of the drug, Peritrate SA (Sustained Action Pentaerythritol tetranitrate) tablets, which was misbranded, and a new drug for which no approval of a New Drug Application was effective for all the purposes for which it was offered.

There are transmitted herewith a suggested form of criminal information and the following exhibits:

1. Copies of Notices of Hearing.
2. A copy of the approved New Drug Application labeling.
3. A copy of the mailing piece "490T718 October 1965" which included a reprint of "Pentaerythritol Tetranitrate As Adjunct Therapy In the Immediate Postinfarction Period" and "The Use of Coronary Vasodilators In Acute Coronary Occlusion."
4. A copy of the advertisement from the *Journal of the American Medical Association* of January 3, 1966, and February 7, 1966, identified PE–GP–527–4C.
5. A copy of the advertisement from the April 15, 1966, and April 22, 1966, issues of *Medical World News*.
6. The package insert for Peritrate SA.

SECTIONS OF THE ACT INVOLVED

Count I of the Information charges violation of 21 U.S.C. 331(a) in that the defendant caused the introduction into interstate commerce of an article of drug which was misbranded within the meaning of the following sections of 21 U.S.C.:

352(a) in that its labeling, namely, the reprints contained in the mailing pieces contained false and misleading statements and representations concerning the drug;

352(f)(1) in that said labeling failed to bear adequate directions for use, and the drug was not exempt, since the labeling was not substantially the same as the labeling in the approved New Drug Application; and

352(n) in that the defendant failed to include in the advertisement caused to be issued by it wth respect to the drug in the January 3, 1966, issue of the *Journal of the American Medical Association*, a true statement of information in brief summary relating to the effectiveness of such drug as required by 21 CFR 1.105(e). Since these charges are set forth at length in the information and were also alleged in the seizure of this drug, they will not be repeated here.

Count II alleges violation of 21 U.S.C 331(d) in that the drug may not be introduced into interstate commerce in that it was a new drug within the meaning of 21 U.S.C. 321(p) since it was not generally recognized as safe and effective for all of the uses for which it was offered in the labeling and approval of a New Drug Application with respect to such uses was not effective.

Count III alleges that a second shipment of the drug was misbranded within the meaning of 21 U.S.C. 352(n) in that the defendant failed to include in the advertisement caused to be issued in the April 15, 1966, and April 22, 1966 issues of *Medical World News*, a true statement of information in brief summary relating to the effectiveness of such drug as required by 21 CFR 1.105(e).

BACKGROUND INFORMATION

Peritrate SA is a trademark held by the defendant for the drug, pentaerythritol tetranitrate (PETN) in a time release dosage form Warner-Chilcott Laboratories submitted to the Food and Drug Administration, a New Drug Application for Peritrate SA which was approved on November 23, 1959. This permitted the drug to be offered for use in angina pectoris patients.

The mailing piece referred to in this case consisted of reprints of articles in the medical literature concerning experimental use of PETN. The mailing piece was actually addressed and mailed by the firm of Clark-O'Neill, Inc., Fairview, New Jersey. The list of doctors to whom the literature was to be sent was supplied by Warner-Chilcott Laboratories by means of sticker labels which were applied by the firm and it has no record of names. However, Mr. John Owens, Executive Vice-President of Clark-O'Neill informed FDA Inspectors that such a mailing usually includes the New York metropolitan area. A total of 91,000 pieces were sent to medical people throughout the country.

The advertisement in the *Journal of the American Medical Association* [*JAMA*] issue of January 3, 1966 is a five page color ad. The copy of the ad

enclosed is in black and white, and the graphs do not reproduce clearly because of the contrasting colors used in the magazine. However, the printing can all be read. If this case goes to trial the FDA will obtain back copies of the magazines from the publishers for use. There are no extra copies available at this time. The ad highlights the study made by Alexander Oscharoff, M.D. and reported in the article "Pentaerythritol Tetranitrate as adjunct Therapy in the Immediate Post Infarction Period." The same ad was rerun in the February 7, 1966 issue of *JAMA*.

The advertisement for the drug which was run in the April 15, 1966 and April 22, 1966 issues of Medical World News is a two page ad which reports a study conducted by B. L. Brofman, M.D. using Peritrate SA.

On February 28, 1966 in the Eastern District of New York, a libel was filed against the shipment represented in Counts I and II and the drug was seized on the same day. The libel alleged that the drug was misbranded in the same manner as Count I does, and also alleged its shipment in violation of the new drug provisions of the Act as now alleged in Count II. Warner-Lambert Pharmaceutical Company filed a claim of ownership and on May 12, 1966 consented to the entry of a decree of condemnation without admitting the allegations of the libel. The rest was then destroyed.

Hearings pursuant to 21 U.S.C. 335

Counts I and II.—On April 18, 1966, a hearing was held in the Food and Drug Administration's offices in New York, New York, with the following people representing Warner-Lambert: Mr. Robert Clark, President, and Dr. Frank DiTraglia, Medical Director, Warner-Chilcott Laboratories, Mr. James Hoge and Mr. William F. Weigel of the law firm of Rogers, Hoge & Hills.

Mr. Weigel stated that the firm recognized the seriousness of the charges, based on the *JAMA* advertisement but denied any violation of the Food, Drug, and Cosmetic Act. He also submitted a written statement referring to the charges set forth in the Notice of Hearing.

Mr. Weigel said that the claims with respect to myocardial blood flow, increased oxygen, and collateral circulation were made prior to October 10, 1962 and were therefore in his opinion grandfathered. This would include the claim concerning collateral circulation in the mailing piece allegedly supported by study of Lumb and Hardy.

The written statement asserts that the firm never intended to make any claim for the use of the drug in the postinfarction period as found in the mailing piece but felt it was necessary to set forth in detail the manner in which the drug had been used in the Oscharoff study.

The statement continued that the Oscharoff studies, which claimed that 22 percent more patients treated with Paritrate SA at a time closely following myocardial infarction remained alive after two years than patients treated with a placebo, were used in good faith and the firm had no reason to question the results of the study. In using these results as part of their labeling and advertising, the firm maintained that it was unaware of the fact that technically it might be making a new claim for the drug. Mr. Weigel indicated that since no case law was established as yet on interpretation of the advertising provisions of the Act, it was his opinion that it should be established first in civil actions before criminal prosecution should be instituted.

Count III.—On July 22, 1966 a second hearing was held with the following people present, representing Warner Lambert Pharmaceutical Company: William F. Weigel, Esq., Attorney with Rogers, Hoge and Hills, Frank J. DiTraglia, M.D., Corporated Medical Control Director, Mr. Frank Markoe, Jr., Senior Vice President, Secretary and General Counsel, Warner Lambert Pharmaceutical Company. This was held to discuss the deficiencies of the advertisement in *Medical World News*.

Again Mr. Weigel stated that the firm admitted that the shipment had been made and that the firm issued the advertising which was the subject of the hearing, but denied any violation of the law. He emphasized that the ad offered the drug only for use in the treatment of angina pectoris, in accordance with the policy of the Food and Drug Administration that nitrate-containing drugs are considered as useful only in the management of angina pectoris. Warner Lambert denied the charges contending that Dr. Brofman's findings were clinically significant and that the manner in which the subjects were chosen, the methodology employed, and the evaluation of the results were in accordance with generally accepted procedures for such studies. Dr. DiTraglia dictated a prepared statement of his interpretation of the study substantially as follows.

Study A as done on 20 patients demonstrated equal therapeutic results for Peritrate and the placebo, but this was not statistically significant because the manner in which the study was run left doubt as to whether the effectiveness of the placebo was not a carry over from the drug which had been administered just prior to the placebo period. In Study B the drug was discontinued for a period prior to use of the placebo thus ruling out any carry-over effect from the drug. Dr. DiTraglia stated that the "Company did not believe that it was justified in portraying this * * * finding concerning methodology (the difference between 'Study A' and 'Study B') and accordingly limited its references to the reports of those patients who received the active medication in the approved manner as demonstrated by 'Study B' ".

CONCLUSIONS

We believe that the evidence indicates that prosecution is warranted in this case. The advertisements in question did not meet the requirements of the Act and would clearly be misleading to physicians who read them. The purpose of these ads is to provide information to the physician who does not have the time to read all of the reports in the medical literature. The law provides that the ad be factual and provide full information on the product, both good and bad, so that the physician can rely on the representations at to the effectiveness and use of drugs without going behind the ad into the studies referred to. Clearly, these ads will not give this service. It is necessary to read beyond what is reported to be fully informed on the studies.

In addition, the labeling for Peritrate SA issued by the firm, contained seriously misleading representations with respect to the drug. Mr. Wiegel is incorrect in his interpretation of the grandfather clause. All claims made before passage of the Kefauver-arris Amendments are not automatically protected. Claims made on October 9, 1962 are grandfathered only if the drug was not a new drug at that time.

Drug companies have the responsibility to follow the law in all respects. When one company has not met its responsibility, it is open to criminal prosecution and we believe that it is warranted in this instance.

WITNESSES

The principal witnesses in this case will be the Government inspectors who collected the samples and other witnesses to prove interstate commerce; and medical officers of the Food and Drug Administration's Bureau of Medicine who can testify as to the approved new drug application, approved labeling, and with other medical experts the serious nature of the alleged labeling and journal advertising misbrandings.

It is requested that, if any form of information is filed other than the one enclosed, the United States Attorney furnish us with a copy thereof. The New York District of the Food and Drug Administration will provide assistance to the United States Attorney. Upon request, this office shall render such further assistance as may be possible.

Very truly yours,

WILLIAM W. GOODRICH,
Assistant General Counsel.

APRIL 23, 1968.

Mr. WILLIAM W. GOODRICH,
Assistant General Counsel, Department of Health, Education, and Welfare, Washington, D.C.

Re Warner Lambert Pharmaceutical Co., FDC No. 53548, Federal Food, Drug, and Cosmetic Act.

DEAR MR. GOODRICH: This is in response to your letter of February 13, 1968, submitting for our consideration a suggested criminal action against Warner Lambert Pharmaceutical Company arising out of the introduction into interstate commerce on April 27, 1966, of the drug "Proloid" which was alleged to have been misbranded because of an advertisement which appeared in certain medical journals during February, April, and May of 1966.

We have carefully examined the allegations set forth in the suggested form of information, your comments relative to the nature of the violations, and the four exhibits enclosed in your letter. The information set forth in your letter and its enclosures is not sufficient to enable us to ascertain the exact manner

in which the advertisement is violative of the statute and regulations. It is observed that the narrative account in your letter which endeavors to explain the offense does so in almost the same language as the allegations of the information, and provides little or no additional explanation of the reasons why the advertisement violates the law.

Inasmuch as the advertisement did not on its face appear to create, at least in the minds of lay persons, the impression and implications seemingly set out in your letter and suggested form of information, we have discussed this matter personally with Dr. Robert S. McCleery, of the Bureau of Medicine, to make certain the position of the FDA and to ascertain the nature of the evidence available to prove the accusation. We have considered the views of Dr. McCleery and have studied the materials submitted by him.

It appears that one of the principal reasons prosecution has been suggested is the contention that the first paragraph of the advertisement creates the impression, in the mind of the reader, that in his paper Greer was comparing liothyronine with Proloid, when in fact he was comparing it with desiccated thyroid. Our own reading of the advertisement does not create that impression. The wording of the advertisement seems to compare liothyronine, not with any particular thyroid product, but with more slowly acting thyroids.

In addition, we understand from Dr. McCleery that liothyronine has a more abrupt effect in raising the metabolic rate than does Proloid, and that as between Proloid and desiccated thyroid there is practically no difference in the rate at which the metabolism is raised. Accordingly, the fact that Greer may have used desiccated thyroid in his studies is of little importance since in this area of comparison there is little or no difference between the action of Proloid and that of desiccated thyroid.

We understand that another of the agency's objections is founded upon the contention that the comparison between liothyronine and Proloid fails to disclose that there is a potential danger of precipitating cardiac complications from the use of Proloid. However, Dr. McCleery has advised that the omission refers not to cardiac complications which arise by reason of any abrupt action on the part of Proloid, but such cardiac reactions as might arise generally from the use of all thyroid preparations. Since the advertisement is comparing the dangers arising from an abrupt action of a drug with the effect of a slower acting product, we fail to see how the omitted information could result in any misrepresentation.

Another of the agency's contentions relates to the failure of the advertisement to state that Proloid is less rapidly metabolized than liothyronine, and, therefore, cannot be withdrawn as rapidly when toxic manifestations appear. Since the gist of the comparison between liothyronine and Proloid is that the latter is slower in raising the metabolism rate, we inquired whether it would not be obvious to a physician that Proloid is less rapidly metabolized and were informed that the rate at which the drug is metabolized is partly dependent upon and partly independent of the general metabolic rate of the body, and, thus, it would be to some extent obvious and to some extent not obvious.

In view of this explanation, and the lack of any statement in the approved labeling which indicates that there is a possibility of such toxic manifestations appearing as would require immediate lessening of the metabolic rate, this ground clearly forms no sound basis for criminal action.

The agency contends that the advertisement lacked fair balance because it failed to include three statements by Greer in two of which he indicated that other products were not superior to desiccated thyroid; the third deals with the caution to be exercised in treating elderly patients or those with known cardiac complications. But since the quotation from Greer is not such as to create an impression that Greer is of the opinion that Proloid is, in general, better than other thyroid products, there would seem to be no necessity that Greer's views as to the relative over-all superiority of the various products or his caveat concerning treatment of certain types of patients be expressed.

Nor is the statement, apparently true, that Proloid is a more precise preparation whose standards exceed USP requirements one which would require the further statement for which the agency contends. The statement in the advertisement is not a quotation and is referenced to a paper by H. S. Kupperman. The language quoted as being omitted is taken from Greer. It seems that the statement in the advertisement is one of fact from which qualified physicians can form their own conclusions. Under these circumstances the opinions of

others as to the medical conclusions to be drawn from the facts are not required.

The last quotation, the omission of which the agency argues creates a criminal offense, does not appear to be related to the use of the drug advertised but seems to refer to a general medical procedure recommended in the use of all thyroid products by elderly patients. Such an omission again seems to be only a failure to set forth an opinion or conclusion of one medical researcher and is not necessary to complete a factual statement about the drug advertised.

There is apparently some basis for questioning the failure of the ad to disclose the chemical identity of some of the components of Proloid with those of the drugs with which the ad undertook to make some comparisons, although we also understand there may be some difference of opinion as to whether there is complete identity, as reflected by the statement of the Company. But assuming the Agency's contention in this regard is supportable, we do not understand you would contend for prosecution on this factor alone.

Accordingly, it is our view that the matter is not one which justifies the bringing of a criminal action. Even if the agency contentions are technically correct, a fact as to which there appears to be at least an arguable basis for a different view, they involve technical refinement of the nuances which flow from the statements used as in our judgment to preclude a successful prosecution. We strongly feel that this is not the kind of a matter in which to undertake criminal action.

Accordingly, prosecution is declined.

Sincerely,

FRED M. VINSON, Jr.,
Assistant Attorney General,
Criminal Division.
By HAROLD P. SHAPIRO,
Chief, Administrative Regulations Section.

DECEMBER 5, 1966.

The Honorable ATTORNEY GENERAL,
Department of Justice,
Washington, D.C.

Attention Harold P. Shapiro, Chief, Administrative Regulations Section.
Re Wyeth Laboratories, Inc., F.D.C. No. 52677, Federal Food, Drug, and Cosmetic Act. Your reference: FMV:JWK:lk, 21-62-326.

DEAR MR. ATTORNEY GENERAL: This is in reply to your letter of October 5, 1966. We enclose a revised form of Information which charges the violative shipment of Serax capsules on July 21, 1965 [in lieu of June 17, 1965], as well as on April 25, 1966.

At your request, the evidence of the July 21, 1965 shipment has been obtained in order to avoid charging a shipment which occurred before the advertisement's publication dates of June 28 and July 5, 1965.

The July 21, 1965 shipment charged in Count I of the revised form of Information involves the introduction into interstate commerce by Wyeth Laboratories, Inc., at Paoli, Pennsylvania, on July 21, 1965, via the Pennsylvania Railroad, of 1248 100-capsule bottles of 15 mg. Serax capsules for delivery to Wyeth Laboratories, Division of American Home Products Corporation, Baltimore, Maryland.

The April 25, 1966 shipment charged in Count II involves the introduction into interstate commerce by Wyeth Laboratories, Inc., at Paoli, Pennsylvania, on April 25, 1966, via Needham's Motor Service, Inc., of 180 500-capsule bottles of 10 mg. Serax capsules, for delivery to Wyeth Laboratories, Division of American Home Products Corporation, Secaucus, New Jersey.

The violative shipments were made pursuant to Wyeth Finished Stock Transfer Orders No. 51481 and 12226, as confirmed by signed statements made by the respective branch managers at the branches where the lots were received after their shipment in interstate commerce.

We have noted your request concerning copies of the advertisements which appeared in the April 25, 1966 issue of the Journal of the American Medical Association, the April 18, 1966 issue of Medical Economics, and in the March 1966 issue of the American Journal of Psychiatry. Because those advertisements do not photocopy well, one set of the actual advertisements has been obtained for your use and is hereby transmitted together with photocopies of the advertisements.

The United States Attorney will be supplied with a set of the actual advertisements by the Philadelphia District of the Food and Drug Administration. We should be happy to render any further assistance as may be possible.

Sincerely yours,

William W. Goodrich,
Assistant General Counsel,
Food and Drug Division.

IN THE UNITED STATES DISTRICT COUNT FOR THE EASTERN DISTRICT OF PENNSYLVANIA

United States of America v. *Wyeth Laboratories. Inc.*, a corporation, No. 21 U.S.C. 331 and 333.

Information

COUNT I

The United States Attorney charges:

That Wyeth Laboratories. Inc., a corporation, organized and existing under the laws of the State of New York, and trading and doing business at Philadelphia and Paoli, Pennsylvania, the defendent herein, did, on or about July 21, 1965, within the Eastern District of Pennsylvania, in violation of the Federal Food, Drug, and Cosmetic Act, [21 U.S.C. 331(a)], unlawfully cause to be introduced and delivered for introduction into interstate commerce at Paoli, Pennsylvania, for delivery to Baltimore, Maryland, a number of bottles containing a drug, namely, Serax;

That displayed upon said bottles was certain labeling which consisted, among other things, of the following printed and graphic matter:

100 capsules
SERAX (Oxaxepam) 15 mg.
Caution: Federal law prohibits dispensing without prescription.
Wyeth Laboratories Inc., Philadelphia, Pa.

That said drug, when caused to be introduced and delivered for introduction into interstate commerce as aforesaid, was misbranded within the meaning of 21 U.S.C. 352(a) in that said drug was a prescripition drug which was a new drug subject to 21 U.S.C. 355 and said defendant, the manufacturer of said drug, failed to include in the advertisements caused to be issued by said defendant with respect to said drug in the June 28, 1965 and July 5, 1965 issues of the Journal of the American Medical Association, a true statement of information in brief summary relating to the side effects, contraindications and effectiveness of said drug as required by regulations, 21 CFR 1.103(e) and (f), to wit, (1) the aforesaid advertisements did not present a brief summary which fairly showed the effectiveness of said drug in the conditions for which it was recommended in the advertisements, together with a showing of all side effects and contraindications of said drug that were pertinent with respect to the uses recommended and suggested in the advertisements, including the information from the approved new drug application labeling for said drug concerning said side effects and contraindications, and (2) the aforesaid advertisements lacked fair balance in presenting with respect to said drug information on effectiveness and information on side effects and contraindications.

COUNT II

The United States Attorney further charges:

That Wyeth Laboratories, Inc., a corporation organized and existing under the laws of the State of New York and trading and doing business at Philadelphia and Paoli, Pennsylvania, the defendant, herein, did, on or about April 23, 1966, within the Eastern District of Pennsylvania, in violation of the Federal Food, Drug, and Cosmetic Act, [21 U.S.C. 331(e)], unlawfully cause to be introduced and delivered for introduction into interstate commerce at Paoli, Pennsylvania, for delivery to Secaucus, New Jersey, a number of bottles containing a drug, namely, Serax;

That displayed upon said bottles was certain labeling which consisted, among other things, of the following printed and graphic matter:

500 capsules
SERAX (Oxaxepam) 10 mg.
Caution: Federal law prohibits dispensing without prescription.
Wyeth Laboratories Inc., Philadelphia, Pa.

That said drug, when caused to be introduced and delivered for introduction into interstate commerce as aforesaid was misbranded within the meaning of 21 U.S.C. 353(n) in that said drug was a prescription drug which was a new drug subject to 21 U.S.C. 355 and said defendant, the manufacturer of said drug, failed to include in the advertisements caused to be issued by said defendant with respect to said drug in the April 25, 1966, issue of the Journal of the American Medical Association, in the March 1966 issue of the American Journal of Psychiatry and in the April 18, 1966 issue of Medical Economics a true statement of information in brief summary relating to the effectiveness of said drug as required by regulations, 21 CFR 1.105(e) and (f), to wit, (1) the aforesaid advertisements did not present a brief summary which fairly showed the effectiveness of said drug in the conditions for which it was recommended in the advertisements, (2) the aforesaid advertisements lacked fair balance in presenting information on the effectiveness of said drug, and (3) the aforesaid advertisements recommended and suggested said drug for uses which were not set forth in the approved new drug application labeling for said drug.

UNITED STATES ATTORNEY FOR THE
EASTERN DISTRICT OF PENNSYLVANIA.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
May 15, 1967.

The Honorable ATTORNEY GENERAL,
Department of Justice,
Washington, D.C.

Attention Harold P. Shapiro, Chief, Administrative Regulations Section.
Re Wyeth Laboratories, Inc., FDC No. 52677, Federal Food, Drug, and Cosmetic Act. Your ref: FMV:JWK:mfs, 21-62-326, 22A-48-20.

DEAR MR. ATTORNEY GENERAL: This is in reply to your letter of February 15, 1967, advising of your tentative conclusion that no violation of 21 U.S.C. 352(n)(3) can be proved against the above named company.

We believe that a violation of that provision has occurred, since the "message" portion of the advertisements contain false and misleading statements of effectiveness of the drug and those misstatements cannot be corrected by a "true statement" of such properties elsewhere in the advertisement under the heading "prescribing information". This conclusion is supported by the language of the section and by the legislative history of 21 U.S.C. 352(n). We think both show that an advertisement cannot meet the "true statement" requirement when it is inconsistent within itself and when it fails to achieve truth in its central theme.

The legislative history shows that Congress intended 21 U.S.C. 352(n) to deal completely with the problems of false and misleading advertising. The requirement that the advertisement include "a true statement of . . . such other information in brief summary relating to side effects, contraindications, and effectiveness as shall be required in regulations which shall be issued by the Secretary" was meant to give the Secretary authority to promote truthful information in the entire advertisement.

In sponsoring the amendment which restored the section on prescription drug advertising to the Senate bill, Senator Kefauver pointed out that "eminent medical authorities testified that much of drug advertising is *misleading* and some is false. They further emphasized that when a doctor is misled, his patient's health is endangered." Senate Report No. 1744, 87th Cong., 2nd Sess., p. 39 (1962) [Emphasis added]. Representative Dingell quoted a study by the American Medical Association, during debate on this measure, stating "the most heinous and despicable practice that doctors found was this—'a company knowingly misleading a doctor through bad advertising'". 103 Cong. Rec. 21086 (September 27, 1962).

This provision was intended to provide for "truth in drug advertising", according to Representative Celler, who likened the desired effect of this amendment to the restrictive regulation of information on securities, stating:

"Our securities laws provide that stock may not be sold to the public against false or misleading information. I fail to see why we should not be equally stringent in the sale of lifesaving—but potentially dangerous—drugs.

"While I am well aware of the many medical miracles wrought by our modern wonder drugs, and while the drug companies have many splendid accomplishments of which they may justly be proud, I am not convinced that false or misleading drug advertising is the price we must pay for pharmaceutical progress." 108 Cong. Rec. p. 21086 (September 27, 1962).

Representative Multer referred to the function of the regulations:

"The Secretary's regulations necessarily would be limited to a fair summarization of side effects, contraindications, as well as effectiveness so that a balanced story appropriate to an advertising page could be presented.

* * * * * * *

"There can be no justification for half truths either in an advertising piece or in labeling copy. We are dealing with drugs that are lifesaving and which are used in serious, debilitating diseases. Fairness alone requires that the message to physicians be a balanced one giving both the good and the bad of the drug, within the limits of advertising copy, and that the patient's interest not be obscured by a glowing picture of the effectiveness of the drug with no mention at all of its possible side effects and contraindications." 108 Cong. Rec. 21091 (September 27, 1962).

These statements illustrate the Congressional concern that the advertisement not mislead the physicians in any way. Certainly, the most obvious way in which advertisements mislead is by omission of side effects and contraindications, and Congress, naturally, focussed a great deal of attention on these facets. However, the frequent use of the term "misleading" and the context in which it was used, clearly demonstrate that Congress was concerned with the truth of the whole advertisement.

This concern is evident in a number of examples of drug advertisements which were presented on the House floor. Representative Blatnik described for his colleagues "two examples of how ads can mislead". 108 Cong. Rec. 21084 (September 27, 1962). The first was a 3-page advertisement for the drug "Singoserp". He pointed out that the headline for the ad states: "For the first time, the drug that lowered this patient's blood pressure without side effects."

Yet elsewhere the ad states that the drug "has infrequent side effects". He criticized, as well, the use of meaningless illustrations:

"Obviously they had quite a bit of space because you notice at the bottom one-third of the lefthand page is a picture of a scale. Now that does not provide any fundamental basic knowledge to a doctor because he knows what a weighing scale looks like, but it is in the picture."

The ad was printed in several medical journals, although the screening comittee for the Journal of the American Medical Association rejected it because: They felt this advertisement, and I quote, "carries a misleading implication of a broad, too all-inclusive nature."

That criticism goes far beyond the mere omission of a "brief summary" of side effects, contraindications, and effectiveness. It is directed to the misleading nature of whole advertisement, and, we submit, reflects the opinion of Representative Blatnik, the sponsor of the floor amendment that was adopted, as to the abuses which the prescription drug advertising provisions were intended to correct.

The second example was an ad for the drug "Tao". Again, Representative Blatnik criticized the waste of space devoted to a picture of a slide rule: Would you not think they would have used that space to tell what the bad effects, the side effects might be? In short, to tell the whole story. They do not need a slide rule to illustrate what the drug does.

He then points out the misleading nature of the ad: Listen to what it says: On the first page it is implied that Tao is a superior antibiotic. And on the other page it says:

> Tao encompasses even strains of common pathogens (notably straphylococci) [sic] resistent to penicillin and erythromycin.

They say it is superior to penicillin. What does the American Medical Association say about it? They said that this was "altogether too strong and misleading" a statement. This is a quote about this particular advertisement. This particular advertisement claimed that the drug has a greater range of efficacy than penicillin. The American Medical Association committee reported to the advertising agency that this claim "seems completely false since clinically it is quite inferior to penicillin in the treatment of most infections."

* * * * * * *

The American Medical Association rejected this as being completely false and misleading, yet 6 months later the same ad appeared in four widely used medical journals * * *

Here again, the criticism is directed to the false and misleading nature of the advertisement as a whole. The statements in the "message" portion of the advertisement were false and misleading. The *addition* of a "ture statement" in a "brief summary" of side effects or contraindications or effectiveness might afford the physician other information on which to judge the drug, but could not itself correct the misleading effect of the advertisement. Certainly, the advertisement would be misleading if it asserts that "Tao" is soperior to penicillin in the "message" portion even if the "brief summary" said that it was not. The total effect would be something less that a "true statement" of effectiveness of the drug.

Similarly, Representative Dingell described an advertisement for the drug "Medrol", as follows:

"I was surprised to find in my study of material involving one medical practitioner that an ad appeared in one of the standard publications on the subject showing the photographs of a patient who allegedly suffered from colitis. I was further surprised to find in my additional study that this so-called reputable manufacturer who was advertising had actually gone so far as to use X-ray photos of persons who had not received the drug.These two different photographs of two different patients appeared in the ad with statements in the advertisement purporting to indicate that it was the same patient on a before and after treatment basis, before and after he had received the drug Medrol."

"This is the kind of advertisement that the amendment to the drug advertisement section trics to correct, to assure that the doctor shall receive to the fullest extent possible the fairest and most complete statement of side effects, contraindications, and efficacy of the drug in simple form." 108 Cong. Rec. 21064 (Sept. 27, 1962). [Emphasis added]

The false illustrations in that advertisement occurred in the "message" portion, and would not be affected by a true statement of side effects, contraindications, or effectiveness, "in brief summary", or otherwise. From this example, the conclusion is inescapable that Representative Dingell believed that section 502(n) was intended to eliminate false and misleading statements throughout the advertisement.

The drug advertising examples given in debate demonstrate that Congress intended to promote truthful drug advertising in all aspects. The concept of truth in drug advertising would be meaningless if it were interpreted to apply to only a portion of an advertisement. Such an interpretation would illogically limit the meaning of the phrase "true statement" and would do violence to the understanding of the provision by Congress. Rather than preventing half-truths, the provision would enable advertisements to mislead, as has occurred in the instant case, by permitting truth to be mixed with fiction.

Certainly, Congress did not want this amendment to promote confusion to physicians. To limit regulation of the advertisement to examination of a portion of it—whether labeled "brief summary" or otherwise—could only have that result. Only if the entire advertisement be subject to the requirement of "a true statement" can 502(n) have the enforcement effect sought by Congress.

This very issue was taken up in the 1963 hearing to establish regulations on prescription drug advertising. The Commissioner stated and the Pharmaceutical Industry agreed that the "true statement" concept applied to the whole ad message. On October 1, 1963, Mr. Larrick wrote to Mr. Gesell, counsel for the industry, as follows:

I. *Fair Balance and Prominence.* It seems clear to us from the legislative history of section 502(n) that Congress intended this new section to deal completely, and not partially, with the problems of false and misleading advertising which had been called to its attention. The legislative history clearly shows that Congress intended the administering agency to have jurisdiction over the entire advertisement and that the phrase "brief summary" was introduced only to authorize use of a stripped-down statement of the drug's effectiveness, side effects, and contraindications when the sponsor wished to limit the size of his ad.

Our regulations are not intended to prohibit use of graphic presentations, headlines, or similar advertising techniques. Our basic purpose is to provide assurance that the advertisement will fairly present the message to the physician of what the drug will do, what its limitations are, and what side effects

and contraindications may attend its use. Somewhat different size type may be used in presenting information with respect to side effects, contraindications, and warnings than that used in the eye-catching headlines. But the regulations would not permit the concealment, subordination, or deemphasis of this essential side effect and contraindication information to minimize its disclosure as a part of the total message the advertisement conveys. With this background, we will answer the first four questions.

This was placed in the record and was taken to be the understanding of the provision and regulations by all parties.

Moreover, this interpretation is consistent with other regulation in this field. The terms "false" and "misleading" have been uniformly interpreted to apply to an entire piece of labeling or advertising. Labeling is false and misleading if it contains ambiguities, exaggerations, half-truths, and over-emphasis in any respect. *United States* v. *95 Barrels * * * Vinegar*, 265 U.S. 438, 442–443 (1924); *V. E. Irons, Inc.* v. *United States*, 224 F.2d 34 (C.A. 1, 1957), cert. den. 354 U.S. 923; *United States* v. *46 Cartons * * * Fairfax Cigarettes*, 113 F. Supp. 336 (D.N.J., 1953). Nor do disclaimers in the piece cure false and misleading statements. *V. E. Irons, Inc.* v. *United States, supra*; *Research Laboratories* v. *United States*, 167 F.2d 410 (C.A. 9, 1948), cert. den. 334 U.S. 843.

The very same considerations apply to advertisements. See *Rhodes Pharmacal Co., Inc.* v. *Federal Trade Commission*, 208 F.2d 382, 387 (C.A. 7, 1953) and *Murray Space Shoe Corporation* v. *Federal Trade Commission*, 304 F.2d 270, 272 (C.A. 2, 1962) where the Court cites the Food and Drug case *United States* v. *95 Barrels of Vinegar, supra*, for the proposition that the advertisement as a whole must be examined, and that if the advertisement contains statements capable of both a misleading and a truthful interpretation, the advertisement is misleading. *P. Lorillard, Inc.* v. *Federal Trade Commission*, 166 F.2d 44 (C.A. 4, 1950); *Beckenstette* v. *Federal Trade Commission*, 134 F.2d 369, 371 (C.A. 10, 1943). The entire context is examined to determine whether or not the overall impression is misleading and deceptive to the audience. *Federal Trade Commission* v. *Standard Education Society*, 303 U.S. 112 (1937); *P. Lorillard, Inc.* v. *Federal Trade Commission, supra*. Even though words and sentences of an advertisement may be literally and tecnically true, when they are framed in a setting which may mislead or deceive, the advertisement is violative. *Beckenstette* v. *Federal Trade Commission, supra*.

We enclose a redrafted information for your consideration which charges that the advertisements in their entirety do not include true statements as to effectiveness, side effects, and contraindications. We believe that this information is sufficient to withstand a motion for a directed verdict.

Very truly yours,

WILLIAM W. GOODRICH,
Assistent General Counsel,
Food and Drug Division.

PREPARED STATEMENTS

Statement by

Neil L. Chayet, Esquire
as Counsel
on behalf of the
Committee for the Care of the Diabetic

before the
Subcommittee on Monopoly
of the
Select Committee on Small Business
U.S. Senate

January 31, 1975

accompanied by
Dr. Robert Bradley
Chairman
Committee for the Care
of the Diabetic

Mr. Chairman:

On behalf of the Committee for the Care of the Diabetic, Dr. Robert Bradley as Chairman and I as Counsel are pleased to testify today before this Committee on a matter of extreme importance to the medical and scientific community: the continuing controversy relating to the UGDP study.

The Committee on the Care of the Diabetic is a group of 180 physicians who represent leading diabetologists and it includes clinicians, researchers and academicians throughout the United States. The group was formed in November 1970 shortly after the UGDP results were released. Its chairman, as I mentioned, is Dr. Robert Bradley, who is here with me today, and its coordinating committee consists of Drs. Henry Dolger, Peter Forsham, Holbrooke Seltzer, and John B. O'Sullivan.

For the last five years, the Committee on the Care of the Diabetic has been engaged in the continuing and often bitter controversy which has surrounded the University Group Diabetes Program (UGDP). This controversy has involved the Congress, the Courts, the National Institutes of Health, the Food and Drug Administration, the manufacturers, and scientists, physicians and patients throughout the United States and, indeed, throughout the world.

At the onset, we wish to state, for the record, the position of the Committee on the Care of the Diabetic with regard to the UGDP study. First it is important to stress what we are not seeking to bring about. We are not asking that the FDA ignore the UGDP findings completely or that these findings not be reflected in the labeling accompanying these drugs. In fact we find it difficult to understand why, some 19 months after this matter was decided by the Court of Appeals for the First Circuit, the FDA has not acted definitively to bring about new labeling. We are seeking new labeling to insure that this study and other relevant studies will be made known to physicians and their patients. However, such labeling must indicate the fact that there is great controversy surrounding this subject and that a material weight of scientific and medical opinion does not accept the results of the UGDP study. In short, what we are seeking is fair balance in the governmental handling of this matter. I realize that nearly eight million dollars is a great deal of money and ten years is a very long time, and criticism of such an effort is neither to be given nor taken lightly; nevertheless, costly mistakes in research, as in all human endeavors, have been made before, and will be made again, and criticism and controversy will not disappear merely because those who seek to justify this study pretend that it either does not exist or is of no account.

We have set out in this testimony some of the fundamental problems confronting analysis of the UGDP as a study and the Biometric Society's report on that study.

I. The need for science to be free from governmental intervention where there exists valid scientific controversy.

The power of government is awesome. It must be wielded with discretion as well as tact, with equity as well as understanding. Partisanship by government throws what can be overwhelming weight into the balances of scientific exchange. Such partisanship fosters positions which are both dangerous and incomprehensible.

After repeatedly seeking the raw UGDP data since 1971, our Committee most recently received a letter from Dr. Whedon of the National Institutes of Health, dated January 27th, stating: "To my knowledge, no one in the Department of Health, Education and Welfare has ever had any of the raw data of the UGDP study." In effect, this data is not available to the experts of our Committee.

Despite our inability to obtain UGDP raw data, we did obtain the Biometric Society report this past Tuesday which states:

"Dr. C. Klimt, the Director of the Coordinating Center, and his staff provided extensive tabulations and original data of the UGDP trial."

The Committee on the Care of the Diabetic has repeatedly protested the partisanship of government agencies in this controversy. The release to the press of the UGDP study before its scientific presentation triggered a storm of controversy. Our criticism of multiple flagrant defects in the UGDP study was and still is, apparently, considered a challenge to the National Institutes of Health which expended over $7.7 million for a study which neither tested oral hypoglycemic therapy as it is practiced nor provided any insights into insulin therapy.

- For years patients were carried in a study monitored by NIH personnel--a study which has become the subject of severe criticism by many of the leading diabetologists in the United States.

- Other agencies in HEW, such as the FDA, have entered the scene and, despite the clear existence of valid scientific controversy, the government has to this day sought to impose its will by excluding from oral hypoglycemic package inserts the very "fair balance" required by its own regulations. When challenged in the courts, it seeks by regulatory means to exempt itself from the preexisting requirement of fairness.

• In a manner not clear to us, a principle investigator of the UGDP was engaged by the FDA an d appears from documents available to us to have participated in the preparation of FDA material relating to the legal aspects of this controversy.

• When challenges to the validity of the study could not be silenced, the NIH arranged for Dr. Thomas C. Chalmers to have the Biometric Society undertake an analysis primarily of the statistical aspects of the study, despite the fact that many if not most of the central criticism was clinical in nature. The same Dr. Chalmers now appears as the author of an editorial in the J. A. M. A. in which he modestly omits his personal role as a government official in arranging for the Biometric Society study as he proceeds to hail its findings, to support it with selections of references relating to experimental and human studies, while omitting all controverting reports in the literature.

I do not know what this is called in science. In politics it has been called a "cover-up". There is need for further inquiry into the whole area of the treatment of diabetes and also the role of government agencies and individuals in the UGDP affair.

The government has continually been a party at interest in the UGDP controversy. Government officials should have been sensitive to American judicial and scientific processes and should have delegated both the selection of the review body and its mandate to an uninvolved, nonpartisan group. Instead, its actions, in effect, were equivalent to being judge, jury and prosecutor, publicist and apologist.

II. The rights of patients to be fully, freely and properly informed

Diabetes is strongly affected by emotional factors. Confidence in the physician-patient relationship is essential for optimal management of diabetes.

As has happened so often in the past with the UGDP study, patients have been exposed to frightening headlines and unsubstantiated charges before the actual report has either appeared in the scientific press or been presented to a jury of its peers. This week, newspapers, TV and radio were flooded with statements unsupported by data before even the experts and diabetologists of our Committee could obtain any relevant information. It does not serve the interests of patients nor of the physician-patient relationship, nor of science itself to repeatedly confront such situations in which there is neither time for suitable study and deliberation nor for corrective action on the part of the medical profession.

This week, the worried diabetic who consults his physician can get little comfort from his doctor who has no data on which he can base an informed opinion on the Biometric Report. Both Dr. Chalmers editorial and the Biometric Report will not appear in J. A. M. A. until February. How is the diabetologist

or the practicing physician to know upon what Dr. Chalmers (in editorial and press release) has based his estimate of 10,000 to 15,000 deaths; how can they determine, as we have, the fact that some of the very references Dr. Chalmers puts forth in support of the validity of the UGDP study are in reality in contravention of the UGDP findings? Trial of medical treatment by headline and press release is as bad for science as it is for law, and results, medically, in disruption of patient treatment as it raises unsupported doubts.

III. Observations on the Biometric Report and the Chalmers Editorial

At the outset, it should be noted that the authors of the Biometric report do not claim to be qualified to appraise the clinical aspects of the UGDP study. The Biometric report states: "The choice of specific selections criteria adopted by the UGDP was a responsibility that was shared with medical experts and is not a topic on which this committee as a whole claims primary competence." This disavowal of clinical competence was well taken, as will be seen below.

The Biometric report recognizes that "the result of [the UGDP] decision to terminate the study [is to] leave us with some residual uncertainty as to the meaning of the findings."

The report further states, "We discovered a puzzling anomaly concerning the distribution of the two sexes in the four treatment groups within clinics... The discrepancy in Seattle alone would represent an unusual event in random allocation... A more important point is whether these findings provide evidence of a breakdown of the randomization

procedure--a contingency which might have grave implications for the credibility of the whole study... We were not able to find an assignable cause for the surprising allocation of the sexes to treatments but have no reason to think the study has been compromised by a breakdown of the randomization to the treatment groups." *

The Biometric Society could have considered other evidence of a possible breakdown of the randomization procedure if they examined the two-fold and even more than three-fold difference in total time at risk as between male and female patients, differences in compliance, autopsy rates, etc. Among the defects in the UGDP study, the Biometric report states, "The omission of a history of smoking was a blunder." This is praising with a faint damn as there were other blundering omissions such as the failure to identify patients on thiazides, as well as the failure to identify those patients with family histories of heart disease.

The Biometric Society mildly observed that the UGDP report "made use of some relevantly unfamiliar and exploratory techniques". These very techniques have, for several years, caused critics to raise the question of statistical manipulation of data.

* It is interesting to note that the calculation of age at death of the data presented by the UGDP shows that all tolbutamide patients, males and females, had a mean age of 65.2 and all placebo patients 61.5 and the difference at death between placebo females and tolbutamide females was six years, 59.8 for placebo and 65.8 for tolbutamide group.

The Biometric Society report notes that "On the question of cardiovascular mortality due to tolbutamide and phenformin we consider that the UGDP trial has raised suspicions which cannot be dismissed on the basis of other evidence presently available." However, we believe the Biometric report incorrectly minimizes some of the evidence which it analyzes, as in the case of the Paasikivi study which is inconsistent with their thesis of the toxicity of tolbutamide. They omit a recent report of a prospective study which has become a landmark in the field of epidemiology, that of the Framingham group. We have included a copy of this report, published in the American Journal of Cardiology, as an appendix to our testimony.

The Biometric group then focuses upon a critical issue:

"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 obtain inadequate control on tolbutamide could be shifted to insulin."

In the conclusions of the UGDP group there is a brief warning against extrapolation of UGDP findings to other dosages and other types of patients.

One could never judge from the press releases, the news stories, the public actions of government officials that both reports related to a hypothetical test situation and not to the actual practice of oral hypoglycemic treatment. Under certain circumstances, the Biometric report finds that "There remains the question whether tolbutamide, although ineffective in a fixed dose regimen, might be an effective therapy as ordinarily used." I am sorry that I cannot supply the page citation but will do so when it is published next month.

In their analysis, the Biometric Report apparently accepts the study of Keen et al as statistically valid and attention is drawn to the fact that those authors concluded "a significant degree of primary protection against cardiovascular events can be conferred by tolbutamide in moderately and mildly hyperglycemic people."

In concluding their analysis of the Paasikivi study they state, "This study neither confirms nor contradicts the UGDP findings as the population under consideration was not

one of maturity onset diabetes, and the patients taking tolbutamide had been exposed to a relatively small dose for a shorter time than applied in the UGDP study." However, the report here is internally inconsistent for the Biometric group elsewhere holds that "The concern about possible tolbutamide toxicity would not really be lessened if it could be shown that the study group contained some nondiabetics. A drug found toxic in such subjects would not likely be counted safe for well documented diabetics either."

If the authors of the Biometric Report are suggesting that cardiotoxicity per se is a central issue, then it becomes difficult to comprehend their failure to accept the Paasikivi report which in any consideration of toxicity qua toxicity is most pertinent. This study was carried out on 178 survivors from a first myocardial infarction. The sensitivity of a damaged heart to cardiotoxic substances is reflected in the narrowing margin between effective and toxic dose of the cardioglycosides when used in such situations. It would be remarkable that a cardiotoxic agent given in the period of greatest danger "during the first 12 months [after myocardial infarction] would show a significant difference in favor of tolbutamide." Fifteen controls died and only six tolbutamide patients--2-1/2 times more controls than the treated patients.

Then 19% of the control group died as compared with 14% of the tolbutamide group with no significant difference in survival after five years. Such a study would weigh heavily against any conclusion that cardiotoxicity was involved in the UGDP tolbutamide patients.

It is also disturbing to note that neither the Biometric Report nor the Chalmers editorial saw fit to call attention to the recent report on the "Role of Diabetes in Congestive Heart Failure, The Framingham Study" (Am. Jrnl. Cardiology 34: 29-34, July 1974). The findings are pertinent to any consideration of cardiotoxic effects of oral hypoglycemics. May we quote from the paper:

"Role of Insulin:

Further examination of the group of patients with diabetes who had congestive heart failure revealed that more than half were taking insulin. Treatment of diabetes was therefore subjected to analysis revealing that the only subgroup of diabetic subjects that sustained a substantial and statistically significant increased risk of congestive failure was the group treated with insulin. This was demonstrated by a bivariate regression analysis accounting for age (Table 9)."

The table reveals that insulin increased the risk of congestive failure over oral hypoglycemic agents and other treatments in both men and women aged 45 to 74 years. This finding, from this classic non-controversial prospective study of 18 years which reviewed 5,209 men and women, is in contradiction to the findings of the briefer UGDP study reporting on 823 patients. The Framingham study is, however, consistent with the findings of Paasikivi study.

We find it exceedingly disturbing that the great Framingham study, acknowledged as a true landmark, was neither referred to by Chalmers in the editorial or in the Biometric Report. To the best of our knowledge it also has been conspicuous by its absence from press releases.

Our cursory review of the UGDP study and other studies such as the Framingham study points out that valid scientific controversy exists with respect to any conclusions to be drawn in this area at this time. There exists important scientific studies challenging some of the fundamental assumptions and conclusions drawn from the UGDP study. In the light not only of the UGDP findings but of the controverting studies there is need for new, truly unbiased and well controlled objec-

tive prospective studies. Action by this Committee can make a significant contribution to the future of American medicine and science by recommending that U.S. governmental agencies divorce themselves from partisan participation in the presence of scientific controversy and that government follow a doctrine of equal opportunity for research and studies by qualified individuals holding different views.

American Journal of Cardiology 34: 29-34. (July 1974).

Role of Diabetes in Congestive Heart Failure: The Framingham Study

WILLIAM B. KANNEL, MD, FACC
MARTHANA HJORTLAND, PhD*
WILLIAM P. CASTELLI, MD

Framingham, Massachusetts
Bethesda, Maryland

The incidence of congestive heart failure was determined in relation to prior diabetic status in 5,209 men and women aged 30 to 62 years followed up for 18 years in the Framingham study. Men aged 45 to 74 years had more than twice the frequency of congestive failure as their nondiabetic cohorts, and diabetic women had a fivefold increased risk. This excessive risk appears to be caused by factors other than accelerated atherogenesis and coronary heart disease. Even when patients with prior coronary or rheumatic heart disease were excluded, the diabetic subjects had a four- to fivefold increased risk of congestive heart failure. In women (but not men) with prior coronary disease, diabetes also imposed a threefold increased risk of congestive failure. Furthermore, the increased risk of heart failure in the diabetic patients persisted after taking into account age, blood pressure, weight and cholesterol values as well as coronary heart disease. Women with diabetes appeared to be especially vulnerable and, irrespective of coronary disease status, had twice the frequency of congestive heart failure as men. The excessive risk of heart failure among diabetic subjects was confined to those treated with insulin. The data suggest that diabetes is another discrete cause of congestive heart failure and that some form of cardiomyopathy is associated with diabetes, as a result of either small vessel disease or metabolic disorders.

Congestive heart failure is a common end stage of heart disease due to a variety of causes. The incidence is far from trivial. The annual rate is 2.3/1,000 men and 1.4/1,000 women aged 30 years and over.[1] Despite the availability of potent glycosides and diuretic agents, congestive heart failure continues to be a lethal process, and half of the patients die within 5 years of onset.[1] Previous study[1] revealed that hypertension and coronary heart disease were the dominant causes, but 14 percent of men and 26 percent of women with congestive failure also had diabetes, an apparent excess. The purpose of this report is to explore the role of diabetes in the development of congestive heart failure and to assess its contribution taking into account the presence of coronary heart disease and atherogenic factors such as hypertension, high serum cholesterol levels, overweight and increased age.

Methods

The Framingham study was initiated in 1949 to explore the epidemiology of cardiovascular disease in a general population sample of 5,209 men and women aged 30 to 62 years. These subjects have been followed up for the development of cardiovascular disease including congestive heart failure. At every biennial examination each participant has had, in addition to a history and physical evaluation, a 13 lead electrocardiogram, a chest X-ray film, tests of vital capacity, urinalysis, measurements of blood sugar, uric acid and cholesterol levels and determinations of Framingham relative body weight.

Detailed descriptions of the sampling procedure, response rate, methods of examination and laboratory procedures and the criteria for the outcome of disease have been reported previously.[2]

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Address for reprints: William B. Kannel, MD, Framingham Heart Disease Epidemiology Study, 123 Lincoln St., Framingham, Mass. 01701.

TABLE I

Criteria for Congestive Heart Failure*

- Major criteria
  - Paroxysmal nocturnal dyspnea or orthopnea
  - Neck vein distension
  - Rales
  - Cardiomegaly
  - Acute pulmonary edema
  - S_3 gallop
  - Increased venous pressure $\geq$16 cm H_2O
  - Circulation time $\geq$25 second
  - Hepatojugular reflux
- Minor criteria
  - Ankle edema
  - Night cough
  - Dyspnea on exertion
  - Hepatomegaly
  - Pleural effusion
  - Vital capacity decreased 1/3 from maximum
  - Tachycardia (rate $\geq$120/min)
- Major or minor criterion
  - Weight loss $\geq$4.5 kg in 5 days in response to treatment

* Patients were considered to have congestive heart failure if two major or one major and two minor criteria were present concurrently.

TABLE II

Annual Incidence of Congestive Heart Failure by Age, Sex and Presence of Prior Coronary or Rheumatic Heart Disease: 18 Year Follow-Up Study

	Total Population			Subjects with Prior CHD or RHD		
Age (yr)	Person Years at Risk	New CHF Events	Incidence per 10,000	Person Years at Risk	New CHF Events	Incidence per 10,000
			Men			
45–54	14,100	28	20	1,074	17	158
55–64	10,414	43	41	1,564	28	179
65–74	3,700	26	70	762	14	184
			Women			
45–54	17,598	11	6	678	5	74
55–64	13,688	41	30	1,202	24	200
65–74	5,232	34	65	766	20	261

CHD = coronary heart disease; CHF = congestive heart failure; RHD = rheumatic heart disease.

Criteria

At each biennial examination a diagnosis of congestive heart failure was entertained on clinical grounds and the opinion of a second examiner obtained. All suspected cases thus uncovered from biennial clinic examinations or from interim information obtained from hospital records and physician's office reports were reviewed by a panel of investigators using uniform criteria. The diagnosis of congestive heart failure was accepted only in persons with at least two major or one major and two minor criteria present concurrently as indicated in Table I. Minor criteria that could be attributed to some other medical condition were rejected. Only about half the persons diagnosed as having congestive heart failure at the time of the clinical examination on the basis of the examination or interim hospital or physician's office information were included in this study.

Persons who had congestive failure at the time of the initial examination were excluded, leaving a population of 5,192 men and women aged 30 to 62 years at risk. Follow-up study during the ensuing 18 years was reasonably complete, with 80 percent of subjects receiving every possible biennial examination. The remaining 20 percent were seen at less frequent intervals, and admissions to the only general hospital in town were monitored daily. Only 2 percent of the sample were completely lost to follow-up study.

Glucose intolerance was assessed from casual blood sugar determinations, urinary sugar values, or a history of clinical "diabetes." Blood sugar levels were determined by the Somogy-Nelson method. A diagnosis of diabetes was made in subjects who (1) had an abnormal glucose tolerance test during hospitalization or their physician's laboratory evaluation, (2) were taking insulin or oral hypoglycemic agents, or (3) had casual blood sugar values > 160 mg/100 ml.

Statistical Techniques

Incidence rates for congestive failure were ascertained according to diabetic status, age, sex and coronary (or rheumatic) heart disease status. Subjects were reclassified by age at each examination; a case was defined as a subject free of congestive heart failure at a given examination but having failure at the time of the next biennial examination. The method of Mantel-Haenzel[3] was used to construct summary chi squares to assess differences in the frequency of congestive heart failure in diabetic and nondiabetic subjects and to estimate the risk of heart failure in the presence of diabetes. To assess the joint and net effect of diabetes taking into account other related atherogenic variables, multivariate coefficients were computed and compared with bivariate coefficients taking only age into account. Analysis was confined to subjects aged 45 to 74 years since too few cases occurred before age 45 for meaningful analysis. The bivariate function to assess the regression of incidence of congestive heart failure on diabetic status and age was estimated by the method of Walker and Duncan.[4] The multivariate function was estimated by the Walker and Duncan maximal likelihood method using, in addition to the variables of age and diabetic status, systolic blood pressure, serum cholesterol and relative weight.

Results

Frequency of congestive heart failure: During the 18 year follow-up period, congestive heart failure, as defined by the specific criteria, developed in 97 men and 86 women aged 45 to 74 years. The incidence of heart failure increased sharply with age. As expected, the incidence was considerably greater in the subjects with prior coronary or rheumatic heart disease. There was a male predominance at all ages (Table II), but this predominance appeared to wane with advancing age. Among subjects with prior coronary or rheumatic heart disease, there was a male predominance only under age 55 years. About half of the subjects with a diagnosis of congestive heart failure had coronary disease; more than three-fourths had hypertension. About 16 percent had antecedent diabetes, an apparent excess over the expected rate.[1]

TABLE III

Annual Incidence of Congestive Heart Failure According to Age, Sex and Diabetic Status at Each Biennial Examination: 18 Year Follow-Up Study

Diabetic Status	Age 45 to 54 Years			Age 55 to 64 Years			Age 65 to 74 Years		
	Person Years at Risk	New CHF Cases	Incidence CHF per/10,000	Person Years at Risk	New CHF Cases	Incidence CHF per/10,000	Person Years at Risk	New CHF Cases	Incidence CHF per/10,000
				Men*					
Nondiabetic	13,696	26	19	9,864	40	41	3,428	20	58
Diabetic	404	2	50	550	3	55	272	6	221
Total	14,100	28	20	10,414	43	41	3,700	26	70
				Women*					
Nondiabetic	17,268	8	5	13,156	36	27	4,904	25	57
Diabetic	330	3	91	532	5	94	328	9	274
Total	17,598	11	6	13,688	41	30	5,232	34	65

* Men: For all ages combined difference in incidence is statistically significant at ($P < 0.05$). (chi square 6.50); relative risk 2.4. Women: For all ages combined difference in incidence is statistically significant ($P < 0.01$) (chi square 42.54); relative risk 5.3. Method of Mantel-Haenzel.

Diabetes and congestive heart failure: During the 18 year study, diabetes was present or developed in 141 men and 151 women, allowing 1,226 person years of follow-up experience for men, 1,190 for women. Almost 40 percent of those labeled "diabetic" were treated with insulin. In most of these patients, diabetes was already evident at entry into the study. Another 40 percent were treated with oral hypoglycemic agents and about 20 percent were following a diet only or were receiving no treatment. Examination of the incidence of congestive heart failure according to diabetic status at each biennial examination revealed a distinct excess risk in diabetic subjects of both sexes and at all ages (Table III). The small numbers do not allow accurate age-specific estimates of risk, but for all ages combined, men had a 2.4-fold increased risk and women a 5-fold increased risk (Table IV).

Role of factors leading to atherogenesis and coronary heart disease: Diabetic subjects are generally believed to have higher than average blood pressures, lipid values and relative weights and to manifest coronary heart disease at an accelerated rate. The excess frequency of congestive heart failure in diabetic subjects could derive from these abnormalities, particularly the hypertension[5] and coronary heart disease. However, an examination of the prevalence of antecedent coronary or rheumatic heart disease in all subjects with congestive heart failure revealed the same proportion of subjects with prior heart disease in the diabetic and nondiabetic groups (Table V). This finding suggests that the increased risk of congestive heart failure in the subjects with diabetes has another cause than accelerated atherogenesis and coronary heart disease although age and severity of coronary disease are not taken into ac-

TABLE IV

Risk of Congestive Heart Failure According to Sex and Diabetic Status at Each Biennial Examination: 18 Year Follow-Up Study

Diabetic Status	Person Years At Risk	Incidence		Relative Risk
		Crude Annual per 10,000	Age-Adjusted* per 10,000	
	Men Aged 45 to 74 years			
Nondiabetic	26,988	31.87	32.14	2.36†
Diabetic	1,226	89.72	75.98	
	Women Aged 45 to 74 years			
Nondiabetic	35,322	19.53	19.75	5.14‡
Diabetic	1,190	142.85	101.60	

* Indirect method.
† Significant at $P < 0.05$ (chi square = 6.50).
‡ Significant at $P < 0.01$ (chi square = 12.53).

TABLE V

Prevalence of Antecedent Coronary (or Rheumatic) Heart Disease (CHD) Among Patients Aged 45 to 74 Years with Congestive Heart Failure (Diabetic vs. Nondiabetic Subjects): 18 Year Follow-Up Study

	Diabetic Subjects		Nondiabetic Subjects	
	With CHD	Without CHD	With CHD	Without CHD
Men	5	6	54	32
Women	10	7	39	30
Total	15	13	93	62

TABLE VI

Annual Incidence of Congestive Heart Failure (CHF) According to Sex and Diabetic Status at Each Biennial Examination Excluding Subjects with Coronary (or Rheumatic) Heart Disease Before the Development of Failure: 18 Year Follow-Up Study

Diabetic Status	Person Years At Risk	New CHF Cases	Annual Incidence: Crude per 10,000	Annual Incidence: Age-Adjusted* per 10,000	Relative Risk
Men aged 45 to 74 Years					
Nondiabetic	23,844	32	13.42	13.53	3.79†
Diabetic	970	6	61.86	51.41	
Total	24,814	38			
Women Aged 45 to 74 Years					
Nondiabetic	32,892	30	9.12	9.23	5.48†
Diabetic	980	7	71.43	50.54	
Total	33,872	37			

* Indirect method.

† Significant at $P < 0.01$ level (chi square = 8.15 and 17.27 for men and women, respectively).

TABLE VII

Annual Incidence of Congestive Heart Failure (CHF) According to Sex and Diabetic Status at Each Biennial Examination in Subjects with Coronary (or Rheumatic) Heart Disease Before the Development of Failure: 18 Year Follow-Up Study

Diabetic Status	Person Years At Risk	New CHF Cases	Incidence: Crude per 10,000	Incidence: Age-Adjusted* per 10,000	Relative Risk
Men Aged 45 to 74 Years					
Nondiabetic	3,144	54	171.76	172.07	1.11
Diabetic	256	5	195.31	190.99	
Total	3,390	59	...	...	...
Women Aged 45 to 74 Years					
Nondiabetic	2,436	39	160.10	147.39	3.16†
Diabetic	210	10	476.19	465.17	
Total	2,646	49	...	...	...

* Indirect method.

† Significant at $P < 0.01$ level (chi square = 8.51).

count in this tabulation. This hypothesis is confirmed by the finding that even when patients with prior coronary or rheumatic heart disease were excluded, patients with diabetes still had a four- to fivefold increased risk of congestive heart failure (Table VI). Also, among persons with prior coronary or rheumatic heart disease, diabetic women had an excess rate of congestive heart failure. This excess could not be demonstrated for men in the small number of cases available (Table VII).

Furthermore, a comparison of the regression coefficients in the bivariate (taking only age into account) and multivariate case (taking into account blood pressure, cholesterol and relative weight as well) indicates that the effect of diabetes is not mediated through these atherogenic traits (Table VIII). An examination of the regression of the incidence of congestive failure on diabetic status in men with and without coronary heart disease also reveals substantial and significant coefficients only for patients without coronary heart disease. The regression coefficients in the multivariate case are only slightly reduced compared with those in the univariate case (Table VIII).

Taking all these facts into consideration it appears unlikely that diabetes promotes congestive failure by accelerating coronary atherogenesis. Nor does it appear that hypertension accounts for the increased risk. In women, significant regressions are noted in both those with and those without prior coronary heart disease although the coefficients are somewhat larger in the latter group. Also, the coefficients are substantially larger in women than in men.

Role of insulin: Further examination of the group of patients with diabetes who had congestive heart failure revealed that more than half were taking insulin. Treatment of diabetes was therefore subjected to analysis, revealing that the only subgroup of diabetic subjects that sustained a substantial and statistically significant increased risk of congestive failure was the group treated with insulin. This was demonstrated by a bivariate regression analysis accounting for age (Table IX).

Discussion

The finding of an increased risk of congestive heart failure in diabetic subjects is not unexpected in view of the frequent association of diabetes with hypertension, hyperlipidemia, obesity and coronary heart disease. The strength of the relation, particularly in women, and the demonstration that the excess risk of myocardial decompensation in the diabetic subject is independent of all these atherogenic traits are unexpected and indicate some other mechanism. It has been suggested that some form of cardiomyopathy is associated with diabetes.[6] The findings reported herein lend some substance to this claim.

Metabolic causes of diabetic cardiomyopathy: Such diabetic cardiomyopathy could result from diabetic microangiopathy or an abnormal myocardial metabolism. The heart normally derives most of its energy for contraction from free fatty acids, although glucose, lactate and pyruvate are also used.[7-11] Any reduction in oxygen tension immediately produces changes in the electrical and contractile performance of the heart. Efficient metabolism of fatty acid and pyruvate is hampered by hypoxia, leaving only the glycolytic pathway to generate the high energy phos-

TABLE VIII

Regression of Incidence of Congestive Heart Failure on Diabetes: 18 Year Follow-Up Study

	Regression Coefficient			
	Men Aged 45 to 74 Years		Women Aged 45 to 74 Years	
	Bivariate*	Multivariate†	Bivariate*	Multivariate†
With Prior CHD or RHD‡				
Coefficient	0.10	0.06	1.13	1.15
t test§	0.21	0.12	3.05	2.97
(no. cases/no. at risk)	(59/1,700)	(58/1,641)	(49/1,323)	(47/1,275)
Without Prior CHD or RHD‖				
Coefficient	1.33	1.01	1.67	1.39
t test	2.94	2.17	3.88	3.15
(no. cases/no. at risk)	(38/12,407)	(36/11,899)	(37/16,936)	(37/16,160)

* The bivariate function was estimated by the method of Walker and Duncan[4] using the variables diabetes and age.

† The multivariate function was estimated by the method of Walker and Duncan[4] using the variables diabetes, age, systolic blood pressure, serum cholesterol and Framingham relative weight.

‡ To be included in this group at a given examination (n), the subject must have had coronary or rheumatic heart disease on or before examination (n + 1).

§ A *t* test value of 1.96 is significant at the 0.05 level.

‖ To be included in this group at a given examination (n), the subject must not have had coronary or rheumatic heart disease on or before examination (n + 1).

phate bonds to fuel the heart's work. It thus appears that glucose and insulin fuel the failing *hypoxic* heart.[7-11] This hypothesis would explain the difficulty of the diabetic ischemic heart but does not account for myocardial decompensation in the absence of hypoxia.

However, in the diabetic heart there is some evidence to suggest that free fatty acids are also not used efficiently. Hearts of rats with alloxan-induced diabetes have been found to accumulate increased myocardial triglyceride in lipid droplets.[8] Human diabetic hearts extract more fatty acid and ketones than the nondiabetic heart, but in the light of the foregoing this phenomenon could indicate that more free fatty acid is being shunted into structural lipid as less is metabolized for energy. It may be that the diabetic heart, because of faulty utilization of fatty acid must, as in the case of ischemia, fall back on glycolytic metabolism for energy. This places it in jeopardy because the utilization of glucose, which is insulin-dependent, is also faulty. This energy crisis may be further compounded in the diabetic subject by a block between pyruvate and the tricarboxylic acid or Krebs cycle.

These major metabolic disturbances could provide a metabolic basis for eventual myocardial failure. The fact that only the insulin-dependent diabetic patient appears peculiarly susceptible to congestive heart failure supports the foregoing in that only these diabetic patients appear to have difficulty with excessive and faulty acid metabolism leading to ketosis as well as impaired glycolysis. The fact that subjects with diabetes of adult onset treated by diet or orally administered drugs have no increased risk of congestive heart failure suggests that the central metabolic defect promoting failure may be ketosis and insulin deficiency. Once heart failure ensues, the process appears to be self-perpetuating since it has been shown that failure further suppresses insulin release.[10]

TABLE IX

Regression of the Incidence of Congestive Heart Failure (Without Prior Coronary or Rheumatic Heart Disease*) on Treatment of Diabetes: 18 Year Follow-Up Study

Treatment	Bivariate Coefficient†	*t* Value‡
Men Aged 45 to 74 Years		
Insulin	1.76	3.26
Oral hypoglycemic agent	0.68	0.66
Other	0.92	0.90
Women Aged 45 to 74 Years		
Insulin	2.21	4.47
Oral hypoglycemic agent	0.56	0.54
Other	1.49	1.45

* To be included in this group at a given examination (n), the subject must not have had coronary or rheumatic heart disease on or before examination (n + 1).

† The bivariate function was estimated by the method of Walker and Duncan[3] using the variables type of diabetic treatment and age.

‡ A *t* value of 1.96 is significant at the 0.05 level.

Role of insulin-treated diabetes: The finding that the excess risk of congestive heart failure is confined to the insulin-treated diabetic subjects raises

three possibilities: (1) Only severe, long-standing diabetes leads to congestive failure. (2) Only insulin-dependent diabetes promotes cardiomyopathy. (3) The insulin treatment itself is damaging to the myocardium. The lack of *any* discernible increased risk of congestive heart failure in the group treated with tolbutamide or diet tends to exclude severity or duration of diabetes as the sole mechanism since an intermediate risk would be expected in this group under this hypothesis. Insulin in itself would not seem to be the culprit since in the patient with keto-resistant diabetes of adult onset endogenous insulin levels are often high either spontaneously or as a result of stimulation by orally administered hypoglycemic agents. Thus, the most tenable hypothesis is the difference in the kind of diabetes, implicating insulin-dependent, ketotic insulinopenic diabetes of early onset as the promoter of cardiac decompensation.

It is hard to exclude duration of diabetes or its severity from consideration. Congestive heart failure could be primarily a function of either factor and hence exhibit a particular relation to insulin-treated diabetes. Data are too scarce in this cohort to assess the effect of the type of treatment required or used versus the duration or severity of diabetes, and these aspects are difficult to disentangle without conducting a controlled experiment. It would be expected that the insulin-treated group would have more small vessel disease such as nephropathy and retinopathy (and perhaps in the heart as well). We cannot tell from our data.

Role of large and small vessel coronary disease: The excess occurrence of heart failure in patients with diabetes could be a result of either large or small vessel disease in the coronary arterial circulation. Such disease, particularly of the small vessels, is more apt to be severe in the insulin-dependent diabetic patient than in the patient not treated with insulin. The ischemic myocardium, which is more dependent on glucose and insulin for energy, would be especially vulnerable. All diabetic subjects should have difficulty in coping with an ischemic myocardial episode in view of the dependence of the hypoxic heart for energy on the glycolytic metabolic pathway, which is impaired regardless of the type of diabetes. And, indeed, once coronary disease develops, the diabetic subject fares worse than the nondiabetic subject in relation not only to congestive failure, but also to recurrence of infarction, myocardial rupture and survival.[12]

Accelerated coronary atherosclerosis has been noted in diabetic subjects, and these patients seem to have more myocardial infarctions, especially silent infarctions.[13] The latter observation suggests some difference in pathogenetic mechanism from that of the nondiabetic infarction. Myocardial and small vessel abnormalities have been studied less extensively than large vessel disease in the diabetic patient.[6] Myocardial hypertrophy and diffuse, patchy fibrosis have been reported more frequently than macroscopic myocardial infarction.[6] Microangiopathy has been well described in the skin, kidney, retina and skeletal muscle, but has not been well documented in the heart.[6] More systematic studies of the diabetic myocardium and its small vessels such as those of Blumenthal and co-workers[13] are urgently needed. These investigators reported more proliferative lesions of arterial branches of all sizes and of venules as well. They also found arteriosclerotic-appearing lesions in the small arteries and arterioles at least twice as frequently in diabetic as in nondiabetic patients with coronary disease.[14]

References

1. McKee PA, Castelli WP, McNamara PM, et al: The natural history of congestive heart failure: the Framingham study. N Engl J Med 285:1441–1446, 1971
2. Gordon T, Kannel WB: The Framingham study: an epidemiological investigation of cardiovascular disease. Sections 1–27, U. S. Gov't Printing Office, NHLI, Bethesda, Md. 1968–1972
3. Mantel N, Haenzel W: Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22: 719–748, 1959
4. Walker SH, Duncan DB: Estimation of the probability of an event as a function of several independent variables. Biometrika 54:167–179, 1967
5. Kannel WB, Castelli WP, McNamara PM, et al: Role of blood pressure in the development of congestive heart failure: the Framingham study. N Engl J Med 287:781–787, 1972
6. Rubler S, Dlugash J, Yuceoglu YZ, et al: New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am J Cardiol 30:595–602, 1972
7. Taylor SH: Insulin and heart failure. Br Heart J 33:329–333, 1971
8. Ungar I, Gilbert M, Siegel A, et al: Studies on myocardial metabolism in diabetes. Am J Med 18:385–396, 1955
9. Opie LM: Metabolism of the heart in health and disease. Parts 1–3. Am Heart J 76:685–598, 1968; 77:100–122, 383–410, 1969
10. Majid PA, Sharma B, Meeran MKM, et al: Insulin and glucose in the treatment of heart failure. Lancet 2:937–931, 1972
11. Editorial: glucose and the heart. Lancet 2:1295–1296, 1972
12. Goldenberg S, Alex M, Blumenthal HT: Sequelae of arteriosclerosis of the aorta and coronary arteries: a statistical study in diabetes mellitus. Diabetes 7:98–108, 1958
13. Kannel WB, McNamara PM, Felnielb M, et al: The unrecognized myocardial infarction: 14 year follow-up experience in the Framingham study. Geriatrics 25:75–87, 1970
14. Blumenthal HT, Alex M, Goldenbert S: A study of lesions of the intramural coronary artery branches in diabetes mellitus. Arch Pathol 70:27–42, 1960

STATEMENT OF

EDWARD M. CHESTER, M.D.

PROFESSOR OF MEDICINE
CASE WESTERN RESERVE UNIVERSITY

DIRECTOR OF THE AMBULATORY MEDICINE TEACHING CLINIC
CLEVELAND METROPOLITAN GENERAL HOSPITAL
3395 SCRANTON ROAD, CLEVELAND, OHIO 44109

BEFORE THE

SUBCOMMITTEE ON MONOPOLY
SENATE SMALL BUSINESS COMMITTEE

U.S. SENATE

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I am pleased to respond to the invitation to testify concerning the use of oral hypoglycemic agents in the treatment of diabetes mellitus.

I am a Professor of Medicine at Case Western Reserve University and Director of the Ambulatory Medicine Teaching Clinic at Cleveland Metropolitan General Hospital. A large segment of my time is devoted to teaching 3rd and 4th year medical students during their clinical clerkships. My research efforts have been directed toward an understanding of the eye changes which are associated with diabetes mellitus. For the past 16 years I have been active in the direction of the Diabetes Clinic at Cleveland Metropolitan General Hospital. Prior to 1959, when I joined the full time faculty of Case Western Reserve University, at Cleveland Metropolitan General Hospital, I had been engaged in the practice of internal medicine for 18 years in a suburban area of Cleveland. My practice dealt chiefly with patients who suffered from cardiovascular disease and/or diabetes mellitus. During the years of practice I served as a part time teacher of Case Western Reserve University at Cleveland Metropolitan General Hospital.

The Diabetes Clinic at Cleveland Metropolitan General Hospital provides care for approximately 500 patients with diabetes mellitus per year. Approximately 80% of the patients have the maturity onset form of the disease. Prior to 1973 the majority of this group of patients were treated with oral hypoglycemic agents with a limited degree of success. Although dietary instruction was provided for the patients, there was little compliance.

When the results of the UGDP study were issued in 1970, we became concerned with our use of the oral hypoglycemic agents. We urged the physicians who cared for patients with diabetes in the clinic and hospital to pay heed to the results of the above study and to re-evaluate their treatment of the maturity onset group of patients. In an attempt to learn the extent of the use of oral hypoglycemic agents and their cost, the amounts of these medications dispensed by our staff were recorded from 1968 to early 1972 (See Table I). Review of these data disclosed an alarming increase in the use of these agents from 1968 through 1970. Response to the recommendations of the UGDP study was reflected by a modest decrease in the use of the oral agents during 1971 and 1972. Because we believed that the use of these agents was still excessive, the following letter was dispatched to the Pharmacy Committee of the hospital early in 1973.

May 24, 1973

Emanuel Wolinsky, M.D.
Chairman of the Pharmacy Committee

Dear Doctor Wolinsky:

The results of the University Group Diabetes Program (UGDP) (Diabetes, 19, Supplement 2, 747-830, 1970) allows one to develop the following conclusions concerning the safety and effectiveness of the oral hypoglycemic drugs, specifically the sulonylurea group (Tolbutamide and Chlorpropamide). (1) In the group treated with Tolbutamide there was a significant increase in deaths from cardiovascular disease, as compared with those treated with either insulin or strict adherence to a calculated diet. (2) That Tolbutamide was not as effective as either insulin or strict adherence to an isocaloric diet in the control of levels of blood sugar.

The UGDP study subsequently reported comparable results with the use of Phenformin (J.A.M.A., 217, #6, 777-784, 1971).

It is only fair to point out that there are skeptics who do not accept the results of the above study.

I accept the results of the study and believe that the use of Sulfonylureas (Tolbutamide and Chlorpropamide) and the Biguanides (Phenformin) should be restricted because they appear to be hazardous to health and are far less effective and more expensive than insulin.

I suggest that we implement a form of control which would restrict the use of Sulfonylurea drugs (Tolbutamide and Chlorpropamide) and Phenformin with the following exceptions:

1. Patients who cannot administer insulin to themselves because of severe visual impairment or other physical handicaps such as neurologic disorders which impair use of arms and hands.

2. Patients who refuse to use insulin.

In order to accomplish such control the department of medicine would provide a list of physicians who could authorize the use of the drugs under discussion. Other services may wish to provide a similar mechanism.

In 1972, $30,000 were expended for Tolbutamide, Phenformin, and Chlorpropamide. Substitution of insulin would be less costly.

Sincerely yours,

Edward M. Chester, M.D.

The results of this educational reminder and form of control produced the results noted in Table I. Table II indirectly indicates that many of the patients previously receiving oral agents were started on insulin therapy. Continuous review of the use of the oral agents is in progress with the intent of further decreasing their use except under the circumstances noted in the letter of May 24, 1973. It is apparent that restriction of the use of these medications in a hospital can be accomplished by education of patients and physicians and by providing a method of control. The problem is unfortunately not as simple for a variety of reasons when one attempts to achieve similar results with patients who are under the care of private physicians. Among these reasons are:

1. That the conclusions of the UGDP study are not accepted by some eminent authorities on diabetes mellitus.

2. That education of physicians lags well behind the knowledge developed through research. Unfortunately drug company literature provides the major source of information for many physicians.

3. The lack of adequate patient education in their understanding of diabetes and the hazards of oral hypoglycemic agents.

4. The failure adequately to impress the patients with sufficient understanding of the importance of a calculated isocaloric diet and their failure to comply in this respect.

5. The ease of using oral medication compared with the injection of insulin.

The UGDP study clearly demonstrated that standard doses of oral hypoglycemic agents did not effectively reduce levels of blood sugar over a 5 year period. These data confirmed previous studies which disclosed that the success rate in managing diabetes with tolbutamide at the end of 5 years was only 13% (DeLawter and Moss, J.A.M.A., 181, 1962, 156). Relapse or secondary failure is recorded as 22% within 5 years (Camerine-Davalos and Marble, J.A.M.A., 181, 1962, 1). Six to seven years after therapy with oral hypoglycemic agents only 6-12% remain well controlled. (A.M.A. Drug Evaluations, Publishing Sciences Group Inc., 2nd Edition, 1973, p. 130, Alton, Massachusetts). Yet despite the ineffectiveness of these hypoglycemic agents and their demonstrated relationship to increased mortality from cardiovascular disease, these drugs are still widely used in the treatment of maturity onset diabetes. I have noted previously the reasons for the failure on the part of physicians and patients to heed the warning of the hazards and ineffectiveness of this group of drugs.

There appear to be 3 approaches to this problem. These include an immediate restriction of their use through firm warning and labelling via the F.D.A., a long term educational process, and the development of more rigid drug testing requirements.

Recommendations:

I. Immediate warning to all physicians of the hazards by a bulletin from the F.D.A. stating the following:

A. A suitably calculated isocaloric diet serves as the cornerstone for the treatment of maturity onset diabetes.

B. A suitable trial of dietary management for several weeks should be instituted first.

C. If adequate levels of blood sugar cannot be obtained with this regimen, even in the absence of symptoms associated with diabetes, insulin therapy should be instituted.

D. The oral hypoglycemic agents are a potential hazard to health and should be used, after the patient has been advised of this fact, with caution only under the following circumstances:

(1) If the patient is handicapped by serious visual loss or other physically incapacitating disorders.

(2) If the patient refuses to use insulin.

The drug companies should be required to include the above facts on the package inserts of medication, despite the fact that physicians infrequently read them. Some method of identifying these medications as hazardous must be developed for patient protection.

II. Long term educational effort. Medical school educators, clinicians who care for patients in university and community hospitals must emphasize the facts known about these drugs to medical students, house officers, and physicians in practice. Efforts should be made to reach the last mentioned through post graduate courses and through the development of self educational units in an attempt to provide more reliable and scientifically based information to counteract the biased and often inaccurate statements issued by pharmaceutical companies and the "throw away" psuedomedical periodicals.

A vital step in the educational process is the need to encourage and support the young investigator. Greater availability of research and training grants through the National Institutes of Health or other government agencies should be encouraged. For it is through the development of such investigators and teachers that the many problems related to diabetes may be resolved.

III. Adequate long term trials before drugs are released for use. Most drugs, and this applies to the oral hypoglycemic agents, were initially tested for their ability to lower levels of blood sugar in animals. Search for toxicity was made as well. These studies were short in duration. After short term trials in man were made by able investigators and clinicians the drugs were released. Subsequent long term studies of these drugs were retrospective and dealt only with their ability to alter levels of blood sugar and lipids. The UGDP study was the first well controlled prospective study and was designed to determine the role of these drugs in the development of vascular disease. Thus many years elapsed before medications, which were commonly used, were found to be hazardous to health and to possess very limited effectiveness. Standards for

long term studies must be developed by the F.D.A. to insure adequate clinical trials of drugs before their release.

The steps indicated above are likely to be met with severe outcry and resistance by pharmaceutical companies and scientists and clinicians who do not accept the conclusions of the UGDP study. Support of the medical societies, particularly the American Diabetes Association would be essential.

Restriction in the use of the oral hypoglycemic agents would significantly alter modes of care for the patient with diabetes. To begin, it would needfully provide a great emphasis on the importance of dietary management. In many instances with adherence to diet adequate reduction of blood sugar and removal of symptoms would follow. Physicians or their assistants would have to instruct patients in the use of insulin when diet alone did not suffice. Thus more teaching would be needed for each patient. Perhaps more teaching related to mechanisms involved in the production of the disease, the need for preventing infection, manifestations of hypoglycemia, and other measures would be taught as well. Since the cost of insulin is considerably less per patient than oral hypoglycemic agents there would be a decrease in total cost.

The issue of the clinical use of research information is exemplified by the mixed reception of the results and recommendations of the UGDP study. Why, one may ask, are there delays in the transmission of research data to its clinical applications? These are several reasons:

1. Early research data may be presented initially to select groups in research societies and published in journals which are read by only highly trained specialists. In addition most articles are not published for at least 6 months after they have been submitted.