

**Interagency coordination in drug research and regulation : hearings before the Subcommittee on Reorganization and International Organizations of the Committee on Government Operations, United States Senate, Eighty-eighth Congress, first session. Agency coordination study, pursuant to S. Res. 27, 88th Cong. Review of cooperation on drug policies among Food and Drug Administration, National Institutes of Health, Veterans' Administration, and other agencies. Mar. 20-June 26, 1963.**

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# INTERAGENCY COORDINATION IN DRUG RESEARCH AND REGULATION

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## HEARINGS

BEFORE THE

SUBCOMMITTEE ON REORGANIZATION AND  
INTERNATIONAL ORGANIZATIONS

OF THE

COMMITTEE ON  
GOVERNMENT OPERATIONS  
UNITED STATES SENATE

EIGHTY-EIGHTH CONGRESS

FIRST SESSION

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### AGENCY COORDINATION STUDY

(PURSUANT TO S. RES. 27, 88TH CONG.)

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REVIEW OF COOPERATION ON DRUG POLICIES AMONG  
FOOD AND DRUG ADMINISTRATION, NATIONAL INSTITUTES  
OF HEALTH, VETERANS' ADMINISTRATION, AND  
OTHER AGENCIES

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MARCH 20, 1963

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PART 3

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THE BUREAU OF MEDICINE IN THE FOOD AND DRUG  
ADMINISTRATION

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Printed for the use of the  
Committee on Government Operations

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# INTERAGENCY COORDINATION IN DRUG RESEARCH AND REGULATION

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#### THE BUREAU OF MEDICINE IN THE FOOD AND DRUG ADMINISTRATION

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Printed for the use of the  
Committee on Government Operations

U.S. GOVERNMENT PRINTING OFFICE  
WASHINGTON : 1963

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The subcommittee met, pursuant to notice, at 10:45 a.m., in room 1318, New Senate Office Building, Senate, Hubert H. Humphrey (chairman) presiding.

Present: Senators Hubert H. Humphrey, Frank Grunow, Claiborne Pell, and Jacob K. Javits.

Also present: John O. Sencer, M.D., medical officer, New Drug Division, Bureau of Medicine, Food and Drug Administration, Department of Health, Education, and Welfare; Charles D. May, M.D., professor of pediatrics, School of Medicine, New York University; Julius N. Kahn, staff director, Subcommittee on Reorganization and International Organizations, Committee on Government Operations; and Jerome Senosky, legislative assistant to Senator Hubert H. Humphrey.

Senator Humphrey (presiding). We will open the hearing. Some of the other Senators will be here in a very short time. We want that we have a conflict with the full Committee on Government Operations since it is now conducting hearings on the proposal for a Joint Committee on the Budget. Those around here for hearings is all personnel, and so we have to go ahead.

**STATEMENT OF SENATOR HUMPHREY**

I want to open this hearing by a statement relating to the purposes of this subcommittee and the procedure that will be followed. I do this before we call upon the witnesses.

This subcommittee is now conducting its hearings on "Interagency Coordination in Drug Research and Regulation." This is an area that is within the jurisdiction of the subcommittee of the Committee on Government Operations.

The hearing is held pursuant to Senate Resolution 27, 86th Congress, 1st session, approved March 31, 1959. This resolution, like preceding resolutions, relating to the Senate's August 1958 authority did not limit in a variety to such procedure of "interagency coordination." The full committee's authority is being delegated to this subcommittee.





### PART 3

## INTERAGENCY COORDINATION IN DRUG RESEARCH AND REGULATION

(Pursuant to S. Res. 27, 88th Cong.)

WEDNESDAY, MARCH 20, 1963

U.S. SENATE,

SUBCOMMITTEE ON REORGANIZATION AND INTERNATIONAL  
ORGANIZATIONS OF THE COMMITTEE ON GOVERNMENT OPERATIONS,  
*Washington, D.C.*

The subcommittee met, pursuant to notice, at 10:05 a.m., in room 1318, New Senate Office Building, Senator Hubert H. Humphrey (chairman) presiding.

Present: Senators Hubert H. Humphrey, Ernest Gruening, Claiborne Pell, and Jacob K. Javits.

Also present: John O. Nestor, M.D., medical officer, New Drug Division, Bureau of Medicine, Food and Drug Administration, Department of Health, Education, and Welfare; Charles D. May, M.D., professor of pediatrics, School of Medicine, New York University; Julius N. Cahn, staff director, Subcommittee on Reorganization and International Organizations, Committee on Government Operations; and Jerome Sonosky, legislative assistant to Senator Ribicoff.

Senator HUMPHREY (presiding). We will open the hearing.

Some of the other Senators will be here in a very short time. We regret that we have a conflict with the full Committee on Government Operations since it is now conducting hearings on the proposal for a Joint Committee on the Budget. Time around here for hearings is at premium, and so we have to go ahead.

#### AUTHORITY FOR SUBCOMMITTEE'S HEARINGS

I want to open this hearing by a statement relating to the purposes of this subcommittee and the procedure that will be followed. I do this before we call upon the witnesses.

This subcommittee is now resuming its hearings on "Interagency Coordination in Drug Research and Regulation." This is an area that is within the jurisdiction of this subcommittee of the Committee on Government Operations.

The hearing is held pursuant to Senate Resolution 27, 88th Congress, 1st session, approved March 14, 1963. This resolution, like preceding resolutions, dating as far back as August 1958, authorizes the committee, as a whole, to study problems of "interagency coordination." The full committee's authority has been delegated to this subcommittee.



## OUR GOAL: AGENCY EXCELLENCE

Our purpose today is to help assure the highest possible standards of administrative and scientific excellence within the Food and Drug Administration and related agencies.

## MUCH PROGRESS TO DATE

Much has happened since this subcommittee's hearings of August 1962.

A new law has been enacted. I believe I played somewhat of a role in accomplishing that objective. New regulations have been promulgated.

An important report by the Second Citizens Advisory Committee on the Food and Drug Administration was released in October 1962. That report contained many suggestions on FDA organization, personnel, and procedure. It contained critical comments as to FDA's past and present record.

We will want to explore with the Department of Health, Education, and Welfare its reactions to that report. We will want to learn what the Department and the agency plan to do to overcome administrative and scientific shortcomings, as described:

(a) In that report, and

(b) In an extensive series of other reports over the past 8 years since the First Citizens Advisory Committee in 1955.<sup>1</sup>

This subcommittee will want to determine what new legislation, if any, may be necessary to achieve the goals of advancing the public health. I should add that any new legislation proposed by this subcommittee will be primarily in the form of administrative structure.

Our interest is in the facts. There is nothing "personal," and never has been anything "personal," in our search for the facts. In fact, I made it quite clear that, on a personal basis, I have sincere friendship and a high regard for the officials of FDA.

We will, however, "let the chips fall where they may"—these were my instructions again to the staff only as late as yesterday—but our concern is with issues, principles, guidelines, standards.

## WITNESSES MAY HAVE TO RETURN OR RESPOND IN WRITING

Our plan is as follows: We will meet today to hear two witnesses. We will meet tomorrow to hear five witnesses in roundtable fashion.

We will try to cover as many of the principal points as possible during these 2 days.

If necessary, we will ask that a witness come back at a later time. I believe this may be necessary with our first witness; or it may be necessary to ask questions and answers in writing, which is the procedure that this subcommittee often uses.

<sup>1</sup> (NOTE BY SENATOR HUMPHREY.—This and succeeding footnotes have been added to the record in order to assist the reader in locating pertinent references and documentation.)

For the reports referred to above, see the first 20 exhibits in "Interagency Coordination in Drug Research and Regulation," pt. 2. These exhibits contain excerpts of reports, speeches, memorandums, and other materials during the period 1955-63, appraising drug activities in the Food and Drug Administration.



## OUR EMPHASIS IS CONSTRUCTIVE

All of the witnesses are appearing at our invitation. Each has been asked to orient comments to the constructive needs of serving the public interest and strengthening the Food and Drug Administration and its related agencies.

## TODAY'S TWO WITNESSES

Our first witness is a medical officer of the New Drug Division, Bureau of Medicine, Food and Drug Administration, Dr. John Nestor.

I am going to have placed in the record at this point a biographical sketch outlining the career and the life of Dr. John O. Nestor of the Food and Drug Administration.

(The biographical sketch referred to follows:)

## EXHIBIT 121

## BIOGRAPHICAL SUMMARY ON JOHN O. NESTOR, M.D.

There follows a biographical summary of Dr. John Nestor.

## CURRICULUM VITAE, JOHN O. NESTOR, M.D., F.A.A.P

Born November 7, 1912, Franklin, N.J.

Attended local grammar and high schools.

Rutgers University, 1930-31.

Surveyor for The New Jersey Zinc Company 1931-33.

Seton Hall College 1933-36.

Georgetown University School of Medicine 1936-40.

St. Michael's Hospital, Newark, N.J.—Rotating Internship 1940-41 including 3 months at the Margaret Hague Maternity Hospital, Jersey City, N.J.

U.S. Army and Air Corps—Flight Surgeon 1941-45. Included nearly 2 years overseas in combat in several campaigns.

Children's Hospital, Washington, D.C. Resident 1945-46; Chief Resident 1946-47.

Private practice of Pediatrics and Pediatric Cardiology in Washington, D.C., metropolitan area, 1947-51.

Diplomate of the Board of Pediatrics 1949.

Fellow of Academy of Pediatrics 1950.

National Heart Institute Trainee in Cardiology: (a) The New York Hospital (Cornell) June 1951 to November 1951 (6 months) under Dr. H. J. Stewart, (b) Johns Hopkins Hospital November 1951 to July 1952 (7 months), Dr. Helen B. Taussig.

Private practice of Pediatric Cardiology, 1952 and 1953.

National Heart Institute Research Grant at Children's Hospital, Washington, D.C., 1954, 1955, 1956.

Private practice of Pediatric Cardiology 1957 to present, including the following activities past and present:

1. Consultant in Pediatric Cardiology at National Heart Institute (formerly).

2. Consultant in Pediatric Cardiology at Children's Convalescent Hospital (presently).

3. Consultant in Pediatric Cardiology, Children's Center, Department of Public Welfare, District of Columbia (formerly).

4. Consultant in Pediatric Cardiology, Arlington Hospital, Va. (presently).

Chief of Pediatric Cardiology Clinic at Alexandria Community Health Center (presently).

Assistant Professor of Pediatrics, Georgetown University School of Medicine (presently).

Associate Professor of Pediatrics, Howard University School of Medicine (formerly).



*Publications**Clinical Proceedings of Children's Hospital, Washington, D.C.*

- "Auricular Flutter in a Newborn Infant," Nov. 1952;
- "Arteriosclerotic Heart Disease in Children," Jan. 1953;
- "The Electrocardiogram in Electrolyte Imbalance," Apr. 1953;
- "Cardiac Failure in Children," May 1953;
- "The Electrocardiogram in Acute Cloromelonephritis," July 1953;
- "Endocardial Fibroelastosis," Jan. 1954;
- "Patent Ductus Arteriosus," Dec. 1954;
- "Coarctation of the Aorta," Jan. 1955;
- "Prophylaxis of Rheumatic Fever," (co-author), Feb. 1955;
- "The Use of Hypothermia in Cardiac Surgery," (reprinted from Medical Annals of D.C.), May 1955.

*Medical Annals of the District of Columbia*

- "Endocardial Fibroelastosis," Dec. 1954;
- "The Use of Hypothermia in Cardiac Surgery, Including a Report of Four Patients," Mar. 1955;
- "The Historical Development of Cardiovascular Surgery," May 1955;
- "Withering and Digitalis," Nov. 1955;
- "Heart Disease in Children," Nov. 1956;
- "Innocent (Functional) Murmur in Childhood," Dec. 1957.

*G.P.*

- "The Use of Hypothermia in Cardiac Surgery," Mar. 1955.

*Circulation*

- "Anomalous Origin of the Left Coronary Artery," (co-author), June 1958.

Senator HUMPHREY. Our second witness will be Dr. Charles May, Department of Pediatrics, New York University.

Our first witness will be presenting what might be termed an "inside" view of problems within the Bureau of Medicine of the Food and Drug Administration.

Our second witness will be presenting, entirely independently, what might be termed an "outsider's" view of the problems of the Bureau of Medicine.

The fact that they appear on the same day merely indicates that we have tried to make available as many judgments as possible to the subcommittee.

The two respective viewpoints are separate and independent, however.

## UNAVOIDABLE ABSENCE OF SENATOR RIBICOFF

I should like to state that my colleague, Senator Ribicoff, the former Secretary of Health, Education, and Welfare, had hoped to be with us this morning, but he has had to return to Hartford to attend a funeral of a friend this morning. His staff assistant, Mr. Sonosky, is here, however.

We are proud to have the benefit of service on the subcommittee of the great former Secretary of Health, Education, and Welfare, who played so vital a role in enactment of the Kefauver-Harris law of 1962. That is the law strengthening the Food, Drug, and Cosmetic Act of 1938.

We have welcomed to the subcommittee, too, Senator Pell and Senator Pearson. We are happy, moreover, to have all the past members of the subcommittee continue with us. I am particularly delighted to see Dr. Ernest Gruening here. I might digress to say he is the "Ben Franklin" of the United States—Senator, doctor, lawyer, journalist, architect, engineer, and statesman. I welcome you.



Senator GRUENING. Thank you.

Senator HUMPHREY. I want to compliment Secretary of Health, Education, and Welfare Anthony J. Celebrezze for numerous improvements which have taken place.

We realize that all improvements cannot be made overnight. FDA has been seriously handicapped for many years by acute shortages of men, money, manpower, material. The Congress has its responsibilities for this shortage and for this limitation. FDA, I think, has never been given the public support that is justified.

#### PLANS FOR FUTURE HEARINGS

We are looking forward to the testimony later on by Mr. Boisfeuillet Jones, Special Assistant to Secretary Celebrezze for Health and Medical Affairs, and to comments by Commissioner Larrick.

In addition, we will hear at that time from witnesses from the American Medical Association. We had hoped to hear from them during the present 2 days of hearings, but it will not be feasible to do so at this time in view of the limited period available.

#### BACKGROUND TO DR. NESTOR'S TESTIMONY

Now, as I said, we will hear first from Dr. John Nestor. Members of the subcommittee and the press have been given a copy of his biographical summary, as well as a copy of his prepared statement.

I should like to make it very clear for the record that Dr. Nestor did not ask to testify. He is an employee of the Food and Drug Administration. It was the chairman of this subcommittee that asked him to testify. He has, however, cooperated with us and with the deepest interest. For this I am grateful, Doctor.

He has met twice with our subcommittee staff at my instruction to the staff and has spoken both frankly and conscientiously, and I have seen the transcript of your discussions with the staff, Doctor.

It will be recalled that on October 3, 1962, I had been happy to praise Dr. Nestor, among other FDA personnel, in a statement which I placed in the Congressional Record.<sup>2</sup> Everything I said then I reiterate now as regards Dr. Nestor and those devoted members of the FDA Bureau of Medicine who have sought within the agency to secure improvements.

Dr. Nestor is a pediatrician. It is he who brought Dr. Frances Kelsey into contact with Dr. Helen Taussig after the latter's return from Germany and her study of the thalidomide tragedy. Subsequently, Dr. Kelsey graciously invited Dr. Nestor to be present with but a small handful of invited guests at the White House ceremony.<sup>3</sup> I recall that very inspiring experience. I was there with you.

That was when President Kennedy awarded Dr. Kelsey the Distinguished Federal Civilian Service Medal.

Dr. Nestor has, I believe, played a large part in several notable actions to protect the public health. We are grateful to you, Doctor, for your willingness to present a comprehensive account of your experi-

<sup>2</sup> Congressional Record, p. 20886.

<sup>3</sup> For comments on individuals invited to the medal award ceremony at the White House see Jonathan, Will, "The Feminine Conscience of FDA—Dr. Frances Oldham Kelsey," Saturday Review, Sept. 1, 1962, pp. 41-43.



ences. We believe that the record will bear out that your actions fulfill the highest tradition of a conscientious Federal employee. The Food and Drug Administration should be proud of you, and I trust that it will accept your testimony as testimony to improve the service and not in any way, injure it.

Your testimony is so important that I do not believe that we can complete our discussion today, but I believe that it will be helpful, at least, to get a brief review of what you have observed, and have your prepared statement on the record as of the present time.

Why do you not proceed, Doctor.

**STATEMENT OF JOHN O. NESTOR, M.D., MEDICAL OFFICER, NEW DRUG DIVISION, BUREAU OF MEDICINE, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE**

Dr. NESTOR. Thank you, Senator Humphrey.

Mr. Chairman and members of the subcommittee, since the time available is short and the work to be done is considerable, I will list, at the outset, a series of points in summary.

These points are based on nearly 2 years' experience in the Bureau of Medicine of the Food and Drug Administration. I will then briefly discuss a few of the points.

First, however, it should be stated that I am here at the invitation of the subcommittee and not on my own initiative. Criticism is offered, but it is intended solely in order to be constructive—in an effort to improve the situation in the FDA for the benefit of the American public.

At the subcommittee's request, I have furnished a biographical summary. It outlines my 23 years of professional experience. I might mention at the outset that I was the first Board-certified pediatrician FDA had ever employed to evaluate New Drug Applications.

As a physician, I have been distressed at the problems encountered in working in the Bureau of Medicine of FDA.<sup>4</sup>

The public is entitled to have the benefit of the knowledge possessed only by the members of the medical profession in the medical aspects

<sup>4</sup> Note by Senator Humphrey, on subcommittee's publication of exhibits relating to Dr. Nestor's views.

Many of the views submitted by Dr. Nestor above and on the pages which follow are the subject of comprehensive exhibits within this volume. These exhibits are in several forms: (a) Official documentation on particular topics mentioned by the witness and furnished to the subcommittee at our request; (b) background articles in the professional and trade press; and (c) a few rebuttals which were received by the subcommittee, disputing the witness' views.

It will be recalled that a footnote in pt. 1, p. 7, had mentioned the subcommittee's desire to develop a well-rounded record. Thus, the oral phase of the subcommittee's study, i.e., the testimony received at its hearings, is regarded as but one part of the subcommittee's overall factfinding effort. The reader's attention is also invited to my statement in the commencement of pt. 2, pp. 309-311. I had reiterated there that, in the interest of completeness, a wide variety of additional written materials would be drawn upon and published. It is hoped that the issuance of this comprehensive record will enable the Congress, the professions, and the Nation to be in the best possible position to judge facts for themselves, rather than to have to rely on any one individual's views. In effect, every effort has been made by the subcommittee to include within this and other volumes, whatever relevant materials might be compiled and rapidly made available in the interest of fairness and accuracy. Thus, the present hearing record was held open until numerous pertinent exhibits (including rejoinders to the witness' views) could be secured and published.

An additional "tool" in the form of a subject index to all of the testimony and exhibits in pt. 3 will appear in a subsequent volume. The index will refer to the contents of later volumes also. In advance of the appearance of the subject index, numerous cross-references are provided in the form of footnotes in the pages which follow. In addition, at the end of this volume, there is published an index of names of individuals and of drugs mentioned in part 3.



of new drugs. Men trained in other scientific disciplines are not qualified to make final medical decisions. Unfortunately, that is the way the Food and Drug Administration has been proceeding. Non-medical men, including laymen, have been making medical decisions.<sup>5</sup>

In the summary and in the statement which follows, I have limited my comments to those situations in which I have personally been involved or which have come to my professional attention. The examples which I will cite are representative of the broad problems indicated.

#### HANDICAPS CONFRONTING FDA

First, however, let me state that I realize the tremendous handicaps—lack of money, facilities, and personnel—under which FDA has labored in the past. I would like to pay tribute to those dedicated and devoted workers who have continued to put forth their greatest effort, despite these handicaps. In fact, my testimony today is designed to help them achieve their objective which is my objective and that is to protect the public health.

I will summarize my principal points, as follows:

#### SUMMARY

1. Certain new drugs should not have been permitted on the market since the data in the New Drug Application did not substantiate safety. (Examples are Entoquel,<sup>6</sup> MER/29,<sup>7</sup> Altafur.<sup>8</sup>

2. Procedures to suspend New Drug Applications and withdraw certain drugs from the market should have been instituted more promptly; needless delays should not have been tolerated; the New Drug Applications should have been complete in the beginning. (Examples are MER/29, Altafur.)

3. At least one food additive petition should have been denied sooner and action instituted to remove this food additive from the market in view of the lack of proof of safety and efficacy and the known potential for toxicity. (Example is menadione, or vitamin K<sub>3</sub>.<sup>9</sup>)

4. There have been new drugs on the market that never were subjected to the necessary preclearance procedure of a New Drug Application to demonstrate safety. Waivers should not have been given verbally and without circularizing the information to the physicians in the Bureau of Medicine. (Examples are Mylicon,<sup>10</sup> Paremycin,<sup>11</sup> Formulase, Coldaid.)

<sup>5</sup> With reference to the above comment on the process of medical decisionmaking in the Food and Drug Administration, see a subsequent article in the American Druggist by Robert Fischelis, Ph. D., formerly secretary of the American Pharmaceutical Association (exhibit 125, p. 813).

<sup>6</sup> On Entoquel, see exhibit 126, p. 814.

<sup>7</sup> On MER/29, see exhibits 127-129, pp. 816 ff.

<sup>8</sup> On Altafur, see exhibits 130 and 131, pp. 945 and 948.

<sup>9</sup> Eight days later, on Mar. 28, 1963, the Food and Drug Administration published in the Federal Register a decision, which had been in process for some time, denying a petition for the continued use of vitamin K<sub>3</sub> at specified dosage in prenatal supplements. For chronology on other views and actions on menadione, see exhibits 132 and 133, pp. 955 and 958.

<sup>10</sup> See exhibit 134, p. 968, for a letter from Stuart Division, Atlas Chemical Industries, on Mylicon.

<sup>11</sup> See exhibit 135, p. 970, for a letter from a law firm, representing Purdue Frederick Co., as regards Paremycin.

(The above and succeeding footnotes have been inserted as indicated by Senator Humphrey on p. 780, as reference aids, at the time of printing of this volume, i.e., subsequent to the hearing.)



5. At least one new drug was permitted to go on the market before the necessary chronic toxicity tests in animals were done or reported. This drug is an ingredient of many over-the-counter products in a smaller dose. (PRN)

6. Many New Drug Applications have been deficient in data necessary to establish the safety and efficacy of the drug.<sup>12</sup> Often the evidence submitted is in the form of anecdotal or testimonial letters and, where individual case histories are furnished, they are lacking in necessary laboratory and clinical details. Far too few of the studies are adequately controlled. (Examples are Entoquel, MER/29, Altafur.)

7. In the past, adequate recognition has not been accorded to the problems of drug therapy in infants and children.<sup>13</sup> There has been a failure to recognize that the metabolism and action of drugs often differ both qualitatively and quantitatively in this special group. The same can be said concerning drug therapy in pregnant women.

8. Certain New Drug Applications contain data suspected of being fraudulent.<sup>14</sup> At least one New Drug Application was approved when it was known to contain questionable data submitted by a medical investigator who was under suspicion. At the minimum, a central file should have been maintained on doubtful clinical investigators.

9. Despite requests from the physicians in the Bureau of Medicine, panels of consultants have not been made readily and easily available for advice and opinion necessary to avoid wrong decisions.<sup>15</sup> To a great extent, we rely on ad hoc panels to solve problems that might never have arisen had consultation been easily available in the beginning.

10. There should be a prompt and thorough reevaluation of such over-the-counter products as antibiotics, antihistamines, vitamins, sedatives, and cold preparations.<sup>16</sup> Special attention should be focused on those promoted for use in infants, children and pregnant women.

#### BACKGROUND OF MY SERVICE IN FDA

In my 23 years background in medicine, first in training and then in practice, which included 4½ years of active duty in the military service, I have learned that drugs are a two-edged sword—they can help a patient or they can do harm. Much depends on how they are used or abused. This was especially noticeable when I was actively engaged in a general pediatric practice. It became apparent that not only were some of the babies I was seeing ill because of disease but also because of medically induced drug toxicity which often caused or contributed to the illness. Too often, unfortunately, the practicing pediatrician was using dosages, concepts and rationales abstracted

<sup>12</sup> The issue of the quality of clinical studies, as reflected in New Drug Applications, is the subject of numerous exhibits within the present, earlier, and succeeding volumes (see, for example, in pt. 2, exhibits 63 and 111, pp. 373 and 688. These exhibits relate to the views of a biostatistician, formerly employed by the Food and Drug Administration, with respect to the caliber of medical evidence which he reviewed. See also exhibit 83, p. 528, for the view of a committee of the New York Academy of Medicine on the subject).

<sup>13</sup> Problems of drug therapy in infants and children are the subject of numerous exhibits in the present and succeeding volumes. In the present volume, see exhibit 136, p. 972.

<sup>14</sup> The issue of alleged fraudulent research is discussed in exhibits 122 and 137, pp. 792 and 975.

<sup>15</sup> For a chronology of views during the years 1955 to 1963 as regards consultation for the Food and Drug Administration, see exhibit 138, p. 978. See exhibit 139, p. 982, for views of the National Academy of Science on the subject.

<sup>16</sup> For a discussion of the use of antibiotics in over-the-counter products, see testimony of Hobart A. Reimann, M.D., in pt. 4, together with related exhibits.



from, and scaled down from, what had been learned during the test period on adults, and not based to any significant extent on observation and study of the effects on children.

In recent years, I have restricted my practice more and more to consultation work in pediatric cardiology and have found that this did not by any means use up my working day. Upon reading in a medical magazine of the problems of FDA in obtaining and retaining qualified physicians, I decided I would like to help out. An appointment was arranged with the Commissioner and the Chief of the Bureau of Medicine during which I offered my services. At this meeting, I pointed out the dilemma of the practicing physician and especially the pediatrician because of the uncertainty of drug information and the lack of medical rationale of many of the drugs. I indicated that it was my opinion that the work of the FDA was important in improving the situation.

Shortly thereafter, I was hired, presumably to furnish my medical knowledge in a frank and open way and to bring the best of current medical opinion to bear upon serious and important public health matters.

Unfortunately, although my frankness was acceptable before I was hired, after joining the organization I found that any medical opinion that raised issues that involved reappraisal of past decisions, past policies, or past commitments to the pharmaceutical industry would be challenged—not in a healthy scientific atmosphere, but, rather, with indifference, disapproval, or even hostility. This, unfortunately, was frequently the case with drugs for pediatric use.

#### NEED FOR STRICT EVALUATION OF PEDIATRIC DRUGS

I found that there had been a disregard of the long- and well-established medical principle that infants and children often react differently to disease and drugs than do adults, and yet the standard of drug testing for infants and children approved by the Administration involved accepting the most perfunctory and meager data to substantiate the safety and efficacy of dosage forms intended for use in this highly vulnerable group. Repeatedly, I found examples of new drugs that were worked out on adults during the tryout test period, and, after the application of the manufacturers to market the drug had been approved, a supplemental application was then submitted for a dosage form for infants and children. It was usually a drop or solution variation of the previously approved tablet drug (because of the difficulty infants and children have taking pills, as compared to a liquid).

These new forms were clearly labeled for pediatric use and the applications were approved for this purpose despite the fact that the testing had been carried out only in a few children and very few infants in many instances. There seemed to be a general disregard for the need to establish the safety of the use of the drug in the pediatric age group. What may be regarded as an "established" drug and, therefore, not a "new" drug in adult medicine is often a new type of treatment for infants and children, raising all the questions of rationale, risks, and usefulness.



## NEW DRUGS WITHOUT A NEW DRUG APPLICATION

I found that a number of drugs promoted for pediatric use had not gone through the preclearance for safety procedures in the form of having an approved and effective New Drug Application. I further found that the internal recordkeeping of these decisions in the Bureau of Medicine was such that it was often not formally recorded when a drug was called not a "new" drug<sup>17</sup> and that many of the commitments to drug houses in this important area had been by telephone. Frequently, I would receive inquiries about a drug from practicing physicians and would find it a difficult and time-consuming process to track down the necessary information concerning the drug in question.

I also discovered that when a physician in the Bureau of Medicine raised the issue of the status of a drug, he was frequently not informed of the subsequent administrative decision. If he felt it was a public health problem of concern, it was necessary to raise the question again and again. It took me over a year to determine the status of one such drug and there are others where my questions still have not been fully resolved concerning the status and final disposition.

A QUESTIONABLE INVESTIGATOR<sup>18</sup>

Shortly after coming to FDA, I was presented with the problem of reviewing the situation involving a new drug for pediatric uses which had been cleared only a few months earlier. A report had come in to the effect that a pediatrician had noted serious reactions in association with the use of this drug in infants. I traveled to Newark, N.J., to discuss the cases personally with the pediatrician involved. In reviewing the data in the New Drug Application that had been cleared by the FDA, I was impressed by the poor way in which this drug had been worked out and tested for use in infants and children. In fact, one of the company-sponsored investigators had submitted data and cases which seemed to be completely at variance with my pediatric experience. Since he had an office in a nearby suburb of Washington, it was comparatively easy for me to confirm my skepticism. I investigated his background of training and experience and consulted with knowledgeable people in his area.

It soon became apparent that it was probable the reports of his investigation were highly questionable since his training, experience, practice, and facilities were such as to preclude his assembling that many cases in a relatively short interval of time.

I reported my findings and suspicions to my supervisor in the Bureau of Medicine and to the officials of the Bureau of Enforcement and urged them to follow up my inquiry. The subsequent investigation established that many major firms had furnished him with drugs for experimentation and that his reports were a part of a number of New Drug Applications which were either pending or had already been passed in the form of an effective New Drug Application.

This case is now up for possible prosecution. The pediatric New Drug Application which led to all this is fortunately no danger or

<sup>17</sup> See exhibit 140, p. 987, for comments as to the problem of when is a drug a "new drug."

<sup>18</sup> For a newspaper discussion of this case, see exhibit 122, p. 792.



threat, as the drug is not being marketed. But, unfortunately, it did clear the FDA procedure and endangered infants until removed from the market. Even had the data of this one physician been reliable, there was little substantial data in the whole application to justify its being allowed on the market as a pediatric drug in the first place.

#### OTHER SUSPICIOUS INVESTIGATORS

It is also of interest that this suspected "researcher" is one of several that are under observation by the FDA, all having operated more or less undetected or unhampered. And this is despite the testimony of the Commissioner of FDA that this is not possible, as outlined on page 12120 of part 22 of the Senate Judiciary Subcommittee Hearings on Administered Prices in the Drug Industry in the following words:

However, it is extremely improbable that falsified or synthetic reports of biological studies would pass for long the scrutiny and review of competent scientists without arousing suspicion.<sup>19</sup>

#### THE CASE OF MER/29<sup>20</sup>

Another drug that obviously should not have been passed and allowed to go into general use is MER/29 (Triparanol). I am restricted from discussing all the details of this, since it is before a Federal grand jury for consideration at the present time.

I was given the responsibility of handling the New Drug Application for this drug after it has been cleared by FDA for general prescription use by the medical profession. At the time, side effects, untoward reactions, and complications were becoming a matter of increasing medical concern. I reviewed the data in the application, consulted with experts, and sought outside medical opinion. It was obvious that this drug had serious potential hazard, and it was also obvious that the application, as cleared by the FDA, did not even have a reasonable amount of data to determine whether it was useful; yet, it had been permitted to go on the market. During its testing period, there were only 160 patients recorded in the New Drug Application that had comparative blood cholesterol measurements prior to and after treatment had been instituted to demonstrate whether or not this drug could lower blood cholesterol. These were the only such paired-value cases in the entire New Drug Application for a drug intended for millions of people. Analyses of these cases showed that the ability to lower cholesterol was significantly less than the company was allowed to claim in their labeling and promotional literature. Furthermore, work done at the National Institutes of Health showed that even though there was some lowering in the cholesterol, this, in time, was replaced by another very closely related fatty substance. Review of the animal toxicity data revealed that there was severe toxicity in some of the animal testing and that the FDA Division of Pharmacology had gone on record calling attention to this.<sup>21</sup> Nevertheless, the Bureau of Medicine personnel in

<sup>19</sup> For other views by the Food and Drug Administration as to alleged "rigged research," see exhibit 137, p. 975.

<sup>20</sup> For an FDA chronology on actions and views in connection with MER/29, see pt. 2, exhibit 77, p. 501.

For additional chronological materials on the history of MER/29, see exhibits 127-129, p. 816ff.

<sup>21</sup> See exhibit 127, p. 840.



FDA allowed the application to pass and the drug went on the market for prescription use.

Among the serious side effects that came to light after the drug went into general use were severe skin rashes, hair loss, and damage to the eye in the form of cataracts. At first, only four cases of cataracts came to my attention; yet, I urged that the FDA make an effort to have the marketing of the drug stopped at least until the possibility that the drug was causing cataracts could be resolved. The Deputy Commissioner of FDA brought out clearly in his talk before the American Bar Association meeting on August 8, 1962, that the FDA physicians and FDA lawyers and administrators differed on the solidness of the grounds for FDA to effectively institute action against this drug.

The Deputy Commissioner has brought out how his view prevailed and the drug was permitted to remain on the market; the medical profession was alerted to look for eye damage; and then more evidence accumulated against the drug, so that the firm withdrew the drug in April 1962. Meanwhile, however, the public was exposed to the drug for an additional 5 months after we urged that immediate action be taken in November 1961.

The Deputy Commissioner in his talk to the American Bar Association admitted the drug should not have been passed in the following words:

In retrospect, it is apparent that the drug should not have gone on the market in the first place.<sup>22</sup>

Nevertheless, there has never been an appraisal within the FDA to determine what factors were operating and what policies and personnel were involved that permitted such an application to be approved. Clearly, neither safety nor usefulness had been demonstrated. In fact, in approving the drug, the FDA letter to the firm contained a statement disclaiming that this drug had been reviewed in the area of efficacy. This was despite the testimony FDA made before the Kefauver, Harris, and Humphrey committees that the danger of drugs are weighed against their usefulness in the new drug evaluation performed by FDA before allowing a new drug on the market.<sup>23</sup> Again on page 12120 of part 22 of the Senate Judiciary Subcommittee's Drug Hearings, the Commissioner of FDA is recorded as saying:

So the medical officer and the other scientists must evaluate safety in the light of the good inherent in the drug and balance it against the hazards. If the good in saving lives or alleviating suffering clearly outweighs the hazards, he will permit the NDA to become effective under labeling which clearly sets forth the hazards of the drug, the contraindicated conditions, the side effects, cautions to be observed, warnings, and directions for use which reduce to a minimum the danger inherent in the use of the drug.

About the time the Deputy Commissioner was citing MER/29 before the American Bar Association as a drug that should not have been passed, he was upholding the Department of Health, Education, and Welfare Hearing Examiner findings on Altafur, a drug which had been passed by FDA for the treatment of severe infections and which later proved to have serious side effects. The Hearing Examiner's find

<sup>22</sup> See address by John L. Harvey, Deputy Commissioner, pt. 2, exhibit 64, p. 380.

<sup>23</sup> For a trade-press writeup of the issue of evaluation of efficacy, prior to enactment of Public Law 87-781, the Drug Amendments of 1962, see exhibit 141, p. 992.



ings clearly demonstrated that the usefulness of this drug had never been established and this was a factor in the safe use of a drug intended for serious infections. Before the Kefauver committee, the Commissioner of FDA had voiced a similar interpretation that drugs for serious conditions must be efficacious if they are to be safely used without depriving the patient of proper and necessary treatment to overcome his infection.

Even though the Deputy Commissioner reviewed and upheld <sup>24</sup> the findings of the HEW Hearing Examiner <sup>25</sup> to suspend the New Drug Application for Altafur, there was never an internal appraisal to determine how this drug was allowed to clear the FDA new drug procedure or why the firm was allowed a 3-month period of grace for further marketing after the risks were known to the FDA.

#### THE CASE OF MENADIONE <sup>26</sup>

Another example of the problems confronting physicians within the FDA is illustrated by menadione (vitamin K<sub>3</sub>). This problem came up in connection with a Food Additive Petition for its inclusion in vitamin capsules for use in pregnancy. Menadione was already on the market in a variety of such preparations for both prescription and over-the-counter distribution. Under the food additives amendment, FDA must consider both safety and efficacy in evaluating a food additive. Both the Division of Nutrition and the Division of Pharmacology were of the opinion that the animal and nutritional data would support the manufacturers who submitted the petition. Unfortunately, it was overlooked that a pregnant woman carries a fetus and that babies are sometimes born with jaundice (hyperbilirubinemia). Thus, in turn, can result in kernicterus, brain damage, spasticity, and death. My colleagues and I recommended that the petition be denied on the basis that there were insufficient data to substantiate the safety or efficacy for this use. As is frequently the case in FDA, we were put in the difficult position of being told of the cost to the pharmaceutical firm. The then Director of the Division of Nutrition, who is now the Assistant Commissioner for Science, did not want to reverse his favorable opinion to allow the petition and cited the expense to the firm of either withdrawing the drug from the market or supporting adequate studies to demonstrate safety and efficacy.

It then became necessary for us to enlist the aid of physicians outside of FDA and I telephoned or wrote to several. The following quote is an illustration of their concern for safety and the doubt of the need or usefulness of menadione in pregnancy vitamin capsules. Dr. William A. Silverman, chairman of the Committee on Fetus and Newborn of the American Academy of Pediatrics, wrote on March 10, 1962:

DEAR DR. NESTOR: As you know, the Committee on Fetus and Newborn has been concerned with the matter of potentially harmful effects on the human fetus produced by drugs administered to the pregnant mother (Pediatrics 28: 278, 1961). In this connection, I was disturbed to hear that it has now been proposed that pregnant women receive daily supplements of menadione to prevent hemorrhagic disease in their offspring.

<sup>24</sup> See exhibit 130, p. 947.

<sup>25</sup> See exhibit 131, p. 948.

<sup>26</sup> For an FDA chronology of actions on the Food Additive Petition on Menadione, see exhibit 132, p. 955. For an additional chronology on the same subject, but prepared from diverse sources, see exhibit 133, p. 958.



I strongly urge that the Food and Drug Administration insist on the presentation of positive evidence that such supplementation is safe and efficacious for the newborn infant. Doxiades (*Lancet* 2: 1040, 1961) has recently suggested that even small doses of vitamin K analogues may intensify hemolysis and produce hyperbilirubinemia (that is, jaundice) in susceptible newborn subjects. In the present state of our knowledge and concern about brain damage associated with neonatal hyperbilirubinemia, I think the burden of proof of safety rests on those who have proposed menadione supplementation in pregnancy.

Yours truly,

WILLIAM A. SILVERMAN, M.D.

The wisdom of these words became apparent when a few months later a letter to the editor of *Pediatrics* from Dr. Raymond G. d'Adesky was printed in the June 1962 issue. The following are quotes:

Recently, I have come across two cases in which the ingestion by the mother of a multivitamin preparation containing 0.5 milligrams of vitamin K daily up to the morning of delivery was followed by the development of hyperbilirubinemia high enough in one case to necessitate two exchange transfusions.

And:

It now seems that the continuous intake of vitamin K-containing preparation by an expectant mother in the terminal phase of a pregnancy might create a similar risk of hyperbilirubinemia to the newborn, particularly so if premature.

Until this can definitely be settled, an attitude of caution should prevail. One of the first questions that comes to the mind concerns the necessity of routine prenatal administration of vitamin K-containing preparation in healthy mothers, in whom nature usually meets the requirements by fabricating enteric vitamin K. Only further investigations will give us our answer.

Since this writing, two additional cases have been observed.

The Federal Register of December 18, 1962, carried notice of a further extension of the Food Additive Petition in question to July 1, 1963. Supposedly, the report of the ad hoc committee of consultants advising that the petition be denied and dated December 4, 1962, arrived after the notice of extension had been forwarded to the Federal Register.

On December 13, 1962, I had an interview with Dr. Morris Feitel of the National Institutes of Health who informed me of a study he was submitting for publication which served to support the medical views of the Bureau of Medicine and the ad hoc committee of consultants that the petition be denied. This was reported to the Assistant Commissioner for Science.

#### MEDICAL DECISIONS BY NONMEDICAL OFFICIALS

What was the final outcome of all this? I have not been able to find out. Perhaps this subcommittee will do so. I can sum up, however, by stating that during this whole time it was necessary to present all these highly technical medical matters to lay administrators in FDA for a decision.

Fortunately, my physician colleagues on the outside supported and substantiated my views.

There are many more examples that could be cited of similar serious public health and medical problems that FDA should or could handle differently. Others have cited examples before, and others will cite them again, but they will merely be voices crying in the wilderness unless the numerous medical and public health suggestions made by the various surveys and appraisals of FDA during the past few years



are given full and earnest consideration. FDA has an important job to do for the public. The physicians who are constantly coming to FDA and then leaving might stay if they could effectively perform their important health mission. However, regardless of the caliber of physicians (who are working, I may say, under distressing conditions "in the pits," so to speak) at the Bureau of Medicine, we will continue to have such drugs as Entoquel, MER/29, Altafur, and menadione until there are good scientific medical and public health decisions at the highest level in the FDA.

I wish to thank the subcommittee for the privilege of serving the Senate of the United States.

Senator HUMPHREY. Dr. Nestor, we appreciate your testimony.

There are a few questions that we will want to ask you, because it is rather hard-hitting testimony, I might add, and obviously will be subject to some cross-examination.

#### ISSUE OF EFFICIENT SYSTEMS OF RECORDS

On page 5 of your prepared statement you refer to the internal recordkeeping of these decisions on New Drug Applications in the Bureau of Medicine. We had discovered here some months ago—in fact, a year or so ago—that the records in many of these Government agencies revealed medical and scientific information systems were inadequate. In fact, I have spent 6 or 7 years, now, trying to get the agencies of this Government to put in modern information equipment, advanced systems such as American business has.

I mean, we have computers; we have electronic devices. There are ways and means of being able to have adequate records and keeping adequate records with a cross-reference of the records so that the total amount of information on any one subject can be readily available.

My question to you is:

Have the records improved in the last month or two in the FDA Bureau of Medicine?

Dr. NESTOR. Well, I believe that they are going through a process now of transcribing many of these data from small cards in notes that were handwritten to a more formal arrangement. But I believe it has been a little bit early for us to benefit too much yet.

Senator HUMPHREY. I want to note for this record that I want the staff to check into what is being done in terms of a better information-and-record system in the Food and Drug Administration,<sup>27</sup> and as such system relates to other agencies of this Government, such as the U.S. Public Health Service, including National Institutes of Health,<sup>28</sup> the Veterans' Administration's Division of Medicine, the Department of Agriculture's Veterinary Medicine Department,<sup>29</sup> and others.

<sup>27</sup> For an official statement by the Food and Drug Administration with respect to its internal information systems as of April 1963, see exhibit 171, p. 1230. See also exhibit 142, p. 994, for an earlier analysis by the National Bureau of Standards on this subject.

<sup>28</sup> For a description of the systems for storing scientific information within each of the then seven National Institutes of Health, see subcommittee hearing, "Coordination of Activities of Federal Agencies in Biomedical Research," August 1960, appendix B, pp. 221 ff.

<sup>29</sup> The subject of information needs in veterinary medicine, with particular reference to the U.S. Department of Agriculture, was considered in the 11th of the subcommittee's series of 11 committee prints on problems of international health. (See "Veterinary Medical Science and Human Health," August 10, 1961, p. 227 ff.) The subject of overall scientific information for the Department of Agriculture as a whole was considered in a mimeographed review by Senator Humphrey, entitled "Memorandum on Agricultural Research Information," S 43-62.



It seems to me that this cross-referencing of information is very vital.

#### PHYSICIANS' NEED FOR IMPROVED INFORMATION SYSTEM

Would you, as a doctor and pediatrician, find it helpful if you had coordinated and collated information from, let us say, private hospitals and Government hospitals on the use of new drugs in the investigational period, as well as in the regular-use period, if all of this information could be readily available in some system?

Dr. NESTOR. I not only think it would be helpful. I think it is an absolute necessity with the situation at the present time. It is not a question whether it would be a desirable thing. It is a thing that we must have.

Senator HUMPHREY. Do we have it?

Dr. NESTOR. No; of course not.

Senator HUMPHREY. This is the problem?

Dr. NESTOR. Yes.

Senator HUMPHREY. We do not have it, and we cannot seem to get anybody very excited about it. I think the public ought to know that there just is not any system of really cross-reference or cross-checking as to the efficacy, the safety, or the therapeutic value of drugs, old or new.

Dr. NESTOR. Senator Humphrey, it has been my experience in private practice that the physicians of this country are pretty much excited and worried about the situation.

Senator HUMPHREY. We have a project that we are going to go into tomorrow; I believe it was called Mediphone, and we will discuss it tomorrow.

Now, one other question:

#### REAPPRAISING PAST FDA DECISIONS

You made a statement here on page 4, Doctor, that is rather abrupt and might appear to indicate some antagonism on your part. I would like just a little further explanation. You said:

Unfortunately, although my frankness was acceptable before I was hired, after joining the organization I found that any medical opinion that raised issues that involved reappraisal of past decisions, past policies, or past commitments to the pharmaceutical industry would be challenged—not in a healthy scientific atmosphere, but, rather, with indifference, disapproval, or even hostility. This, unfortunately, was frequently the case with drugs for pediatric use.

Would you like to document that a little bit, Doctor, because that is a pretty rough statement. You are talking, now, about your associates, and you are talking about your superiors in this organization.

Dr. NESTOR. I think I might elaborate this way:

What the problem seemed to be was that in making present decisions, it was sort of a sacrosanct situation that we were not to question decisions made in the past. This put us in an impossible position, because many times our decisions had to be based, not only on what was in the past, but also what we had available at the present. Many of our decisions were based on the sum of this information, the total information, and it really made it impossible unless we could question past decisions.



Senator HUMPHREY. When you say it was your observations or your opinions that were greeted with disapproval or indifference or even hostility—by whom?

Dr. NESTOR. Well, I would say that it is not a class or a group. I think we are dealing with individuals, and I would rather not mention names, because I cannot say it was physicians in the Bureau of Medicine or it was lay administrators. I think it was a combination of both, and I would rather not mention any individual names.

Senator HUMPHREY. How long have you been with FDA?

Dr. NESTOR. A little less than 2 years.

Senator HUMPHREY. A little less than 2 years?

Dr. NESTOR. Yes.

Senator HUMPHREY. Are you under civil service?

Dr. NESTOR. Yes, I am.

Senator HUMPHREY. Your previous medical practice, I have forgotten—

Dr. NESTOR. Pediatrics and pediatrics cardiology.

Senator HUMPHREY. Where?

Dr. NESTOR. In Arlington, Va., in the metropolitan area here.

Senator HUMPHREY. Have you had any difficulties getting along with personnel in general, Doctor?

Dr. NESTOR. Well, I do not think so. I think, as a matter of fact, that, in general, I have been very much liked. Others might disagree with me.

Senator HUMPHREY. Quite frankly, what I am simply saying is you are not just a "crank" about this subject matter.

Dr. NESTOR. I do not think so; no.

Senator HUMPHREY. I do not think so, either, but I just wanted to find out how you viewed yourself, because, when you make a statement as you have here, it might indicate to some people that you have sort of a "burn" on, as they say, you know.

Dr. NESTOR. Well, I have very positive opinions, Senator.

Senator HUMPHREY. Yes.

Dr. NESTOR. And I do not hesitate to express them. Fortunately, that is one of the things I fought for.

Senator HUMPHREY. We will come around a little more on those opinions.

#### SUSPECTED MEDICAL INVESTIGATOR

You spoke of a medical investigator who is now subject to possible court action, prosecution?

Dr. NESTOR. Correct.

Senator HUMPHREY. The case of Dr. Z, as was revealed here in the Sunday Star of Washington on December 9, 1962, "A Look at Drug Testing" by Miriam Ottenberg. Are you familiar with that article?<sup>30</sup>

Dr. NESTOR. I have read it; yes, sir.

Senator HUMPHREY. Is this the case to which you refer?

Dr. NESTOR. I presume it is.

Senator HUMPHREY. This is the one of the pediatric New Drug Applications.

<sup>30</sup> See exhibit 122, p. 792.



Dr. NESTOR. There were two articles by Miriam Ottenberg. Just to be certain I am not making an error, would you give me just a little more information so I can positively identify this one?

Senator HUMPHREY. All right.

This is a drug that related to infant diarrhea.

Dr. NESTOR. That is correct.

Senator HUMPHREY. And it is this particular drug that you found to be improperly investigated and that the investigator was incompetent or did not possess the qualifications and the experience and the background that could make for a competent investigation?

Dr. NESTOR. I think I used the word "questionable."

Senator HUMPHREY. "Questionable?"

Dr. NESTOR. Yes, but you express my opinions very accurately, Senator.

Senator HUMPHREY. Now, what do you mean by "questionable," Doctor?

Dr. NESTOR. Well, I feel that the data submitted, combined with his background and experience, and evaluated from my background and experience, were completely at variance with my whole past training and experience. I did not think it was possible that this could be so.

Senator HUMPHREY. Did anybody else agree with you—that is, a medical man?

Dr. NESTOR. Well, the Bureau of Medicine, I believe, has agreed with me. At least Food and Drug has, because they have taken it off the market.

Senator HUMPHREY. At the time that you had doubts as to the qualifications of this investigator for this new drug, did you find any of your colleagues in the Bureau of Medicine agreeing with your analysis and your evaluation?

Dr. NESTOR. Yes.

There was no disagreement with this drug. The Bureau of Medicine went with this problem to the Bureau of Enforcement and presented it to the Bureau of Enforcement. There was no disagreement here at all.

#### EXHIBIT 122

#### ARTICLE IN WASHINGTON SUNDAY STAR ON ALLEGED FRAUD COMMITTED BY A CLINICAL INVESTIGATOR

The following article appeared in the September 9, 1962, issue of the Sunday Star of Washington, D.C. The article by Miriam Ottenberg was entitled, "The Case of Dr. Z—A Look at Drug Testing".

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[From the Sunday Star, Washington, D.C., Sept. 9, 1962]

#### THE CASE OF DOCTOR Z

#### A LOOK AT DRUG TESTING

(By Miriam Ottenberg, Star Staff Writer)

The Food and Drug Administration is making an intensive investigation of a Washington area doctor suspected of providing drug firms with false reports on his testing of new drugs.

FDA inspectors have visited nearly a dozen drug firms across the country for which the doctor did clinical investigations.



In one case, as one of a handful of doctors who tested a drug to check diarrhea in children, he reported on more cases than any of the other investigators. His tests, as he later reported in a paper submitted to a medical journal, were, first, to define a pattern of response to various doses and, secondly, to evaluate the dosage which appeared to be most useful in children.

After two children were hospitalized and FDA began investigating, the company—although not conceding that the drug was dangerous for children—withdrew it from the market.

In another case, the work of this doctor—Doctor Z—was used in a New Drug Application to allow a prescription drug to be sold over the counter. He reported that the drug was "safe and remarkably effective" for treatment of nausea and vomiting from a variety of causes. The company, however, withdrew its application for over-the-counter sales.

Doctor Z's tests were included in the New Drug Application for a drug to treat diseases of the artery in older people, which required specialized knowledge. The firm has since said that his report was suspect because the results were too good. The firm, however, must submit all its reports of tests to FDA. That drug is on the market.

By his own account, Doctor Z filled out the clinical investigator's form to test Kevadon, the thalidomide that Dr. Frances O. Kelsey kept off the market, but he said he didn't follow through on the test and never received the drug.

He said he did receive Contergan, another thalidomide preparation, but only used it on children.

In a period of less than 2 years, Doctor Z:

Was given drugs to test for more than a dozen firms.

Wrote at least eight articles praising the drugs without reservation. Of these at least 4 were published in medical journals.

Represented that, during the 2 years, he tested more than 800 patients on the various drugs—ranging from 100 elderly people for one test to 185 children suffering from diarrhea for another test.

On the basis of his reported tests, his patients included infants, pregnant women, victims of pneumonia, postoperative cases and sufferers from a variety of ailments, from bronchitis to stomach disorders.

At the height of his testing, Doctor Z was 31 years old, had had a 1-year internship but no residency training and had been practicing medicine for 3 to 4 years.

Interest in his case already has been expressed on Capitol Hill. Senator Humphrey, Democrat, of Minnesota, whose Senate Government Operations subcommittee on reorganization recently held hearings on drug research, has asked Welfare Secretary Anthony J. Celebrezze to make available HEW's file on the case.

#### FDA ASSENTS TO PLEA

In reply to the Humphrey request, FDA said the information would be made available subject to protection of the public interest. The subcommittee interpreted this to mean that the case will be sent to the Justice Department for possible prosecution.

If the Justice Department decides on prosecution, it could be a landmark case. This would be the first time that a clinical investigator has ever been prosecuted for providing false information, which a drug firm later supplied to FDA.

Legislation to strengthen FDA's hand in dealing with investigation of drugs before they go on the market has passed the Senate and awaits House action. The Senate bill would provide a firm legal basis for the kind of regulations recently proposed by Secretary Celebrezze to strengthen controls over clinical testing of new drugs.

Drug firms questioned by The Star emphasized that most of the doctors and scientists testing drugs before they go on the market are dedicated men whose work has contributed largely to making American drugs the safest in the world.

#### EXPRESS HOPE ON RULES

Medical research men in the firms expressed the hope that regulations ultimately issued on drug testing will not discourage the dedicated scientists.

Several drug spokesmen, however, candidly admitted that the Washington area doctor was not the only one at the general practitioner level whose work had been questioned by the firms themselves.



And the Pharmaceutical Manufacturers Association has already informed Secretary Celebrezze that its member firms generally are in sympathy with the objectives of the proposed regulations on clinical testing. An association spokesman, however, left the door open to question the details of the regulations on reporting requirements after clinical studies get underway on new drugs.

The case of Doctor Z illustrates why both the legislators closest to the current drug investigations and FDA want to make sure that the men whose tests are vital in clearing the way for a drug to go on the market are qualified by training and experience to do the job.

#### DENIED BY DOCTOR

Doctor Z denied to The Star that he ever made up his findings. He denied that he ever reported the results of tests that he didn't actually make. He also denied that he ever approached the drug firms to let him make tests for them. And he denied that he was aware FDA was interested in his reports to the drug firms.

Outside of confirming that an investigation was in progress—a fact known to at least a dozen drug companies—FDA declined comment on Doctor Z. From other sources, including the drug firms which have cooperated with FDA in the investigation, The Star pieced together this story of Doctor Z:

A drug for diarrhea in children had been approved by the FDA and was on the market when the manufacturer was informed that two infants in New Jersey had suffered violent reactions to the drug.

The company proposed to change its labeling to warn that the drug should not be given to children who were dehydrated, but an FDA doctor insisted that the drug itself had caused the dehydration.

#### FDA URGES WARNING

FDA proposed that the warning should caution against giving the drug to infants but the company insisted the drug was not dangerous. Finally, FDA made several seizures of the drug on the ground that letters to doctors promoted the drug for more severe pediatric disorders than were approved in the labeling cleared by FDA.

While an FDA doctor was checking on the drug, he went back to study the clinical studies included in the New Drug Application. There, he found the report of Doctor Z.

From the number of children with diarrhea reported in Doctor Z's study, the FDA doctor got the impression he was looking at the work of an extremely busy pediatrician. He found instead the young general practitioner.

He found that Doctor Z had submitted a paper on the diarrhea drug to a medical journal which had accepted but not yet printed it. In the paper, Doctor Z reported only minor side effects in 4 percent of the children who received the drug and concluded that the drug was effective and generally well tolerated at a dosage which the FDA doctor was convinced would have caused serious effects in infants.

#### ALL TESTS INVESTIGATED

On the basis of the FDA doctor's findings, an FDA investigation of all Doctor Z's tests was launched.

Going over some of the same ground, The Star questioned some of the drug firms for whom Doctor Z had worked. In every case checked, Doctor Z had been given a grant to finance the test. This varied from \$10 to \$15 per patient tested and averaged out to approximately \$2,000 a test.

All the drug firms checked were asked the same basic questions: How did Doctor Z come to test for you? What checks did you make on his qualifications? What kind of reports did he make? Here are some of their answers:

*The controversial diarrhea drug.*—Doctor Z indicated he was interested in working on the drug. Two of the firm's physicians visited his office and checked on his facilities. In their opinion, he had sufficient practice to collect the data. After he began testing, the data he reported looked bona fide. It checked fairly closely with that of another clinical tester, whose work had been supplied to him.

*A drug for diseases of the artery.*—Doctor Z wrote the drug firm to say he wanted to do clinical testing and had the facilities for it. A regional research manager for the firm went over his patient list. The firm was later convinced that this check on Doctor Z was inadequate. The research manager who did the checking was supposed to ask the local medical society about Doctor Z but did



not and somehow got the impression that Doctor Z had served a residency, which he hadn't. Doctor Z was approved by the firm and turned in findings which the firm considered "too good." The drug had been used previously in Europe, so Doctor Z had an idea what the drug should do. He wrote a paper for a medical journal but it was rejected.

*An antibiotic.*—Doctor Z approached the drug firm and offered to study a drug already on the market. If any check was made on him, the drug firm didn't mention it. The firm spokesman said when doctors ask to study a drug already on the market the firm is inclined to agree to the study in order to pick up rare side effects that might not have shown up in the previous clinical investigation. Doctor Z wrote a paper on this drug which was published. He reported testing the drug on 73 office patients suffering from things from pneumonia to post-surgical infection. He reported excellent results in 67 cases, good results in 6 cases and no side effects.

#### A DRUG TO CONTROL COUGHING

*A drug to control nausea and vomiting.*—Doctor Z was suggested for testing by someone in the Washington area, possibly one of the firm's sales representatives. He was considered "an opinion molder" because of the articles he had published in medical journals.

The drug was already on the market and he was approved for testing of it to determine safety for over-the-counter use. Since it is difficult to find doctors willing to take the time for clinical investigation, the firm is inclined to go along with an investigator until some question turns up. The firm acknowledges there has been slipshod investigation of investigators. On this drug, Doctor Z published an article calling it "a safe and remarkably effective drug for the treatment of nausea and vomiting from a variety of causes." The only side effect he reported was a slight drowsiness in 14 of the 101 patients he tested. Nevertheless, the firm withdrew its application for over-the-counter distribution. Even before the FDA inspector visited the firm, Doctor Z had been put on the firm's "restricted list." The reason was not given.

Doctor Z wrote the firm a letter offering his services for certain types of tests. He was called on twice by representatives of the firm's medical department. The drug did not involve a New Drug Application. His report sounded so good that the firm got a little suspicious. Overall, 81 percent of those tested, he reported, had excellent results from the drug and the remaining patients had good results. His findings were published in a medical journal. Although he asked to make more investigations for the company, it was decided not to use him again.

The drug firms were not the only ones who got leery about his enthusiastic reports. One of the journals rejected an article on an antihistamine for allergies after it was shown to a specialist in the field.

The specialist said that different persons with different conditions vary tremendously in their response to antihistamines. According to Doctor Z, the specialist said, "all the conditions respond equally well and this I doubt."

#### EARLY TEST CITED

The drug firms checked by The Star emphasized that in the early stages of an investigation, only well-known clinical investigators—usually connected with a teaching hospital—do the testing. They said they used general practitioners later to see how the drug would work when it went into doctors' offices and was under less carefully controlled circumstances.

All of them denied what was charged at the time FDA reported that thalidomide had been sent to more than 1,200 doctors—that the clinical testing on this scale was to create a demand for the product before FDA cleared it for safety.

Doctor Z told The Star he was approached by the drug firms to do their testing. He estimated that he did at least five or six a year but added that he was not doing it any more because he had changed offices and lacked the room to store all the drug samples. Besides, he said, he was now too busy.

#### DOCTOR CITES ARTICLES

He said he sees between 30 and 40 patients a day and his usual test encompasses about 100 patients. He used the same figure of 30 to 40 patients a day several years ago in his first correspondence with drug companies.

He estimated that eight of his articles have been published over the past 2 years and indicated that was why the drug firms had contacted him.



A good deal of the work, he said, was handled by his nurse who took blood pressures, measured weights and made notes on the case history forms he submitted to the drug companies.

He said each test took 3 or 4 months to complete, sometimes longer. Sometimes, he said, he requested a grant to finance the work.

Most of the drugs he tested, he said, worked out pretty well and he added: "If the results are favorable, it helps the sales."

He was asked if he had the records for all the tests he had made, particularly since he had said he often identified the patients used in the test only by initials or numbers. He said he kept the records and the code to identify the patients for at least 6 months after reporting his findings to the drug company and then he destroyed the records. He said he destroyed the records because "it invades the doctor-patient relationship."

#### COMMENTS ON ALLEGATIONS

When he was asked to comment on allegations that he had reported testing more patients than he had actually seen, he replied:

"That's definitely not true. Every patient I put down I saw myself or my nurse treated—not treated—took blood pressure."

The Senate-passed legislation clears the way for regulations. This would make sure that the reports on clinical testing enable the Food and Drug Administration to make an accurate evaluation of the safety and effectiveness of drugs before they go on the market.

The legislation also specifically refers to "adequate and well-controlled investigations \* \* \* by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved \* \* \*."

#### PURPOSE OF RULES TOLD

The proposed regulations on which all shades of opinion have been invited were drawn, said Secretary Celebrezze, "with the purpose clearly in mind of imposing no unneeded restrictions on the conduct of investigational research, while providing assurance that the public will be fully protected against risks that may attend the development of new drugs."

Under the proposed regulations, each clinical investigator would have to supply the drug firm with a full statement of his education and experience; a description of the hospital, institutional and laboratory facilities available to him and an outline of the plan of testing he intends to follow. He would have to maintain complete records of his disposition of the drug and case histories of the patients to whom he administered the drug and furnish adequate reports to the drug firm as soon as he finishes his trials. These records would be open to FDA inspection on request.

As Doctor Z himself noted, the regulations would require clinical investigators to keep records that he is not keeping now.

#### DELAY IN ACTION ON ALTAFUR

Senator HUMPHREY. I want to move along here on your statement, and I have some other questions to ask you.

Why these periods of grace? Why are these granted? For example, on page 10, this relates to Altafur; Altafur was a drug to combat infection, is that correct?

Dr. NESTOR. Serious infection, yes.

Senator HUMPHREY. Serious infection. You state as follows:

Even though the Deputy Commissioner reviewed and upheld the findings of the HEW hearing examiner to suspend the New Drug Application for Altafur, there was never an internal appraisal to determine how this drug was allowed to clear the FDA new drug procedure or why the firm was allowed a 3-month period of grace for further marketing after the risks were known to the FDA.

Why do you have to have a period of grace after you find that a drug has a high degree of risk?

Dr. NESTOR. I think that is the question I am asking.



Senator HUMPHREY. Well, what do they say? You work for the FDA. I am going to get the Commissioner up here a little later and talk to him about these things.

Dr. NESTOR. Why is there a—

Senator HUMPHREY. Why do you think they gave 3 months?

Dr. NESTOR. I simply do not have an answer to it, Senator.

Senator HUMPHREY. Do you think it was a hazard to public health?

Dr. NESTOR. Oh, yes; I certainly do. This is only one example. I have quoted others. For instance, on MER/29 there was a 5-month wait.

Senator HUMPHREY. And even after there had been evidence that it was harmful and dangerous?

Dr. NESTOR. The Bureau of Medicine recommended in November 1961 that this drug come off the market, or that proceedings be instituted to take this drug off the market. It did not come off the market until April of 1962, and then the company withdrew it voluntarily. The FDA did not take it off, and that was a 5-month interval.<sup>31</sup>

Senator HUMPHREY. Is the FDA powerless to compel a drug to be taken off the market?

Dr. NESTOR. Of course, their power has changed since October 10, 1962.

Senator HUMPHREY. What about before October 10, 1962?

Dr. NESTOR. I believe you are in an area where I, as a physician, am not competent to make a statement. I just think it is out of my range of competence.

Senator HUMPHREY. All right.

I surely would not want to press you on it. We will get the administrative personnel up here to talk about that. Somebody had better be prepared with a mighty good explanation as to why a drug, declared to be harmful and injurious by the Bureau of Medicine of the Food and Drug Administration, is left on the market, so that you can "clean the shelves," so-called.

Dr. NESTOR. May I make an addition, Senator?

Senator HUMPHREY. Yes.

Dr. NESTOR. With reference to Altafur.

You see, even after this 3-months delay, which was given to the company so that they could collect additional data, the burden of proof would still be on the FDA at that time to prove that this was "unsafe."

Senator HUMPHREY. FDA licenses these drugs, does it not?

Dr. NESTOR. No.

FDA makes effective a New Drug Application which permits the firm then to go ahead and put it on the market.

#### "NEW" DRUGS ON MARKET WITHOUT NEW DRUG APPLICATION

Senator HUMPHREY. In other words, you cannot put a new drug on the market for commercial use or for prescription use unless FDA approves the application for a new drug, is that not correct?

Dr. NESTOR. You are not supposed to, but, as I pointed out in my testimony, there are several drugs on the market without the benefit of a New Drug Application.

<sup>31</sup> See official FDA chronology on Altafur, pt. 2, exhibit 78, p. 504.



Senator HUMPHREY. Has that been remedied since October 1962?

Dr. NESTOR. No, sir. It is in existence right now.

Senator HUMPHREY. Could you name some of those new drugs?

Dr. NESTOR. I did name them in my testimony. I will refer to them.

Senator HUMPHREY. Those are the first ones that you named?

Dr. NESTOR. I want to be sure—

Senator HUMPHREY. You are saying those new drugs are on the market for prescription use, or you used the common phrase "commercial use," without having had a New Drug Application approved by FDA?

Dr. NESTOR. In my summary, point No. 4, if you will, on page 1-A, I said:

There have been new drugs on the market that never were subjected to the necessary preclearance procedure of a New Drug Application to demonstrate safety. Waivers should not have been given verbally and without circularizing the information to the physicians in the Bureau of Medicine. (Examples are Mylicon, Paremycin, Formulase, Coldaid.)

Senator HUMPHREY. Is this done by telephonic communication?

Dr. NESTOR. Well, frankly, I do not know how it is done, and this is the point we are trying to get across: That there ought to be better records kept so that the physicians in the Bureau of Medicine know what decisions are made.

I can mention two of these that are on the market at the present time, if you would like to know.

Senator HUMPHREY. Yes, please, I would like to hear them.

Dr. NESTOR. They are Paremycin and Coldaid,<sup>32</sup> and I am not sure of Formulase. It may or may not be on the market at the present time without a New Drug Application.

Senator HUMPHREY. You are saying that those drugs have been placed on the market without having been processed through the New Drug Application procedure, right?

Dr. NESTOR. I am saying, first of all, they are "new" drugs.

Senator HUMPHREY. Yes.

Dr. NESTOR. Secondly, they are on the market without the benefit of an effective New Drug Application, or they were.

Senator HUMPHREY. What do you mean by "effective"? Those words slip in there.

Dr. NESTOR. When a New Drug Application comes in, it has to be reviewed, and then, when it is approved, it is called "effective." It is made "effective." This is the terminology we used under the old law, and I think we are changing it now to the expression or the term "approved." But there is a great deal of difficulty about this change in terms right at the present time.

<sup>32</sup> On Mar. 21, 1963, 1 day after the hearing, the company withdrew its New Drug Application for Coldaid from the market "under protest."



Senator HUMPHREY. There are, undoubtedly, representatives of the Food and Drug Administration here in the room. I hope they will have a very good explanation that will satisfy the public interest in this matter as to why these so-called new drugs have been put on the market without having met the standards of a New Drug Application or the approval of a New Drug Application.

#### PEDIATRIC USE OF MYLICON

Dr. Nestor, there is the case of Mylicon.

Dr. NESTOR. Yes, sir; that is the way to pronounce it.

Senator HUMPHREY. You pronounce these new drugs with such facility that I hesitate to even visit with you about them. That one word you had was a tongue twister.

Dr. NESTOR. I am envious that you are envious.

Senator HUMPHREY. Thank you, sir.

I would like to clarify the situation with regard to this Mylicon. As I understand it, you pointed out that the drug Mylicon is intended for pediatric use and had never been cleared as a New Drug Application. You had succeeded in having the Bureau of Medicine identify this drug as definitely being a "new" drug within the definition of the law.

The drug was then withdrawn from the market as a pediatric drug.

However, I see that in the March 1, 1963, issue of the trade publication, Medical World News, this drug is still being advertised as if it were, in part, for children. The advertisement carries the definite implication that it can be used for children. The ad had the phrase, "Children under 12 years as directed by a physician."

It would appear, then, that the company is effectively circumventing the fact that you caused its elimination from the market as a pediatric drug. Thus, even though it had never had a New Drug Application as a pediatric drug, it can still be used in that way for all intents and purposes, is that the case?

Dr. NESTOR. That, I think, is the correct interpretation. Otherwise, they would have to state on there, "Not to be used in children under 12 years of age."

Senator HUMPHREY. And, yet, the ad does say specifically, "Children under 12 years of age as directed by a physician," and here is a copy of the ad right here, torn out from a magazine, the Medical World News.



Senator Gruening, you would be very interested in this. The dosage is prescribed as:

One 40-milligram Mylicon tablet to be chewed after each meal, at bedtime; in the form of liquid drops 0.6 of a cubic centimeter to be taken orally after each meal and at bedtime may be dropped directly on the tongue or mixed in water or other liquids. Children under 12 years as directed by a physician.

So here is a drug that did not meet the standards of a New Drug Application for pediatric use. The drug was ordered to be withdrawn from the market for pediatric use, and the company persists in advertising it for children under 12 years of age, is that a fact?

Dr. NESTOR. That is a fact, Senator.

Senator HUMPHREY. What about Paremycin?

Dr. NESTOR. I wonder if I may comment first?

Senator HUMPHREY. Let us get the other one out of the way, Doctor.

Dr. NESTOR. All right.

I just wanted to say that this was a surprise to me that the drug was still being promoted for children.

Senator HUMPHREY. I do not know whether they would call it "promotion," but they surely refer to children.

Dr. NESTOR. Yes.

Senator HUMPHREY. And they say, "Children under 12 years as directed by a physician." They obviously do not give dosage there. This is a very subtle circumvention, it seems to me.

Dr. NESTOR. I believe they give it higher up on the page in 0.6 of a cubic centimeter, if I am not mistaken.

#### EXHIBIT 123

##### A 1962 REFERENCE IN A MEDICAL MAGAZINE TO USE OF MYLICON IN INFANTS

The July 1962 issue of the magazine *Modern Drugs* contained in its section on "New Drugs" the following reference (p. 436).

##### *MYLICON (Rx) Antiflatulant, pediatric (Stuart)*

New Form: MYLICON—Drops—Bottles of 30 cubic centimeters. Each 0.6 cubic centimeter of pink liquid contains methylpolysiloxane, 40 milligrams. Relieves flatulence by dispersing and preventing formation of mucous-surrounded gas pockets in the gastrointestinal tract. For use in the relief of infant colic resulting from entrapment of air or gas. *Administration:* Orally. Infants—0.3 to 0.6 cubic centimeter with each feeding.

Another form has appeared in *Modern Drug Encyclopedia*, Eighth edition, 1961, page 785.



## EXHIBIT 124

1963 ADVERTISEMENT ON MYLICON IN MEDICAL WORLD NEWS

There follows the advertisement referred to by Dr. Nestor in his testimony. The advertisement appeared in Medical World News, March 1, 1963.

# MYLICON<sup>®</sup>

## *For Gastric Distress Due to Gas Entrapment*

**Indications:** For treatment of gastrointestinal distress resulting from entrapment of gas due to functional or organic conditions. Mylicon is a valuable adjunct in the treatment of many conditions in which the retention of gas is a problem.

Entrapment of gas and resultant distention is commonly encountered in the following conditions: air swallowing, spastic colitis, postoperative gas, postgastrectomy syndrome, duodenal and peptic ulcers, hiatus hernia, diverticulitis.

**Advantages:** Mylicon has a defoaming action that relieves flatulence by dispersing and preventing the formation of mucus-surrounded gas pockets in the gastrointestinal tract. Mylicon acts in the stomach and intestines to change the surface tension of gas bubbles enabling them to coalesce, thus the gas is freed and is eliminated more easily by belching or passing flatus. Mylicon is physiologically inert and nontoxic.

**Administration and Dosage:**  
Adults and children 12 years and older:

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### Composition:

*Mylicon Tablets contain 40 mg. of Simethicone (activated Methylpolysiloxane), a silicone, per tablet.*

*Mylicon Drops contain 40 mg. of Simethicone (activated Methylpolysiloxane), a silicone, per 0.6 cc.*

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Tablets—One 40 mg. Mylicon tablet to be chewed after each meal and at bedtime. Drops—0.6 cc. to be taken orally after each meal and at bedtime. May be dropped directly on the tongue or mixed in water or other liquids. Children under 12 years—As directed by a physician.

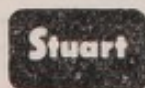
**Side Effects:** None.

**Contraindications:** None.


**Supplied:** Available in bottles of 100 and 500 white, scored, chewable tablets and dropper bottles of 30 cc. pink, pleasant tasting liquid at all pharmacies.

*Literature available on request.*

Quality Pharmaceuticals at Low Patient Cost



The Stuart Company PASADENA, CALIFORNIA

Division of ATLAS CHEMICAL INDUSTRIES, INC. 



Senator HUMPHREY. Yes, that is right, they do.

#### PEDIATRIC USE OF PAREMYCIN

Here is an ad that comes from the Medical Tribune relating to neomycin or Paremycin Elixir. It says it is a rapid, decisive control of common infectious and nonspecific diarrheas. This is the one to which you referred earlier?

Dr. NESTOR. Yes.

Senator HUMPHREY (reading):

Usual dosage, infants under 2 years of age, one-half to one teaspoonful; children over 2 years, one to two teaspoonsful; adults, one to two tablespoonsful.

Now, this drug is on the market. Was not this drug declared to be ineligible for pediatric use?

Dr. NESTOR. Yes, sir; it was declared to be a "new" drug, and it did not have an effective New Drug Application.

Senator HUMPHREY. When was that declared to be a new drug and did not have an effective New Drug Application?

Dr. NESTOR. I cannot give you an exact date, but I would estimate a year or more ago.

Senator HUMPHREY. This ad appeared November 30, 1962. What do you do with companies that do this sort of thing? Is there anything, Doctor, that can be done?

Dr. NESTOR. I think there is plenty that can be done, but I do not know what it is.

Senator HUMPHREY. Have you any suggestions?

Dr. NESTOR. Well, it would take a long time. I had better keep out of that field.

Senator HUMPHREY. Maybe we had better give it to the lawyers. I have some ideas as to what can be done about it. I consider it irresponsible, first of all, and the companies in question ought to be reexamining some of their ethics.

#### DECISIONMAKING ON MENADIONE

Doctor, with reference to menadione, I would like the record to be clear on this particular point.

Congress and the American people have assumed that the medical officers within the FDA are the ones responsible for coming to medical decisions. However, in the case of menadione, a food additive with important medical implications, you indicate that the judgment, not just of yourself, but of the Bureau of Medicine, was overruled by a judgment at a higher administrative level, is that a fact?

Dr. NESTOR. That is correct.

Senator HUMPHREY. In other words, the Bureau of Medicine was overruled by an administrative officer?

Dr. NESTOR. Or a group of administrative officers.

Senator HUMPHREY. Or a group of administrative officers?

Dr. NESTOR. That is correct.

Senator HUMPHREY. Now, that judgment, the Bureau of Medicine's judgment, was based on the previous recommendations of two other bureaus, the Bureau of Pharmacology and the Bureau of Nutrition, is that right?



Dr. NESTOR. The Bureau of Medicine's recommendation was counter.

Senator HUMPHREY. Oh, was counter?

Dr. NESTOR. To their recommendation.

Senator HUMPHREY. That is right, was counter to the Bureau of Pharmacology and the Bureau of Nutrition. I believe that the members of those bureaus are, by and large, Ph.D.'s, is that correct?

Dr. NESTOR. There are a variety of backgrounds, yes, sir. Many are Ph. D.'s.

Senator HUMPHREY. Are there any doctors?

Dr. NESTOR. I do not believe so, but I am not sure.

There were no doctors, as far as I knew, in making this decision.

Senator HUMPHREY. You mean in terms of the Bureau of Pharmacology and the Bureau of Nutrition?

Dr. NESTOR. That is correct.

Senator HUMPHREY. Let me just say, for the record, that the Bureau of Nutrition in the FDA is a very good bureau. Who is the head of that bureau?

Dr. NESTOR. It was Dr. Kline, who is now the Assistant Commissioner for Science.

Senator HUMPHREY. He is a very competent nutritionist. I just want the record to be clear that, while these scientific decisions may differ, it does not necessarily mean that people who head these particular bureaus have any lack of competence or experience or professional qualifications, because some of these people are very well respected in their areas, or in their disciplines.

#### ISSUE OF MEDICAL JUDGMENT ON MEDICAL DECISIONS

The point is: How is it that a person who is not an M.D., in another FDA bureau, is permitted to refute the medical judgment of the medical officers in the Bureau of Medicine concerning a medical matter?

I think this is the issue.

Dr. NESTOR. I think this is the issue, too. I think it is simply because there are not people of broad, medical ability and training at the highest echelon in FDA to make this decision. I think it takes medical knowledge and background to decide when a medical problem has become an imminent hazard to the public health.

Senator HUMPHREY. In this instance on menadione, this is vitamin K?

Dr. NESTOR. Vitamin K<sub>3</sub>.

Senator HUMPHREY. It may well have been that this was looked upon, not as a pharmaceutical item as such, but primarily a food additive?

Dr. NESTOR. Yes, sir.

Senator HUMPHREY. And, therefore, the medical aspects were downgraded, as compared to the nutritional aspects?

Dr. NESTOR. That is correct. They did not see the medical problem.

#### VOLUNTARY WITHDRAWAL OF VITAMIN K<sub>3</sub> BY ONE COMPANY

Senator HUMPHREY. In reference to that particular drug, I have a couple of samples here that have the vitamin K additive, showing



that a drug company, in some instances, voluntarily withdraws a drug from the market—not only in some instances, but in many instances?

Dr. NESTOR. Yes.

Senator HUMPHREY. Packet No. 1 is a sample packet of Parke, Davis' supplement for pregnant mothers, Parke, Davis being one of the great pharmaceutical firms of our country. To the credit of this company, it promptly withdrew its product, known as Natabec capsules, that had the vitamin K additive as soon as reports were substantiated as to a possible harmful effect from vitamin K.

You checked with physicians of an Army hospital, did you not, on this subject, Doctor?

Dr. NESTOR. I checked with Dr. Morris Feitel, who is now at NIH, but at the time he did his study in 1960, he was at Valley Forge Army Hospital.

Senator HUMPHREY. And you found there that vitamin K was implicated as possibly causing jaundice in mothers and could cause brain damage to babies?

Dr. NESTOR. This was the conclusion of his article, which he was just then submitting for publication, and he informed me at the time that, on the basis of the information, Parke, Davis had decided to take the vitamin K<sub>3</sub> out of the prenatal supplement which you have seen.

Senator HUMPHREY. This was the first time that any really solid information had been developed in terms of a rather extensive study as to the injurious effect of vitamin K, right?

Dr. NESTOR. Yes, sir.

The point in reviewing this whole problem is that there is this great lack of data of either safety or efficacy to support the petition in the first place. We have a tremendous need for data in this field. It just has not been done.

Senator HUMPHREY. I want to commend Parke, Davis. Sometimes some of the companies feel that we are only out to give them a "rough time"; that is not the case at all. They responded promptly, is that correct?

Dr. NESTOR. Well, I do not know any of the details. I was simply told this by Dr. Feitel.

Senator HUMPHREY. However, I ought to note that there are other companies that continue to use vitamin K despite these findings that you gave to us, is that correct?

Dr. NESTOR. It is my understanding that there are, perhaps, 50 to 70 products, many of them over the counter, where a pregnant woman can go in and buy them in a drugstore, and take them, you see.

Senator HUMPHREY. Now, this is the drug that you discussed in your testimony to quite a degree. Where was this, what part of your testimony was that, Doctor?

Dr. NESTOR. On menadione, it is near the end, I believe.

Senator HUMPHREY. Bottom of page 10, yes.

Dr. NESTOR. Yes.

Senator HUMPHREY. It is the drug that is still on the market, is that correct, with the additive?

Dr. NESTOR. I do not know the exact status at the present time. The last I knew was the fact that it had been extended, again, up to possibly July 1, 1963. It appeared in the Federal Register, I believe, on December 18, if I am not in error.



Senator HUMPHREY. That is what you said.

Dr. NESTOR. And has been extended.

Now, just the conditions of this extension, whether this was changed in the last few days or not, I do not know.

Senator HUMPHREY. At least on December 18 it was extended, is that correct?

Dr. NESTOR. That is correct.

Senator HUMPHREY. Doctor, did I understand you to say that there was a panel of specialists that had concurred with the findings of—

Dr. NESTOR. The Bureau of Medicine.

Senator HUMPHREY. The Bureau of Medicine?

Dr. NESTOR. That is correct.

Senator HUMPHREY. There was also the letter to the editor of Pediatrics by Raymond G. d'Adesky on this item?

Dr. NESTOR. To this effect, yes. It was only one small bit of information.

Senator HUMPHREY. Dr. William A. Silverman, chairman of the Committee on Fetus and Newborn of the American Academy of Pediatrics, has, likewise, expressed concern?

Dr. NESTOR. That is correct.

Senator HUMPHREY. Who expresses the feeling that it is all right?

Who says that this is a great thing for pregnant mothers, pregnant women, to take?

Dr. NESTOR. Well, I do not know of anybody who has, frankly. There are simply no data to establish that giving vitamin K<sub>3</sub> daily throughout pregnancy to a pregnant woman has any significant—well, I should not say “significant”—effect, but it just has not been proved what this will do. It simply has not been studied that much.

Senator HUMPHREY. Has it been proved that it may have some injurious effect?

Dr. NESTOR. Well, it has been proved in this way, and this is why the question arose about possible toxicity.

You see, we learned a few years ago that water-soluble analogues of menadione, which are not as powerful, as potent, as menadione, itself, when given to newborn infants after birth to prevent so-called hemorrhagic disease of the newborn, these water-soluble analogues in very small amounts, as little as 5 milligrams, have produced hyperbilirubinemia in newborn, which as you know, is a very serious condition.

It requires exchange transfusions for treatment, and, may, despite exchange transfusions, end in kernicterus, death, spasticity, mental deficiency, and so on.

Senator HUMPHREY. Doctor, the only point I am raising is that, according to your testimony, unless facts have been changed in the last two or three—or in the last week or so, there is an extension of the use of this food additive, is that correct?

Dr. NESTOR. That is correct.

Senator HUMPHREY. You know of no change in regulation that would withdraw vitamin K<sub>3</sub> from the market?

Dr. NESTOR. No, I just do not know the status at the present time.

Senator HUMPHREY. But at least on December 18, 1962, it was extended until July 1?



Dr. NESTOR. I believe there were certain conditions in this extension where it could be taken off sooner, but I do not know enough about the administration of this to clarify it.

Senator HUMPHREY. Now, what is your view, as a professional man, Doctor, when there is a rising degree of evidence that a particular drug or food additive may have an injurious or harmful effect?

Do you believe that the use of that drug should be promptly stopped; that is, in terms of prescription of commercial basis, or do you believe that it should be permitted to continue under certain limitations of reporting and investigative procedure?

Dr. NESTOR. You have asked me for a strictly medical opinion—

Senator HUMPHREY. That is correct.

Dr. NESTOR (continuing). And not an opinion on administration or law? If I make that statement first and base it strictly on medicine, then my opinion is that, as soon as there is reasonable evidence of danger, of lack of safety that is not warranted by the usefulness of the drug, the drug should be removed from the market until the situation is clarified.

Now, I must qualify that, because I believe the law gives the Commissioner the right to do this where "imminent hazard" exists.

Senator HUMPHREY. Yes.

Dr. NESTOR. And I am not qualified to get into a discussion of the exact meaning of the law.

But, from a strictly medical point of view, where there is reasonable doubt, I think we ought to stop until we solve the problem.

Senator HUMPHREY. All right, Doctor, we wanted your point of view.

Now, I am going to turn this over to Senator Gruening for a moment. I have one question in reference to the clinical evidence that is gathered on these new drugs.

The American people have been given to understand, even prior to the new law on October 10 of this past year, and I now quote from the testimony:

No New Drug Application was approved unless there was substantial clinical evidence at least as to safety.

We ought to make it clear here that there is a difference between "safety" and "efficacy," and even "therapeutic value." In your sixth point you state: "The evidence is often insufficient."

In addition, in your comments to the staff you refer to the clinical evidence in at least the instance of one drug as "ludicrous." I have your confidential statement, you know, Doctor.

Dr. NESTOR. Yes.

Senator HUMPHREY. You cited the fact that the entire amount of evidence supporting a particular drug boiled down to histories involving a mere 30 patients.

#### REVIEW OF BOTH SAFETY AND EFFICACY FOR CURRENT SUPPLEMENTS TO DRUGS

Now, my question is this: There are thousands of drugs now on the market. Many of these drugs will be filing supplements for new dosage. These supplements will be coming into the FDA.



If the clinical evidence in the original New Drug Application turns out to have been flimsy or inadequate, as you believe has sometimes been the case, will not FDA have a particularly mountainous or big job, even under a 2-year "grandfather" clause, as to the drug's efficacy?

Dr. NESTOR. Yes.

It will be a tremendous job, and it poses a dilemma for the physician in the Bureau of Medicine and I do not know how it will be solved. If I may refer to this particular drug with the inadequate data, when I reviewed this new drug, this supplement for a drug that had been on the market for a number of years, 2 or 3 years, I had to review it entirely from the viewpoint of both "safety" and "efficacy" now under the new law. From this point of view, I found there was insufficient data to substantiate either safety or efficacy, and I had no choice under the policy but to recommend that, since the data was insufficient, the drug should be removed from the market.

Now, we are faced with a drug that is on the market, that is being used, and here is a doctor in the Bureau of Medicine who says this drug should come off the market.

I do not know the solution. I do not know what is going to happen to it.

Senator HUMPHREY. These are matters that we will have to discuss with the administrative personnel.

Dr. NESTOR. Yes.

Senator HUMPHREY. I am going to turn the questioning over to Senator Gruening. Senator Gruening is an M.D. in his own right, so, as I said, he is more than qualified for this interrogation.

Go ahead, Senator.

#### SERIOUS CONCERN OVER FDA SITUATION, AS DESCRIBED

Senator GRUENING. Dr. Nestor, first of all, I want to congratulate you on your testimony. I think you have rendered a very great public service in bringing these things to the attention of the committee, and, while I wish to withhold my judgment on your various allegations until I have heard the other side, I feel that, if any considerable part of your testimony or even a moderate fractional part is correct and substantiated, it constitutes a shocking indictment of the administration of the Food and Drug Administration. I hope that we will go into the matter very thoroughly and ascertain just how much of the very serious allegations that you make exists and why they have not been corrected.

I consider it very shocking that the reasoned opinions of competent professional people, physicians, be overruled by nonprofessional administrators.

While I know that there would be differences of opinion between physicians, that doctors disagree frequently, nevertheless, when there is any doubt, the benefit of the doubt, in my judgment, should be resolved in favor of the drug user and not in favor of the drug producer.

I think it is very important that we clarify the question of conflict of interest between the welfare of the ultimate user of a drug, the risk and danger to which he or she might be exposed, and the financial interest of the producer.



I think, if there is any question of conflict, the doubt should be resolved clearly in favor of the prospective user.

#### QUESTION OF IMPARTIALITY OF INVESTIGATORS

There are many things in your testimony that call for discussion. On page 5, at the bottom of the page, you speak of "company-sponsored investigators," and their findings seem to be at complete variance with your pediatric experience.

I wonder if you have discussed the question whether a company-sponsored investigator can be an objective investigator, whether he is not bound to be influenced by the financial interests of the firm which employs him. That would seem to be a reasonable assumption, but I would like to have your views on that.

Dr. NESTOR. I have been trying to find this statement about the—

Senator GRUENING. I am asking whether a company-sponsored investigator can be an objective, trustworthy, and impartial investigator. I do not indict any person's good intentions, but it is inevitable that in the case of a person hired, who is financially involved, it is going to be difficult for his judgment to be completely unbiased, and for him not to give the fullest benefit of the doubt to the financial interest of the company which employs him.<sup>33</sup>

Dr. NESTOR. Well, I agree that the ideal thing would be to have men doing these studies who are not subjected to this sort of prejudice or influence, let us say.

I would like to state, however, that I feel that by far the great majority of men doing this work are doing an honest job, a good job. Their reports may not reflect how well they have done the job, but I want to make plain right here that we are only questioning a very small number of people, and the great majority of physicians doing this work are good men.

Senator GRUENING. Well, I am glad you feel that way, and I would like to assume that this is the case. But, it seems to me that the occasional disaster should be guarded against at all costs.

We must assume that the majority of the people, both in the manufacture and in the bureau, are well-intentioned and high-minded. But it is the occasional tragedy and the occasional mistake that is the one thing we want to prevent.

There seem to be in the bureau, in the Food and Drug Administration, so many loose practices that it would seem that something should be done to tighten these up. Merely administratively, it seems to be extremely loose.

You say, for instance, on the upper part of page 5, you—

found that the internal recordkeeping of these decisions in the Bureau of Medicine was such that it was often not formally recorded when a drug was called not a new drug and that many of the commitments to drug houses in this important area had been by telephone.

Well, that is a matter which, it seems to me, could be easily corrected administratively. Some of your challenges here have to do with matters of administration that do not go deeply into the question of conflict of opinion and interest, which I think should be tightened up.

<sup>33</sup> For editorial comments by the New England Journal of Medicine on honoraria and other phases of certain commercial sponsorship of some drug study, see exhibit 143, p. 1018.



## NEED FOR CAUTION WHEN PHYSICIANS EXPRESS DOUBT AS TO SAFETY

That is not particularly your function. But I am interested in the fact that, somehow, when the opinion of medical men has been given and raises doubt in the safety of a given drug, there should immediately, in my judgment, be a red "warning" flag up on any such preparation. Such a drug should not be allowed to go out. It should be withheld, until it is completely proved to be satisfactory and without dangerous aspects.

Is it your opinion—I think your testimony so indicates—that the opinion of professional people is overruled by administrators?

Dr. NESTOR. Well, I so indicated with reference to the drugs I have in my testimony.

Senator GRUENING. I appreciate that the expert can be mistaken, but his conclusions should then be challenged by other experts. You may have the well-known situation of doctors in disagreement, and, when they are in disagreement, that is the place to stop the issuance of the product. But, if the overruling takes place by nonprofessional people, I think it is basically wrong, and we should do something to correct it.

I think that is all, Doctor. I think you have rendered a very great service here.

## CAREFUL REVIEW OF ALLEGATIONS PLANNED

I have no doubt that much that you say has validity, but I want to wait and hear the refutation, which I hope will be forthcoming, to see just how serious your indictment is. I think it constitutes, *prima facie*, a very serious indictment of the Food and Drug Administration.

Senator HUMPHREY. Thank you very much, Senator Gruening. As the Senator has indicated, of course, all of these allegations will be subject to cross-examination, Doctor, because you surely would not want the committee to prejudge the case. We will obviously ask other officers of the FDA for their comment.<sup>34</sup> But, again, I must join with the Senator in saying that, for what you have given us this morning, it is most distressing and disturbing, and I agree with the adjective and descriptive phrase used by Senator Gruening. It is shocking, what we are talking about, and that is the potential danger to the public health.

## INADEQUATE PROTECTION OF "TRADE SECRETS" IN FDA FILES

I would like to enter into the record now—Senator Gruening, I think you will be interested in this—a communication between myself, as chairman of the subcommittee, and Commissioner Larrick of the Food and Drug Administration. It relates to review by the staff to ascertain if certain records and files in the Food and Drug Administration are being properly cared for. You have heard the allegation made many times that foreign countries and pharmaceutical firms in foreign countries have been able to get formulas from the

<sup>34</sup> See exhibits 144 and 147, pp. 1018 and 1023, for comments by the Food and Drug Administration in the form of rebuttal to views expressed by Dr. Nestor. See exhibit 145, p. 1020, for Senator Humphrey's comments on the agency's initial reactions.



American pharmaceutical industry and, thereby, to enter into competition with our own pharmaceutical industry to the disadvantage of the American firms.

Now, our pharmaceutical industry spends a great deal of money developing new drugs, and, I think, this record ought to be clear that, while we have had instances where new drugs have been on the market prematurely or have not been withdrawn readily or soon enough, the American pharmaceutical industry has done an admirable job in developing new drugs that have been of great benefit to mankind.

And, needless to say, they would like to have some protection of their formulas and of their product.

Well, I discovered, much to my surprise, the files of the Food and Drug Administration that contained the formulas of many of these new drugs were unlocked, were not adequately protected. We have files of other departments of Government that really do not have much more in them than interoffice memos on inconsequential subjects that are labeled "confidential," and they have big, red seals on them, with a big steel bar going down through the handles. You cannot actually get in, sometimes, when you ought to, to even find a telephone number for an agency.

As the chairman of this subcommittee, I directed Mr. Cahn to inquire as to the matter I have just mentioned, and I have the following letter:

DEAR SENATOR HUMPHREY: On March 4, 1963, Mr. Julius Cahn asked that we look into the question of improving our security measures for protecting information relating to authentic samples of tablet and capsule drugs used in drug identification operations in the Division of Microbiology. The files relating to these authentic samples contain information subject to protection as trade secrets.

We have investigated the handling of such information in the Division of Microbiology and have found the Division maintains a card file in a cabinet in the identification laboratory containing information used in the day-to-day identification of the manufacturing sources of tablets and capsules. The information in this file includes data on the composition of the tablets and capsules as manufactured by various firms. *This file cabinet was not provided with a lock* and was kept in the laboratory subject to normal building security provisions. Other factory information and authentic drug samples are kept in locked cabinets.

The following steps have been taken to *improve the security measures* in the handling of these files in the Division of Microbiology:

1. The card file containing information on the composition of drug tablets and capsules is now kept in a locked cabinet when not in use.
2. The keys to all locked cabinets and files in the laboratory are kept under lock and key with access limited to the two or three professional scientists engaged in drug identification operations.
3. The Division of Microbiology is arranging to purchase a security filing cabinet provided with a combination lock for the storage of the information on the composition of drug tablets and capsules, for earliest possible delivery.

We appreciate your calling this matter to our attention.

Sincerely yours,

GEORGE P. LARRICK,  
Commissioner of Food and Drugs.



I just wanted the pharmaceutical industry to know that the committee was also trying to protect its economical and professional interests, as well as other matters.<sup>35</sup>

I believe we are going to let you go on your way now, Doctor. We will have to contact you later on to go over some other matters that we have to discuss with you.

Thank you very much, Dr. Nestor. We appreciate your testimony.

<sup>35</sup> The issue of the confidentiality of information in the New Drug Application file has been discussed on previous occasions within the Congress, the professional and the trade press. For an exhibit with respect to this subject as related to the withholding of information to committees of Congress, see exhibit 168, p. 1186. For other phases of the issue of trade secrets, see reply from the Food and Drug Administration to a letter of inquiry from an attorney, exhibit 127, p. 893. See also exhibit 169, p. 1192 for a newspaper writeup of the subject of confidentiality of NDA information.

Dr. Nestor wrote the following column on medical decisionmaking on new drugs. Dr. Nestor was formerly Secretary of the American Pharmaceutical Association.

#### What Should Be Done To Improve A Doctor's

(By Robert F. Nestor)

Written especially for readers of *American Druggist*

In drug therapy becoming so complex and so highly scientific that there must be careful supervision of all drug therapy as well as drug regulation, in order to safeguard the health and lives of the American people.

Following is a reading between the lines of the testimony at the hearings before the Senate Subcommittee on Government Operations, Reorganization, and International Organizations, held May 29 and 31, 1962, on the subject of drug regulation.

To What Purpose? The ultimate purpose of this subcommittee, headed by Senator Humphrey, is to learn to what extent the FDA, DHEW, and other related Federal agencies are cooperating in a interchange and collection of information pertinent to the development of their functions with respect to approval of new drugs and the withdrawal from the market of those drugs which have given evidence of being harmful to some respect.

Apparently, the determination of FDA policy with respect to when shall finally decide whether a New Drug Application is to be approved has not been entirely satisfactory.

Senator Humphrey, in his opening speech, referred to the recommendations of the most recent National Advisory Commission with respect to reorganization of the Bureau of Medicine in the Army and Navy Administration. He stated whether whether a medical product with regard to New Drug Application was being covered by the Administration and the answer that a medical product was covered by the FDA was in the affirmative.

Apparently, Senator Humphrey is not willing to give to the effort to be responsible for drug regulation on medical products upon which the drug industry is dependent.

As a result of all of the action up to the present time between medical and lay opinion with regard to what is and what is not a safe drug or what is and what is not proper in the advertising and labeling which accompanies drug products.

The conflict of opinion is by no means confined to the Food and Drug Administration. Anyone who has had experience in the drug industry knows that the conflict between views of the medical profession and the marketing and promotion departments is frequently just as pronounced as the conflict of opinion between medical and lay administration of the Food and Drug Administration.

The pharmaceutical industry is the production and distribution of drugs from the standpoint of manufacturers or distributors. The conventional physician's view is geared to the health and safety of patients with little regard for the businessman's problem, if he happens to be affiliated with the drug industry.

The Kefauver subcommittee hearings also revealed with testimony of physicians who have been employed in pharmaceutical manufacturing organizations and who left those organizations because they were overruled by lay administrators in matters involving the safety and effectiveness of drugs to be marketed.



I just want the pharmaceutical industry to know that the government is not going to let them get away with this. I want to see the government take action to protect the public health.

I want to see the government take action to protect the public health. I want to see the government take action to protect the public health.

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ADDITIONAL EXHIBITS ON ISSUES REFERRED TO BY DR. JOHN O.  
NESTOR

EXHIBIT 125

ARTICLE BY ROBERT P. FISCHELIS, PH. D., IN AMERICAN DRUGGIST ON MEDICAL  
EVALUATION OF NEW DRUGS

In the April 1, 1963, issue of the American Druggist, Robert P. Fischelis, Ph. D., wrote the following column on medical decisionmaking on new drugs. Dr. Fischelis was formerly Secretary of the American Pharmaceutical Association.

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WHO SHOULD DECIDE TO RELEASE A DRUG?

(By Robert P. Fischelis)

*Written especially for readers of American Druggist*

Is drug therapy becoming so complex and so highly scientific that there must be medical supervision of all drug development as well as drug regulation, in order to safeguard the health and lives of the American people?

Listening to and reading between the lines of the testimony at the hearings before the Senate Subcommittee on Government Operations, Reorganization, and International Organizations, on March 20 and 21, one could easily come to that conclusion.

*To What Extent?*—The ostensible purpose of this subcommittee, headed by Senator Humphrey, is to learn to what extent the FDA, USPHS, and other related Federal agencies are cooperating in an interchange and collection of information germane to the discharge of their functions with respect to approval of new drugs and the withdrawal from the market of those drugs which have given evidence of being harmful in some respects.

Apparently, the determination of FDA policy with respect to who shall finally decide whether a New Drug Application is to be approved has not been settled definitely.

Senator Humphrey, in his opening remarks, referred to the recommendations of the most recent Citizens Advisory Committee with respect to reorganization of the Bureau of Medicine in the Food and Drug Administration. He wanted to know whether some medical opinion with regard to New Drug Applications was being overruled by lay administrators, and the answer from a medical witness employed in the FDA was in the affirmative.

Apparently, Senator Humphrey is not willing to give up the effort to fix responsibility for final decisions on medical matters upon medical men.

*Age-Old Conflict.*—All of this points up the age-old conflict between medical and lay opinion with regard to what is and what is not a safe drug or what is and what is not truthful in the advertising and labeling which accompanies drug products.

This conflict of opinion is by no means confined to the Food and Drug Administration. Anyone who has had experience in the drug industry knows that the conflict between views of the medical personnel and the merchandising and promotion departments is frequently just as pronounced as the conflict of opinion between medical and lay administrators in the Food and Drug Administration.

The businessman views the production and distribution of drugs from the standpoint of stockholders or investors. The conscientious physician's view is geared to the health and safety of patients, with due regard for the businessman's problems, if he happens to be affiliated with the drug industry.

The Kefauver subcommittee hearings are replete with testimony of physicians who have been employed in pharmaceutical manufacturing organizations and who left these organizations because they were overruled by lay administrators in matters involving the safety and effectiveness of drugs to be marketed.



*Inevitable Showdown.*—One could not help but wonder as the testimony of physician witnesses before the subcommittee unfolded, how far off the inevitable showdown as to who shall control what drugs go on the market really is. The Kefauver-Harris amendments, and the new regulations thereunder, will eventually give the medical staff of the Food and Drug Administration a new lease on life.

When new drug regulatory control in FDA is finally placed in the hands of the medical profession, the medical staffs of drug manufacturers will also come into their own, because it will be necessary for industry to match medical control with equally competent medical service.

If, as the American Medical Association keeps pointing out, only physicians are competent to determine the drug and dosage form of choice for the treatment of patients, then the safety of the patient requires that the selection and production of drugs and regulation of their safety and effectiveness should also be a medical function.

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#### EXHIBIT 126

#### BACKGROUND MATERIALS WITH REGARD TO WITHDRAWAL OF ENTOQUEL FROM THE MARKET

On page 782 of his testimony and on succeeding pages, Dr. Nestor referred to the drug Entoquel. The following materials relate to the withdrawal of this drug from the market. As in the instance of other chronological series published within this volume, the initial information consists of the date of the item and the originating source; these are printed at the left of the column, preceding each document.

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#### (Drug Warning Letter)

August 1961.

WHITE LABORATORIES, INC.

DEAR DOCTOR: Entoquel (thihexinol methylbromide), a newer anticholinergic, was introduced earlier this year as an antidiarrheal primarily for pediatric use, after having undergone premarket clinical studies which demonstrated to our complete satisfaction the safety and efficacy of the drug when used in accordance with directions. This drug was marketed as Entoquel syrup and Entoquel with neomycin syrup.

Some months after their introduction, a pediatrician using these preparations brought to our attention the occurrence of severe atropine-like reactions in two infants (3½ and 6 months of age) who had severe diarrhea with complicating dehydration. The reactions were manifested by marked lethargy and mydriasis in one case and by lethargy, paralytic ileus and urinary retention in the other. In both cases the reactions rapidly subsided within 24 hours after discontinuance of the medication. Aside from these two episodes only infrequent and ordinarily mild parasympatholytic side effects, as set forth in the Entoquel labeling, have been observed.

In view of the foregoing reports, and because of a current divergence of medical opinion relating to the ability of infants and younger children to tolerate anticholinergics, *White Laboratories has decided to discontinue the marketing of Entoquel syrup and Entoquel with neomycin syrup.* Until such time as this difference of medical opinion is resolved, Entoquel syrup and Entoquel with neomycin syrup will not be available for your prescription.

White Laboratories has consistently followed a policy of marketing safe and effective pharmaceutical specialties. To preserve this record and to continue to merit the confidence of the medical profession, we have brought this matter to your attention.

Sincerely,

EDWARD R. NEARY, M.D.,  
Medical Director.



August 30, 1961.

JOHN O. NESTOR, M.D.

*(Internal Agency Document)*

To: Dr. Kessenich, Medical Director.

From: John O. Nestor, M.D.

Subject: Change in regulations to require inclusion of essential biographical data of Medical Investigators in each New Drug Application.

It is obvious in this highly technical and scientific world that the fact that a man is a physician with an M.D. degree does not automatically or necessarily make him a qualified medical investigator.

A large proportion of the clinical evidence submitted by pharmaceutical companies in support of New Drug Applications consist of medical testimonials from practitioners, general practitioners, or specialists. Much of this work is done on an outpatient basis without controls and frequently without laboratory studies. The following is an example of this.

Recently (February 1961) Entoquel Syrup and Entoquel with Neomycin Syrup (White Laboratories) were the subjects of effective New Drug Applications. The clinical investigations furnished in support of their use in diarrhea of infancy and childhood was entirely on the basis of observation made by practitioners, pediatricians, and general practitioners. Apparently, all the patients treated had only mild cases and were treated on an outpatient basis without any laboratory control.

The physician who submitted the largest number of cases and who, in effect, determined the dose of this drug for use in sick children was a young general practitioner who was graduated from Howard Medical School in 1955, and then had a 1-year rotating internship at D.C. General Hospital. This was not known when the NDA's became effective and only came to light when the Entoquel started producing dangerous side reactions. Subsequent investigation has uncovered the fact that this relatively inexperienced and untrained physician had, in the short period of a few months, written several articles on a variety of highly specialized subjects. Several of these have been published, at least one has been accepted for publication, two have been rejected in the present form, and no action has been taken on others. The worst part is that several of these articles have been included in NDA's which have been made effective.

The pharmaceutical companies who have utilized this man as a clinical investigator include Hoffman La Roche; Smith Kline and French; Squibb; Mead Johnson; Winthrop; White, Schering, and Irwin Neisler.

A statistical analysis of his papers indicates that, in general, his results are impossible. A superficial investigation indicates that the man has a very small practice, and that he is having both financial and personal difficulties. He is not held in high esteem by his own medical society.

The inescapable conclusion is that this man is a fraud and manufactured his papers without seeing the patients or without actually having the laboratory work done.

In view of this, I am suggesting that we require in our New Drug Applications a brief biography or curriculum vitae of each clinical investigator whose work is included. In this way, we can form some idea of the value of his contribution in establishing the safety and efficacy of the drug.

JOHN O. NESTOR, M.D.

January 18, 1962.

FDA BUREAU OF MEDICINE.

*(Internal Agency Document)*

UNITED STATES GOVERNMENT MEMORANDUM

To: Commissioner of Food and Drugs.

From: Bureau of Medicine.

Subject: NDA 12-620 Entoquel Syrup.

NDA 12-621 Entoquel with Neomycin Syrup.

BRIEFING MEMORANDUM

WHITE LABORATORIES, INC., Kenilworth, N.J. AF 13-620

Attached is an order to suspend the two above-named New Drug Applications. White Laboratories, Inc., Kenilworth, N.J., in a letter dated December 18, 1961,



have waived notice of hearing as provided for under section 505(e) of the act and requested that they be suspended.

The suspension order is based on our finding that clinical experience shows the drugs are unsafe and that the applications contain untrue statements of material fact. The firm does not agree with this finding.

The applications for these products became effective on February 9, 1961. The Entoquel syrup was recommended for the symptomatic treatment of diarrheal disorders and the Entoquel with neomycin syrup for the treatment of diarrheas due to neomycin-susceptible organisms and for symptomatic relief in diarrheal states prior to definitive diagnosis. Entoquel is the trade name for thihexinol methylbromide (alpha-dithienyl-(4 dimethylaminocyclohexyl)-carbinol-methylbromide).

The firm called to our attention in early April of 1961 serious atropine-like reactions in the use of Entoquel with neomycin in two infants to whom the drug was administered as recommended in its labeling. Our medical officers considered these reactions to present a grave hazard that may result in death or serious injury to infants and small children. In investigating these reactions, it was determined that White Laboratories was using promotional literature for these products that differed materially from that provided for in the New Drug Applications and also suggested materially different conditions for use from the conditions stated in the effective applications.

In conferences with the firm in May and July they expressed their unwillingness to delete from the labeling a recommendation for use of the product in children under 6 years of age. This revision we considered essential to assure safe labeling for the products.

In view of the serious nature of the adverse reaction and lack of cooperation by the firm and in order to remove the products from the market more promptly than could be anticipated under the new drug suspension procedure, it was agreed as a result of discussion with our General Counsel's office and the Bureau of Enforcement that multiple seizures would be undertaken. Five seizures were made (20908R et al.).

In a conference with representatives of the firm held in connection with the multiple seizures, they agreed to remove the products from the market and not to resume marketing until all deficiencies in the evidence with respect to the safety of these drugs had been corrected. The drugs were removed from the market in August 1961.

White Laboratories submitted a supplement to these applications on October 13, 1961, to provide for revised labeling and enclosing additional data directed toward establishing the safety of the product. This supplement was called incomplete. It was the opinion of the Division of New Drugs that this supplement was not an acceptable substitute for the course of action agreed to by the firm. This position was called to their attention in our letter of December 14, 1961, at which time we indicated that if we did not receive their request for suspension of the applications within 10 days that we would recommend to the Commissioner that a notice of hearing issue with a view to suspending the applications.

In their December 18 letter requesting suspension, the firm pointed out their reasons for making this request were based solely on business and trade considerations. They repeated their disagreement with our contention that the products are not safe or efficacious. It remains their opinion that the safety and efficacy of both products have been established without any question by adequate scientific evaluation.

WILLIAM H. KESSENICH, M.D.

#### EXHIBIT 127

##### MER/29—A CHRONOLOGICAL COMPILATION OF BROCHURES, DOCUMENTS, LETTERS, ARTICLES AND OTHER RECORDS ON THE HISTORY OF THE DRUG

The drug triparanol (brand name, MER/29) has been mentioned frequently in submissions to the Senate subcommittee, including in the testimony by Dr. John O. Nestor (pp. 781 and 785 ff).

In order to provide information in depth, there are offered herewith the present exhibit and the two exhibits which follow (a chronology of correspondence by a National Heart Institute Investigator and of actions in and by the Mayo Clinic).

In addition, background information is presented in the following memorandum by the subcommittee chairman.



MEMORANDUM FROM SENATOR HUBERT H. HUMPHREY ON BACKGROUND TO  
EXHIBITS ON MER/29

## NATURE OF THIS EXHIBIT

This exhibit consists of a chronological reprinting of pertinent materials in the history of triparanol (MER/29). These materials have been compiled by the staff under my direction. The materials are drawn from many sources. Some are relatively new; others old. Most have appeared in the open literature. A few have been confidential until this time. The materials include:

1. Articles in the professional and trade press, as well as in laymen's publications;
2. Internal agency documents—for example, memoranda from divisions of the Food and Drug Administration;
3. Subcommittee correspondence.

## FOUR PAST EXHIBITS

The present exhibit should be read in connection with earlier exhibits in the two preceding volumes. These include:

1. Part 1, exhibit 49, a letter from the National Institutes of Health with respect to its activities in connection with MER/29.
2. Part 2, exhibit 77, an official chronology on actions with respect to MER/29, furnished by the Food and Drug Administration;
3. Part 2, exhibit 97, an article on the history of the drug, written by Miriam Ottenberg of the Washington Star;
4. Part 2, exhibit 90, p. 566, a letter from the Veterans Administration with respect to its use of MER/29.

Additional references to MER/29 will be found in the index in part 2, p. 768.

## PURPOSE—A STUDY IN DEPTH FOR INCREASED UNDERSTANDING

The purpose in publishing these materials is to help further the understanding of the record with respect to this drug by the Congress, the medical profession and the public. Thereby, it is hoped, we may all benefit from past experience; increased insight may be provided as to the best course for future Federal and private policy on new drugs.

It will be noted that of all the drugs mentioned in the subcommittee's volumes, more records are set forth with respect to this drug than as regards any other—with but one exception—thalidomide.

Our reason for interest in thalidomide is, of course, obvious. It was the thalidomide tragedy which prompted the subcommittee to utilize its broad background in science information and focus on issues of drug information. Thalidomide was not released by the Food and Drug Administration; MER/29 was released, but had to be withdrawn because of toxic reactions and ineffectiveness for the intended purpose.

The case histories of thalidomide and of MER/29 can offer considerable guidance to those who are genuinely interested in improving communications, as well as what might be called "line" policies of drug research and regulation.

It should not be thought that the history of thalidomide or of MER/29 is "representative" of that of "all" or "many" or "most" new drugs; the fact is that there is a wide variation in new drugs and in their histories; these two particular cases are, in some respects, quite unique. Yet, the subcommittee has been advised by competent authorities, that each of these case histories does offer a striking degree of "leads" as to general practices and procedures which have been followed, for better or worse, for a number of years, and which do therefore bear review.

In sum, generalizations, based on the record with respect to these two drugs, should be drawn, if at all, with care. But the record should be studied in depth for "clues." If, in additional case histories, these "clues" recur, it will not be unreasonable to draw generalized conclusions.

One fact should be noted at this point—both of these drugs happen to have been produced by the same manufacturer. That fact in no way relates to our choice of the two drugs for a case history approach. The subcommittee does not presume to evaluate this particular company's record (or the record of any other company whose drugs were not released, or were released and later withdrawn). Irrespective of which company happens to be involved, our interest is in sound Federal policy and in protection of the public health.



## SIGNIFICANCE OF MER/29

A number of reasons justified selection of MER/29 for a case history approach.

1. *Importance of the drug's purpose.*—MER/29, intended as an anticholesterol agent, was designed to reduce the toll of a major U.S. disease, atherosclerosis. The conquest of this disease does represent one of the great medical challenges of our time. The hoped-for solution of this disease involves the health and well-being of countless Americans—both those now afflicted and those who may fall victim in the years to come. A vast medical assault is being made on this disease. The assault involves considerable expenditures of money, large numbers of eminent scientists and institutions, many drugs, and, in addition, many other experimental therapeutic concepts, including changes in nutrition.

We are thus dealing here, not with some simple "open and shut" case on a simple disease and a simple drug, but rather with mysteries, imponderables, and enigmas. These circumstances are not unusual. They emphasize the importance of humility and care in review. No one is all-wise; no one can be sure which scientific theory and therapy on atherosclerosis is really "the best."

2. *Federal interest.*—MER/29 offers a useful case history, because it involves the Federal Government in a great many respects and not merely in terms of the Food and Drug Administration. Federal money, i.e., taxpayers' funds, went into some of the early MER/29 research, as well as into research in later stages. Over the years, National Heart Institute studies on MER/29 were mentioned in testimony before House and Senate Appropriations Subcommittees. MER/29 was used, although to a very limited extent, in veterans' hospitals.

3. *Multiplicity of other sources involved.*—MER/29 also involved as wide a range of other organizations and sources as virtually any other drug in recent times. These sources include, in addition to the company and the Federal agencies, a variety of professional and voluntary organizations; e.g., (a) the American Medical Association; (b) the American Heart Association; (c) the American Diabetes Association.

In addition, as the compendium notes, many other sources were directly or indirectly involved—professional journals, the trade press, the general press, individual physicians and laymen, particularly some 300,000 patients.

In summary, MER/29 was an important drug, according to virtually all those who commented upon it at the time. It was a major new chemical entity. It was studied by many investigators, including researchers recognized by their peers as outstanding in their field. The record of what happened, how, when, and why does, therefore, bear close study. This is particularly so, because, in the judgment by the Food and Drug Administration, as stated by Deputy Commissioner John Harvey,<sup>1</sup> "in retrospect, it is apparent that the drug should not have gone on the market in the first place."

In the light of Mr. Harvey's statement, a great many questions should be answered as to how and why the drug was allowed "to go on the market in the first place?"

Was it because, as FDA contends, the law, prior to October 1962, did not permit a decision otherwise?

Or was it because of other deeper-seated reasons, including reasons which may perhaps persist, despite the new law?

The record may help to provide answers to these and other questions.

## LIMITATIONS OF THIS COMPILATION

The record in the subcommittee's volumes, it should be noted, is necessarily incomplete. Thus:

1. Although these exhibits are fairly extensive in comparison with other exhibits, they represent only a tiny fraction of a much vaster collection which would be necessary to do full justice to the complex history of this drug.

2. Our principal guide to obtaining exhibit materials was the chronology prepared by the Food and Drug Administration. Unfortunately, the FDA chronology is seriously incomplete, according to medical experts. The chronology omits certain key dates, comments, and actions. Inevitably, the subcommittee's compilation may not include certain documents which we might otherwise have sought, had we known of their existence.

<sup>1</sup> Pt. 2, exhibit 64, p. 383.



3. Even in that circumstance, the documents might not have been obtainable. The reason is that many FDA documents on MER/29 have been placed at the disposal of a Federal grand jury. Neither the subcommittee nor the staff have ever seen the MER/29 files as such. Moreover, witnesses whom we might otherwise have interviewed in depth have stated that they were not in a position to comment on numerous specific topics which might have been of interest to us. The subcommittee has, of course, sought to avoid any line of questioning or comment which might in any way delay or hamper the grand jury.

It may be noted, incidentally, that the subcommittee invited the Department of Justice to review the subcommittee's files for any items which we had obtained from a variety of sources and in which the Department might have interest. A representative of the Department did examine certain files, did indicate an interest in a few items and was, of course, promptly furnished with them.

4. Ideally, extensive hearings might have been held on MER/29 (subject to the limitation as to avoiding phases which might impair the grand jury's study). Unfortunately, the subcommittee did not have the time or resources for such specialized hearings. The subcommittee has had to spread its review across a multitude of major policy issues. (It should be noted that our entire drug study has been conducted with the aid of but a single professional employee, the staff director, assisted by a small number of editing, clerical, and stenographic employees. This small staff has had other duties as well in certain fields, other than drugs.)

#### TIMING—THE CRUCIAL DIMENSION

Notwithstanding these limitations, it is felt that the compilation on MER/29 does offer valuable information.

The materials are, of course, arranged in chronological order. Thus, this compendium should be read side by side with the other chronologies—the FDA's summary, the Washington Star article, the chronology of correspondence by and to Daniel Steinberg, M.D., of the National Heart Institute, and the Mayo Clinic chronology. The two last named items appear separately in exhibits 128 and 129 which follow.

In the various chronologies, the dates are all-important, for the essence of drug research and drug regulation is not only what is discovered or decided upon, but when. Timing is crucial.

In order to facilitate the reader's inquiry, a few key dates from the FDA chronology have been summarized in this exhibit.

#### THE CRUCIAL MONTH OF NOVEMBER 1961

Consider, for example, the crucial month of November 1961. This compilation and the other chronologies show the following juxtaposition of circumstances:

1. MER/29 had by then been available on prescription for 19 months. So swift is modern manufacturing and marketing that MER/29 had been prescribed for 300,000 patients.

2. According to FDA's Deputy Commissioner John Harvey:<sup>2</sup>

\* \* \* by mid-November 1961, FDA knew of 4 cases in which patients receiving MER/29 had developed cataracts. These cases, plus the animal evidence in file, raised substantial doubt as to the safety of the drug, and the Government scientists recommended that the application be suspended and the drug removed from the market.

\* \* \* at that time FDA did not have sufficient evidence to satisfy the requirements set forth in the law for suspension of the application. That is, the Government could not yet prove that the drug was unsafe in the dosage recommended in the labeling.

3. As stated by Miss Ottenberg:<sup>3</sup>

While the doctors were futilely struggling to get the drug off the market, a two-page company advertisement appeared in the weekly Journal of the American Medical Association on November 4, 1961. The ad said at one

<sup>2</sup> Ibid., p. 383.

<sup>3</sup> Ibid., p. 619.



point: "We know that, after use in more than 300,000 patients, few toxic or serious side effects have been reported, thus tending to reaffirm the safety margins previously established."

4. In the following issue of the Journal of the American Medical Association, November 11, 1961, the monograph of the Council on Drugs strongly questioned MER/29's efficacy. In addition, it mentioned that "present clinical studies have not been pursued long enough to insure that multifarious and serious alterations may not occur, especially on prolonged therapy. Triparanol is contraindicated in pregnancy."

It concluded:

It is the opinion of the council and its consultants that all patients receiving triparanol be maintained under the carefully controlled conditions of clinical investigations and that the only indications for its use at present should be severe atherosclerosis or hypercholesteremia unresponsive to other types of therapy such as diet, nicotinic acid, or polyunsaturated oils.

(See p. 894 for the AMA Council's evaluation and for dates of references to prior comment in the council's bulletins. It may be noted that 13 months earlier, in October 1960, as the chronology reveals, the independent Medical Letter on Drugs and Therapeutics published an evaluation which also cautioned as to acceptance of MER/29's claims.)

5. According to a trade publication (dated November 20, 1961, p. 895):

\* \* \* By questioning MER/29 efficacy, the AMA council confronted the Food and Drug Administration (FDA) with a regulatory decision on whether it should shift its attention away from the side effects and focus on the much-harder-to-handle efficacy matter. If FDA followed its traditional procedure, it has passed the buck to Merrell for the initial decision on whether the next step will be "voluntary" or "regulatory."

6. On November 17, 1961, the Chief of the Section on Metabolism of the National Heart Institute, in response to a request from the Deputy Medical Director, Bureau of Medicine, FDA, had written a detailed letter. This letter (p. 936) disputed many claims made in the MER/29 brochure. The letter was part of a commendable series of contacts between the FDA and NIH scientists, which had been originated by Dr. John Nestor, when he had taken charge of the drug case a few months earlier.

7. On November 19, 1961, conferences were held between FDA and the firm. According to the same trade publication (in its December 4th issue, p. 897):

The future of the drug was at stake in the Merrell-FDA conferences, and the regulatory discussions ran the full range—from no action to stiffer labeling and a "dear doctor" letter to "voluntary" removal from the market to forced removal by suspension of the New Drug Application (NDA) in a legal proceeding that could be contested.

8. Meanwhile, in Rochester, Minnesota, Mayo Clinic scientists were in touch with the company and with FDA relative to the cases of cataract and loss of hair, under treatment there.

9. In the Veterans' Administration, which was no doubt unaware of the discussion inside FDA, "the first neurologic patient received the drug, November 9, 1961," and "the first hypertensive patient" received the drug the same day. (See pt. 2, exhibit 90, p. 566.)

#### SCIENCE MUST EVALUATE DECISION-MAKING

The above sequence (a composite from the various chronologies) underlines the importance of this type of record, for through it (supplemented, it is hoped, by additional materials), interested sources may reconstruct, if only in part, the circumstances as they existed at the time. They will, thus, avoid a faulty practice against which we have always cautioned—the hazard of "20-20 hindsight." By contrast, by reason of this chronology, we see the facts as they appeared then and not with the "perfect vision" of discovery later on. We glimpse how little was actually known or how much, by whom and when. We learn who informed whom, or who tried to inform whom or who did not know whom to inform or who did not bother to inform others.

Most important, a basis is laid for fair, impartial evaluation.

Medical science, thus, can begin to determine who it was who made the right decisions as of a particular time, and whose decisions may have been questionable, who acted promptly, and who, it appears, may have been tardy, who was prudent and who, it appears, may have been rash. This type of evaluation is a crucial part of the tradition of medical science. Even a layman knows that medicine must learn from its record—its mistakes, as well as its achievements.



But let this point be clear: infallibility is impossible. No thinking person expects it of medicine, in drug therapy or in any other phase. The fact that some of the many professional decisions, which were made in good faith and on the basis of expert professional judgment, later proved to be wrong should not come as a surprise; nor should this fact be over-estimated or used as a basis for snap conclusions on any individual or institution. Every scientist must be encouraged to have the strength of his convictions; a policy of professional timidity "in order to avoid all error" would, in itself, be a policy of error. Some mistakes have been made in the past; some will be made in the future; the task is to minimize error to the extent it is avoidable. It will never be completely unavoidable. Risks must be taken on new drugs, or else there will never be new drugs.

One of the ways to minimize future error is to get the facts about the past, get the most competent people to interpret them, in a fair, scientific manner, and come to reasonable conclusions.

This the subcommittee has sought to do. It has not, however, attempted to interpret the highly technical scientific information within this compilation. It did ask competent scientists to help us do so. It was on the basis of such views, submitted late last year, that I offered the comments in October 1962, reprinted herein. My release of that date summed up my views as of that time on the policy issues involved in MER/29's record. Findings by the subcommittee since that date have, I believe, fully confirmed the judgment which I expressed.

#### PROFESSION SHOULD MAKE SCHOLARLY ANALYSES

One of the reasons prompting this detailed treatment of the drug may now be clear.

It is to satisfy the profession's and the public's right to know about a subject which has heretofore been cloaked, partly in mystery, partly in indifference and ignorance.

As Miss Ottenberg stated in her helpful and comprehensive article:

Except for trade journal reports and Mr. Harvey's speech to the American Bar Association, where he cited MER/29 in calling for new drug control laws, little has been said publicly about the drug.

Other observers have remarked that it is "strange" how relatively silent so many sources have been on a case history such as this which so concerns the public health.<sup>4</sup>

Many months ago, one observer stated to the subcommittee:

The medical profession seems oddly disinterested in the way FDA goes about making its decisions. Only if the agency imposes new forms or other requirements is there an uproar. Otherwise, the profession shows little curiosity as to whether the basic decisions on New Drug Applications or in drug withdrawals are made soundly and promptly. With the exception of thalidomide, you will look in vain if you try to find in any medical journal a detailed "postmortem" on any drug fiasco. Perhaps the post-mortem might upset too many people.

That was one man's opinion. The subcommittee would be interested in receiving other opinions on the subject; it would be particularly interested to see evidence on both sides of the question. Little evidence has appeared to date which would confirm detailed interest in the case histories of New Drug Applications on the part of professional organizations.

At times, the withdrawal of a drug has resulted in a few pages of analysis in professional journals. But it is a fact that few detailed, scholarly evaluations of drug failures seem to show up in the literature. One reason is, of course, that FDA's internal records are not available for direct professional scrutiny, without intercession by the Congress.

The issue of the "confidentiality" of virtually the entire files on New Drug Applications is an important one in its own right. It is not a simple issue; it involves interpretation of the 1938 law, as well as protection of the universally recognized right of confidentiality of doctor-patient relationship. FDA's policy on the subject is mentioned at length on several occasions in the subcommittee's hearings and exhibits. Suffice it to say for the moment that even when a House subcommittee sought direct study of the FDA MER/29 file, permission was denied by the agency.<sup>5</sup>

<sup>4</sup> Ibid, p. 616. One of the few other sources to analyze the history of MER/29 in a daily newspaper was Barbara Yuncker in the New York Post (pp. 909-912).

<sup>5</sup> Pt. 3, exhibit 168, p. 1187.



It is in part understandable, therefore, why so little analysis by the medical profession itself<sup>6</sup> has been made of FDA's internal record.

An illustration of the gap in information which results from inaccessibility of NDA files was provided in the June 1962 report by the Committee on Public Health of the New York Academy of Medicine. In its valuable report on the clinical testing of drugs, the committee stated:<sup>7</sup>

Since the committee does not have access to the files of the pharmaceutical industry or of the Food and Drug Administration, it has not had the opportunity to scan clinical reports on drugs as actually submitted. Instead, it has had to take recourse in evidence gleaned from the literature, supplemented by personal observations. Because of the selectivity in publication, the bias in this approach is in the direction of minimizing any depreciative view of clinical testing.

The problem of the unavailability of NDA information to the professional community might be less significant if there were abundant evidence that the Food and Drug Administration has made intensive analyses of its NDA experience—both successes and failures, in terms of the protection of the public interest.

No such evidence has come to the subcommittee's attention to date.

Insofar as Dr. Nestor's judgment is concerned, FDA definitely has not conducted such analyses.

He said with respect to MER/29<sup>8</sup> " \* \* \* there has never been an appraisal within the FDA to determine what factors were operating and what policies and personnel were involved which permitted such an application to be approved."

He added with respect to another withdrawn drug, Altafur,<sup>9</sup> "Even though the Deputy Commissioner reviewed and upheld the findings of the HEW Hearing Examiner to suspend the New Drug Application for Altafur, there was never an internal appraisal to determine how this drug was allowed to clear the FDA new drug procedure or why the firm was allowed a 3-month period of grace for further marketing after the risks were known \* \* \*."

#### KEY QUESTIONS SHOULD BE ANSWERED

The Food and Drug Administration will, of course, be furnished with a copy of this and all other pertinent comments on its activities and invited to make further reply for the record. Irrespective of this subcommittee's suggestion to do so, it behooves the Food and Drug Administration to ask itself substantive questions about the case history of MER/29. It should ask:

What can be learned from this experience? What mistakes were made? To what extent were the mistakes avoidable? How? What steps have since been taken to minimize repetition of mistakes?

Even more specific questions than these should be asked by FDA of itself (if the agency, as Dr. Nestor contends, has not already done so). Thus,

(a) If, as Deputy Commissioner John Harvey contended, approval of the New Drug Application was not warranted on the basis of the preclinical and clinical reports, what test information should have been required?—with how many test animals of how many species, e.g., as to possible cataract formation? for how many patients? with what minimal results? over how long a period of time?

(b) Did the FDA medical reviewer who approved the NDA otherwise fulfill his responsibility? Did he consult with other expert sources prior to coming

<sup>6</sup> One major analysis was made in 1960 by a distinguished National Academy of Sciences panel, headed by C. Phillip Miller, M.D. However, according to numerous medical scientists, the panel's review was necessarily unlike the broad-gaged analysis which is suggested herein. In such an analysis, a single major drug or, preferably, a representative cross-section of New Drug Applications, e.g., cardiovascular, psychiatric, etc., would be studied in great depth and in open hearings. By contrast, according to our correspondents, the review by the Miller panel was necessarily limited by such facts as these:

(a) The review was made in response to an urgent request by the Secretary of Health, Education, and Welfare, Arthur Flemming, to determine whether a conflict of interest situation in the Division of Antibiotics had undermined the regulatory process; (b) of 27 drugs appraised, most were antibiotics; (c) the panel consisted mostly of experts in anti-infective agents; (d) they relied on FDA furnishing them the records; (e) the panel held no public hearings, called no public witnesses; (f) made available no detailed case-by-case analysis; (g) devoted so brief a time, relatively speaking, that definitive analysis of the type suggested above was not feasible.

<sup>7</sup> "Interagency Consideration of Drug Research and Regulations," pt. 2, exhibit 83, p. 534.

<sup>8</sup> Pt. 3, p. 786.

<sup>9</sup> Ibid., p. 787.



to his decision? Did circumstances within the agency permit and foster such consultation?

(c) Specifically, was that reviewer's ultimate decision, as Miss Ottenberg contended, a "one-man decision" (although the matter ultimately affected not less than the well-being of 300,000 patients)?

(d) Was there effective communication, consultation and collaboration within the Food and Drug Administration, e.g., between the New Drug Division and the Division of Pharmacology? (See p. 840 for the extremely significant memorandum from the Division of Pharmacology in February 1960 opposing approval of the New Drug Application.)

(e) Did the office of the Commissioner, Food and Drug Administration, make the right decision in November 1961 in (1) allowing the drug to remain on the market, while (2) only requiring the company to send out a "Dear Doctor" warning letter? Did FDA have a real alternative to this action from a legal standpoint? Was the action sound from a scientific standpoint? A moral standpoint?

(f) Was there effective communication, consultation, and collaboration between agencies of the U.S. Government, i.e., as among the National Institutes of Health, the Veterans' Administration, and the Food and Drug Administration at various key stages? If so, by whom; if not, whose responsibility was it to have assured such teamwork?

(g) Did the pharmaceutical company make full disclosure of pertinent information at the various phases of the drug's development to—

(1) Clinical investigators?

(2) The Food and Drug Administration?

(3) (After approval) to practitioners—through advertisements, the package insert, warning letter, statements to the lay and professional press, etc.?

Nongovernmental sources involved in the drug's history might likewise interrogate themselves. Thus,

(a) Did the professional organizations of medical science and allied healing arts adequately and promptly fulfill their responsibilities at the various important stages of the drug? Did the advertisements in medical journals satisfy sound professional standards? (The subcommittee has been informed that at least one professional journal rejected one ad for MER/29 which the Journal of the American Medical Association accepted.)

(b) Was there prompt communication and evaluation of information based on experience with the drug, e.g., as between cardiovascular, diabetes, and ophthalmological experts and general practitioners?

(c) Was all that might reasonably have been expected actually done by the American Heart Association and American Diabetes Association (whose Committee on Nutrition spokesman did contact FDA—see July, September, and November, 1960 contacts)?

The subcommittee would not presume to answer these and other complex, professional questions, particularly as they relate to nongovernmental organizations. The very listing of the questions indicates, however, how considerable must be the information which would have to be secured if scholarly answers are to be provided.

The three chronologies within exhibits 127, 128, and 129 will only begin to serve as a basis for such answers; at least, however, they offer a better beginning than has thus far been available.

#### CONCLUSION—LEARN WHAT THE PAST TEACHES

If these exhibits serve no other purpose than to stimulate the curiosity of Government and of the professions to seek the necessary facts with respect to this and similar case histories, the exhibits will have fulfilled their purpose in serving the public interest.

In effect, science should not allow itself to be so preoccupied with today's and tomorrow's drugs that it fails to capitalize on experiences with yesterday's drugs.

Science should not overly dwell on these past experiences; but neither should it "close the book" on a subject like MER/29 which will remain "open" for so long a time to come in the lives of so many patients.

Science should get the facts, all the facts—to the extent this is possible; it should interpret the facts carefully and candidly and then disseminate its conclusions to all concerned.



## CHRONOLOGY ON MER/29

(NOTE.—The format used in the chronology highlights the date and the issuing source; these items of information appear before each reprinted document in a flush left position. Above, italicized in the center appears a brief indication as to the nature of the document.)

(1958. See exhibit 128, pp. 922 ff. for early investigative history on the drug during this year.)

June 1958. Company circulates to clinical investigators a 36-page "confidential" brochure on MER/29, "An Inhibitor of Cholesterol Synthesis."

See also a subsequent item in this chronology, a New York Post article of August 8, 1962, for a report as to activity by the William S. Merrell Company in the period prior to filing of New York Drug Application on MER/29—p. 911.

*(Medical Supplement in the Open Literature)*

DECEMBER 16-17, 1958.

PROCEEDINGS OF THE PRINCETON, NEW JERSEY, CONFERENCE ON MER/29.<sup>1</sup>

## PROCEEDINGS OF THE CONFERENCE ON MER/29

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<sup>1</sup> Progress in Cardiovascular Diseases, Special Supplement, vol. 2, No. 6, pt. 1, May 1960.

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#### INTRODUCTION TO THE PROCEEDINGS

These proceedings constitute an account of the scientific reports and spontaneous discussions at a timely conference conducted December 16 and 17, 1959, at the Princeton Inn, Princeton, New Jersey. Representing disciplines ranging from basic biochemistry to clinical cardiology, 37 investigators and clinicians assembled at the invitation of The Wm. S. Merrell Company, to exchange views and experiences with respect to triparanol (MER/29), a non-steroid compound shown by Blohm et al. and by Hollander and associates to interfere with cholesterol biosynthesis.

Although the chemical and biological behavior of MER/29 comprised the primary theme of the conference, discussion extended into many widely diversified areas, keynoted perhaps by certain revelations made during the first evening (the Basic Science Section). It became apparent that the use of MER/29 as an investigative tool has contributed greatly to a clarification of the pathway of cholesterol synthesis in man. The demonstration by Drs. Avigan and Steinberg, and supported by the data of Dr. Frantz, that the MER/29 block in synthesis appears to occur at the last reductive step before cholesterol itself, emphasized the possible importance of the building up of late cholesterol precursors. Thus, conversation and speculation turned to desmosterol, or 24-dehydrocholesterol, which is not normally present in appreciable quantity in mammalian blood or liver.



Certain therapeutic potentialities of MER/29 were explored during the second day of the conference (Clinical Sections I and II), with primary interest centering around the efficacy of the compound as a cholesterol lowering agent. Pertinent questions, which were exhaustively pursued, ranged from the variability of blood cholesterol levels on the one hand to the paucity of objective parameters for evaluating angina pectoris and coronary artery disease on the other. The significance and validity of clinical improvement as suggested by exercise tolerance tests were aired thoroughly. The inadequacies of methodology, at both the clinical and laboratory level, were stressed.

In preparing these proceedings for publication, an effort has been made to preserve one feature of this conference which served to distinguish it from others of its kind—the spontaneity and stimulation resulting from free discussion between the basic science investigator and the clinician. Informality was encouraged by the chairman, and presentations frequently were interrupted for pertinent questions. In editing, a similar attempt has been made to retain the spontaneity of the exchanges by preserving the continuity of discussion. In some instances the continuity of the scientific report has been sacrificed to accomplish this.

Most of the participants submitted manuscripts which simplified the task of editing; others reviewed their comments from an excellent stenotyped transcript (Mr. George A. Sakson, CSR). Personal thanks are due Dr. Robert McMaster for his effective handling of publication arrangements with the various contributors.

The preparation of these proceedings has provided a stimulating and educational experience for the editor. It seems obvious that the biochemist is advancing rapidly in his attempts to clarify the intermediary metabolism of cholesterol. To keep pace, the clinician must continue to extend his efforts to delineate and translate these biochemical advances in terms of human health.

ALBERT A. BRUST, M.D.

*University of Cincinnati, February 1, 1960.*

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#### EDITORIAL NOTE

With this issue of Progress in Cardiovascular Disease, subscribers are receiving a supplement containing the report of a symposium on MER/29 (triparanol) by a distinguished group of investigators. The importance of this agent which is capable of inhibiting cholesterol synthesis, the great interest in cholesterol metabolism and its possible relationship to atherosclerosis and the high level at which this symposium was conducted appeared to justify the publication of this supplement. However, it should be pointed out that the editor of Progress in Cardiovascular Disease was not instrumental in the choice of the participants or individual subjects in the symposium or in the editing of the manuscripts, and that such publication should not be interpreted as implying approval or disapproval of the clinical use of the drug on the basis of the data reported.

THE EDITOR.

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#### BASIC SCIENCE SECTION

*Wednesday Evening, December 16, 1958*

#### WELCOMING REMARKS

By R. H. McMaster

Ladies and gentlemen: It is my pleasure to welcome you to the Princeton Conference on MER/29. It has been and is an unusual privilege to have been so closely associated with you in the basic and clinical development of this most interesting new agent.

As a matter of policy, we of The Wm. S. Merrell Company wish to assure each of you as participants in the discussions to come that this is your meeting entirely. Your chairman, Dr. Irving S. Wright, in whose capable hands I now place the conduct of the conference, will be in complete charge. Dr. Wright.



## INTRODUCTORY REMARKS

By Irving S. Wright

It is a great privilege and a pleasure to be here with you all tonight. Many are old friends who have been together in this very town for previous conferences dedicated to the same objectives, namely, finding the truth. We all know that the truth is elusive and indeed may never exist since the so-called truths of past generations are rapidly tumbling this way and that, under the impact of new knowledge, technique and equipment. Still as physicians and scientists we are rightly compulsive in our drive to get as close to it as we can. What we learn, though brittle, shines brightly and can often be put to good use while it lasts.

We are not gathered here to prove that Triparanol is a good drug or that it cures any disease. I doubt that any of this carefully selected group would have come for this meeting if that were the objective. I imagine that most of you, like myself, have come to learn of new work with a new tool and to exchange our experiences with this interesting substance. We can be most productive during the next day and a half if each finding is placed under the glare of a spotlight, and surveyed in the most critical manner, if each stone is raised to see what is in the shadow under it. Being critical in the true sense will in no way injure the findings based on careful work. It may well point out flaws in the past and better methods for the future. It should be constructive wherever possible.

This should be truly a working conference figuratively and literally; if you desire with your coats off and your sleeves rolled up. In this spirit we can all learn much. In this spirit we can contribute most to those who will read the transactions of the conference which will serve as a progress report.

\* \* \* \* \*

## THE TOXICOLOGY OF MER/29

(By William M. King<sup>2</sup>)

Physiologically occurring cholesterol has been shown to play an important role in many vital body processes. Blohm et al.,<sup>3</sup> have shown that MER/29 (Triparanol) inhibits the biosynthesis of cholesterol at a late stage. It therefore becomes of considerable importance to determine, through whole animal responses, whether or not the inhibition of cholesterol would be reflected in any of the measurable parameters of toxicology.

## I. ACUTE TOXICITY

The acute toxicity of MER/29 and its citrate salt was determined in both mice and rats. These determinations were carried out in 18-22 gram female mice and in 300 gram male rats. The soluble form was dissolved in physiological saline solution, and the insoluble base was suspended in 1.0 percent carboxymethylcellulose in physiological saline solution. The LD<sub>50</sub> was determined for a 24-hour interval, and standard errors were estimated by the method of Miller and Tainter. The rats were held for 7 days to observe for delayed deaths. Death appeared to be due to respiratory failure. The acute toxicity data are shown in table 1. These data indicate a low level of relative acute toxicity. The acute toxicities of the soluble citrate salt would suggest that MER/29 is somewhat more toxic in the female than in the male.

## II. SUBACUTE TOXICITY IN THE RAT

MER/29 was studied in both male and female rats at doses of 37.5 and 75 milligram/kilogram/day for 6 weeks, and at doses of 25 and 50 milligram/kilogram/day for 3 months. In each study, one group of males and one group of females served as controls and received 5 percent gum acacia, the suspending agent, in volumes equivalent to the drug groups.

<sup>2</sup> The Department of Toxicology and Pathology, Scientific Division, The Wm. S. Merrell Company, Cincinnati, Ohio.

<sup>3</sup> Blohm, T. R., and MacKenzie, R. D.: Specific inhibition of cholesterol biosynthesis by a synthetic compound (MER/29). Arch. Biochem. and Biophys., 85:245-249, 1959.

(NOTE BY EDITOR OF SUBCOMMITTEE VOLUME.—The above and succeeding footnotes in this exhibit are reproduced from the footnotes of the original journal supplement on the 1958 proceedings.)



At 75 milligram/kilogram/day, both male and female rats showed a significant reduction in food consumption and body weight gains. The lower dose of 37.5 milligram/kilogram/day, however, was well tolerated by both males and females. Histopathologic examination of the tissues of the 75 milligram/kilogram/day animals revealed moderate fatty infiltration of the liver. These changes were consistent with the reduction in food intake.

TABLE 1.—*Acute toxicity—MER/29*

Species	Route	LD <sub>50</sub>
<i>MER/29 Base:</i>		
Mouse.....	I.P.....	1600±132
Mouse.....	Orally.....	>2000
Rat.....	I.P.....	>2000
Rat.....	Orally.....	>2000
<i>Citrate Salt of MER/29:</i>		
Mouse.....	I.P.....	355±15
Mouse.....	Orally.....	1700±88
Rat.....	I.P.....	960±150

A dose of 50 milligram/kilogram/day was tolerated well by the males, but the females gained little weight after the drug was started, and the female group was autopsied at 6 weeks. Doses of 25 milligram/kilogram/day were well tolerated by both sexes.

Hematologic determinations were carried out before the drug was started, and immediately prior to sacrifice. The hematologic values were similar for the drug-treated animals and for the controls, and all values were within normal limits.

The adrenals showed one consistent histopathologic change. This adrenal change consisted of a partial depletion of the sudanophilic contents of the zona fasciculata.

It has been shown previously that the minimal effective dose of MER/29 in the rat is approximately 2 milligram/kilogram/day. The toxicologic data indicate that the maximum tolerated dose in the rat approximated 50 milligram/kilogram/day for the male and 35 milligram/kilogram/day for the female. These data suggest a comfortable margin of safety.

### III. CHRONIC TOXICITY

The chronic toxicity of MER/29 was studied in the rat, dog and monkey.

Figures 1 and 2 show the growth curves for male and female rats on a long-term oral study. The daily oral dose was 3 and 10 milligram/kilogram for 8 months, and 25 milligram/kilogram for 3 months. At the two lower doses, the body weights of the drug-treated animals parallel those of the controls. At a dose 25 milligram/kilogram for 3 months, the male drug animals were 6 percent below control values, and the females were 16 percent below control values.

A 6-month study was completed in male and female adult mongrel dogs. The daily oral dose was 25 milligram/kilogram. At this dose, MER/29 did not affect food consumption or body weight in the dog. Hematologic determinations were performed initially, at 3 months, and at 6 months. All values were within normal limits for the dog. Terminal bone marrow studies were likewise normal.

Gross and microscopic examination of tissues failed to reveal drug-induced changes other than the adrenal changes also observed in other species.



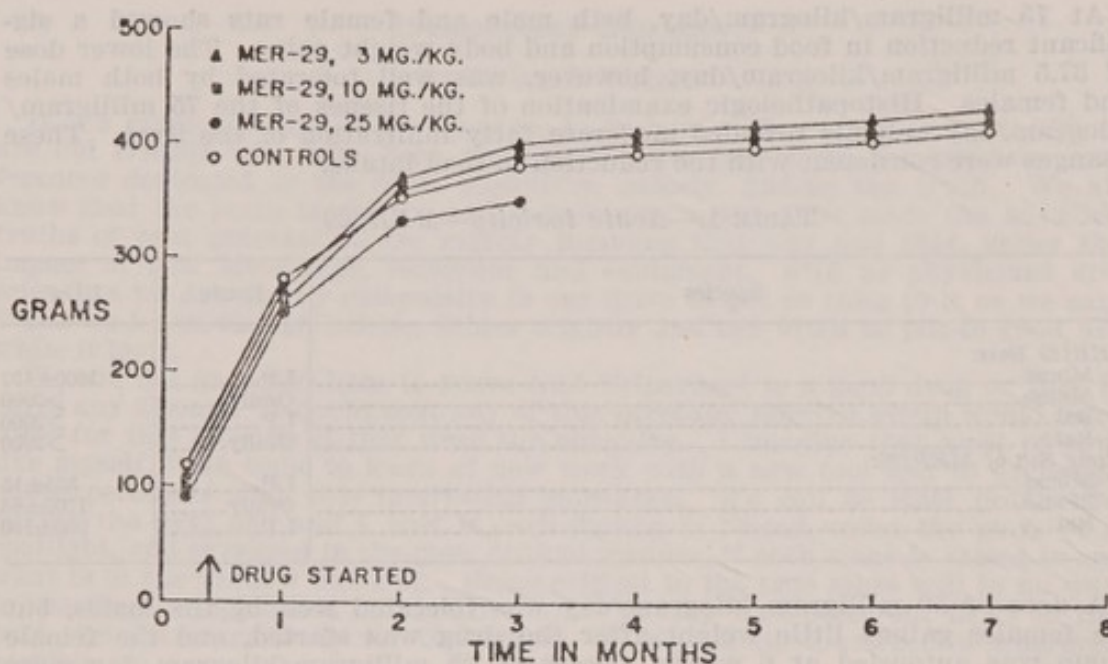


Fig. 1.—Body weights of male rats

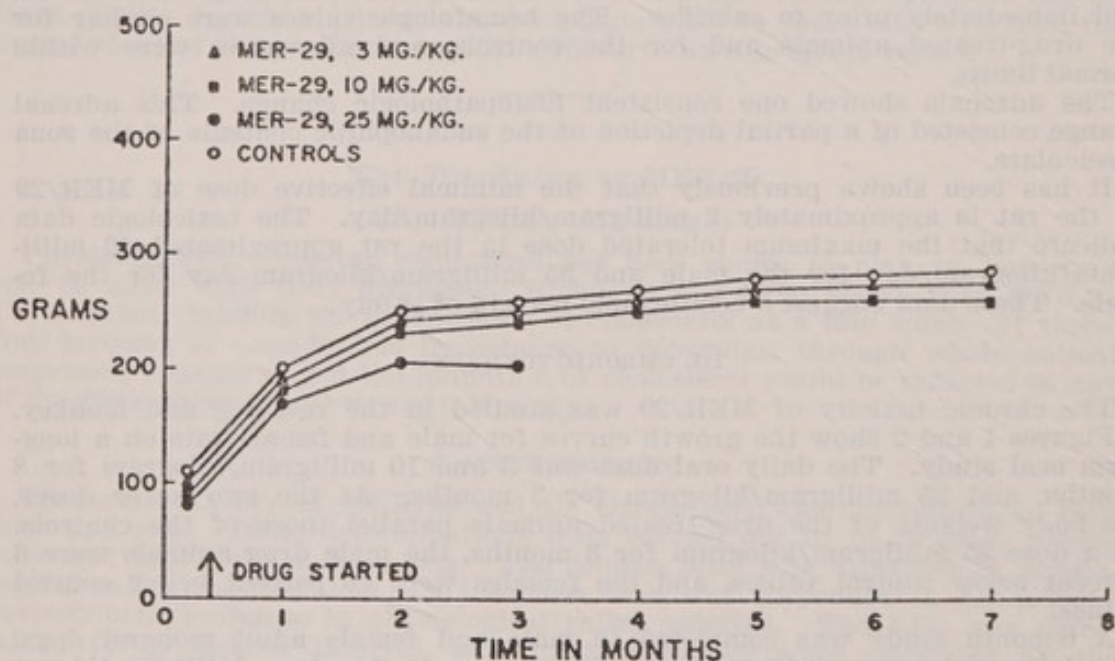


Fig. 2.—Body weights of female rats

## IV. CHRONIC TOXICITY IN MONKEYS

Four adult rhesus monkeys were utilized in this study with paired controls of the same sex and similar age and weight. One male monkey was given MER/29 in a daily oral dose of 40 milligram/kilogram and was sacrificed with his control at 7 months. Two additional males and one female were given MER/29 in a daily oral dose of 20 milligram/kilogram for 16 months.



TABLE 2.—*Hematologic values for MER/29-treated monkeys*

Animal No.	Hemoglobin		Hematocrit		Leucocytes		Granulocytes	
	Initial	Final	Initial	Final	Initial	Final	Initial	Final
34 male*	14.3	14.6	48.5	42.0	8.8	6.3	46	45
49 female*	14.8	12.3	50.5	41.0	14.3	15.4	70	67
51 male*	14.3	12.4	46.0	40.0	17.9	5.0	25	53
25 male†	15.5	12.8	50.0	43.0	12.3	9.9	69	58

*Controls*

48 male	15.8	13.3	52.0	45.5	11.3	8.7	62	41
33 male	16.0	13.8	48.0	40.0	20.5	6.1	78	43
35 male	14.8	14.2	48.0	44.0	18.5	15.8	71	66
39 female	10.3	13.4	37.0	43.0	19.3	14.2	64	55

\*20 mg./kg. 16 months.

†40 mg./kg. 7 months

TABLE 3.—*Liver function studies in MER/29-treated monkeys—16 months*

Animal	Dose	Serum Bilirubin total mg./100 cc.	Alk. P'tase K-A units	Trans- aminase SGOT units	BSP percent retention
M-25 Male	20 mg./kg.	0.2	6	18	0.5
M-34 Male	20 mg./kg.	0.4	9	10	0.0
M-51 Male	20 mg./kg.	0.2	16	30	1.0
M-49 Female	20 mg./kg.	0.2	13	22	0.0
M-35 Male	Control	0.1	12	16	0.0
M-39 Female	Control	0.5	6	20	1.5

Chronic administration of relatively high doses of MER/29 did not affect the body weight. Furthermore, MER/29 did not significantly alter the peripheral blood values and did not produce any demonstrable changes in the bone marrow. Table 2 shows the hematologic responses of these animals. The values are similar for the drug-treated monkeys and for the controls, and all are within normal limits for the monkey.

Serum bilirubin, alkaline phosphatase, serum transaminase, and bromsulfalein retention determinations were carried out in these monkeys. These data are shown in table 3. One drug animal (M-51) had a slightly elevated alkaline phosphatase value (16 K-A units) (13 K-A units and below are normal in the monkey). All other values were similar for the drug-treated animals, and the controls and are within normal limits for the monkey. These data indicate that MER/29 does not alter measurable liver function in the monkey.

Postmortem studies revealed one consistent change in adrenal morphology, as observed in other species. Figure 3 [not included herein] shows such an adrenal section with sections from a paired control. The change is limited to partial lipid depletion of the cells of the zona fasciculata. Careful morphologic study reveals no change in the normal architectural pattern of the tissue, and it was not possible to demonstrate changes in adrenal function, as determined by the animal's response to ACTH and urinary and circulating corticoid levels.

In summary, our data suggest that:

1. MER/29 has a low level of acute toxicity.
2. The spread between the minimal effect dose and the maximum tolerated dose provides a comfortable margin of safety.



3. No untoward hematopoietic response has been demonstrated in the rat, dog or monkey.

4. MER/29 does not affect measurable liver function in the monkey.

5. A consistent change is seen in all species in the adrenal glands; this change consists of partial lipid depletion in the cells of the zona fasciculata (spongocytes).

6. No other gross or microscopic pathology was demonstrated in any tissues.

\* \* \* \* \*

#### CLINICAL SECTION I

*Thursday Morning, December 17, 1959*

Dr. Irving S. Wright: Ladies and gentlemen, this morning we begin the discussion of the clinical aspects of this interesting subject. Our first reports will come from Dr. Kountz and Dr. Toro. Dr. Kountz will open their discussion.

#### CLINICAL OBSERVATIONS ON THE EFFECTS OF MER/29

By William B. Kountz<sup>4</sup>

Being the first speaker in the morning, especially on a clinical study, I have some feeling of hesitancy in my report on the subject. The problem is one of much interest as we all know. But the clinical aspect is difficult to present because a number of factors enter in which might lead one to misinterpretation. As an example of the question that came up in our mind, I shall tell a brief experience.

One afternoon in my office, a 71-year-old individual came in for consultation. I had studied him previously and established the fact that he had vascular disease. As he walked into the consulting room, he handed me a package with the remark, "I certainly owe you these."

Recognizing that the package was frozen food of some sort, I asked him what it was, and he told me it was a half-dozen quail. I asked him why he felt so indebted and he replied that this was the first season that he had been able to go quail hunting for the past 2 years. In the course of the conversation I asked him to what he attributed his improvement. He answered, "Those mouse-gray capsules you have been giving me." This of course was the MER/29.

After this discussion I had him remove his shoes and socks. I felt for the pulse in his feet, which I had never been able to find before nor could I at this time. I did feel, however, that his feet were somewhat warmer than they had been previously. In previous examinations I had measured his claudication in the hall outside our office to determine how far he might be able to walk. I asked him again to go out in the hall and repeat the performance, which he did. On previous occasions he had been unable to walk more than half the distance without pain. At this time he made the complete trip and said he felt no pain. He asked to make it again with just a brief rest and repeated this several times.

Clinically I would say without any question that this man demonstrated much improvement in his ability to walk. We of course are not certain as to the cause of this man's improvement. We feel, as he does, that probably the MER/29 and change in his cholesterol did this. We have studied him further by x-ray and sweat test and have found no dramatic change in his blood vessel condition. We have found, however, a persistence in the improvement in his ability to walk. It is true that he did have some treatment a year and a half before which consisted of intravenous iodine, low fat diet, etc. So we ask you the question and hope you will help us answer it. What improved his claudication?

Actually we have been at this study for a year and a half and have followed a total of 103 individuals. Twenty-eight were in the chronic hospital where they could be thoroughly controlled. Seventy-five of them were observed in private practice and were people of good economic status.

<sup>4</sup> The Gerontological Research Foundation, 5600 Arsenal St., St. Louis, Mo.



Of these 75 individuals of whom I shall chiefly speak, 28 had moderately severe arteriosclerosis and manifestations of vascular disease of one sort or another. In this group were individuals who had had coronary disease (12 patients) or manifestations of peripheral vascular disease (5 patients). The remainder were examined by a psychiatrist, and a diagnosis of cerebral arteriosclerosis with basilar artery syndrome was made. Fifteen other individuals had mild cardiovascular disease with essential hypertension, anginal pains, and shortness of breath. The age of these individuals ranged from 34 to 79. Others in this group had symptoms of such nature as to lead to the diagnosis of post-menopausal changes, tachycardia, hypothyroidism, and so forth.

In the total group of patients, and particularly in the hospital group, there were patients with advanced arteriosclerosis, hypertension, angina pectoris, diabetes, atherosclerosis, and myocardial infarction.

The method of study consisted of complete physical and mental evaluation. When symptoms were referable to the nervous system, observations were made by a neurologist as well as by a physician.

Laboratory tests were run which consisted of routine hemograms, urinalysis, blood chemistries including urea nitrogen, fasting sugar, uric acid, and cholesterol, as well as basal metabolism, electrocardiograms and chest x-rays, and any other laboratory tests indicated.

In a selected group of the patients, liver function tests were done which consisted of bromsulfalein retention, cephalin flocculation, prothrombin time, alkaline and acid phosphatase, and thymol turbidity. Kidney function tests were likewise performed, as well as tests of thyroid function, since we have been particularly interested in metabolic considerations.

Glucose tolerance tests were run in the private group, especially in those whose blood sugar in the initial period was abnormal, or where there was a family history of diabetes. In addition, the 17-ketosteroids were determined, and vaginal cytology was done in women.

After the preliminary study, the individuals were started and maintained on a 250 milligram capsule of MER/29 once daily. In 5 patients, the dose was increased to 1 capsule twice a day, or 500 milligrams daily.

Findings and observations: No toxic or side effects were noted in the patients when the dose of 250 milligrams was given. This applied to the private patients as well as those in the hospital. Occasionally a substance was found in the urine which initially was thought to be protein, but which was later demonstrated not to be since it did not show a positive biuret reaction.

Clinical improvement was observed and also was reported to us by patients. In some instances the anginal pain improved very much.

One individual who had had coronary thrombosis 4 years before and whose electrocardiogram had remained stationary over a period of at least 2 years, showed some suggestive improvement after taking the medication. It is interesting that he reported that his angina had practically disappeared in the course of 3 months after beginning the medication. Other patients have reported that, in addition to feeling better, they do not fatigue as easily as before. Many of these improvements can possibly be considered as resulting from psychological suggestion.

In the private group the complications were minor. One individual reported vaginal bleeding after having been on the drug for 4 months. Two of the private male patients reported decreased libido which lasted for only a few weeks.

Laboratory findings after administration of the drug revealed normal hemograms. Blood morphology was performed by the Hematology Department of Washington University School of Medicine on a group of patients, and normal findings were reported. Urinalysis had been negative with occasional false positive albuminuria in some patients. It was noted in individuals in the private group that there were 3 types of reaction from the standpoint of cholesterol: (1) In 15 there was a reduction of as much as 30 to 32 percent of the initial cholesterol level; (2) the greatest number of the individuals however, had a drop of from 15 to 20 percent in the course of the first 2 months, which within the next 90 days ranged upward; (3) in 4 of our patients the



cholesterol remained high in spite of an increase in the dose of the substance. This latter group included patients whose thyroid function had been depressed by radioactive iodine in an attempt to relieve angina pectoris.

In some of these individuals we have been able to compare MER/29 with various other forms of therapy such as lecithin, niacin, estrogen, and so forth, which had been used previously. We found that MER/29 is more efficient, more uniform in response, and had less undesirable side reactions than any of the other substances we have given.

The rise in the cholesterol value after administration of MER/29 for a period was a problem that we considered with much interest. In the selected group of patients the observations which were made on 17 ketosteroids and the hydroxysteroids showed no changes. Lipoprotein studies also showed no important changes. The vaginal cytology, however, revealed interesting and important changes. Our findings showed that there is a definite but mild estrogenic effect. We assume that this is a direct effect of the drug and its estrogenic qualities, although it is well known that some drugs stimulate the adrenal cortex, thereby producing an estrogenic response.

In summary, we would say that MER/29 is a very interesting drug. It has a definite cholesterol-lowering effect. In our experience it does not produce any untoward symptoms when given in a dose of 250 milligrams once or twice daily. In a previous experience with 1,000 milligrams a day we found no clinical evidence of disturbance aside from the appearance of the false albumin in the urine.

It is suggested that these studies should be continued since our results reveal a most interesting response as far as the cholesterol and clinical symptoms are concerned.

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#### SUMMARY OF CLINICAL SECTION I

By Robert W. Wilkins

I think this has been a fascinating symposium thus far, and certainly much philosophizing could be done about what we have heard.

First of all, while there are many things which have been said and others which could have been said, the first thing that should be said is: MER/29 is an important drug. You may ask, if it's important, why is it important? I think the first obvious answer is that it must do something worthwhile clinically for people or we would not be here talking about it. Second, it cannot be very toxic. Third, it must be usable over long periods of time if it is to be used in a long-term disease. It must be usable for as long as is necessary to alter the course of that disease. The one big question which we have not addressed ourselves to at all, except by implication is: Does the drug have any value for preventing atherosclerotic disease as well as in relieving it? These questions occur to one philosophically when he attends any meeting like this.

Other philosophizing that I have done this morning was to compare the history of this drug's going from the clinician to the laboratory expert and back to the clinician again. As you know, many drugs have this experience and certainly MER/29 has taken this course in our conference from last night's almost esoteric treatment by the laboratory experts to this morning's introductory remarks by pure clinicians on the use of the drug in patients, and then we have been brought by Dr. Steinberg's concluding remarks back to the laboratory findings as to what this is really doing basically to the sterol profile, if you will, the sterol profile of the blood.

Another thing I thought of all morning is the influence of a mental set in the investigator when he tackles a problem like this. It has been perfectly obvious that each of those who has studied this agent has done so with a bias. There is nothing wrong about a bias unless we fool ourselves that we don't have one. All of us have taken a certain "tack." Dr. Wright and his group naturally looked at this from the coagulation point of view. Dr. Kountz and his associate looked at it from the clinical point of view.



Now, I would suggest that we need to get outside of our own bias, outside of our own mental set. We can accept that MER/29 does influence sterol synthesis or biosynthesis, and that it does do some favorable things clinically. (I think we'll have to accept the latter, in spite of Dr. Russek's rather devastating step test data, because clinicians have been impressed that this drug does help angina at least.) But we should ask ourselves, do these two things really have anything to do with each other? Or are they just coexistent phenomena? Nothing is easier to slip into, in drug work, than to get a drug from the laboratory or even from folklore medicine which has one well-recognized action and to project from that well-recognized physiological or clinical action that all its other effects are on the same basis. We have seen this happen, of course, in the reserpine field, in the serotonin and anti-serotonin squabble, and so on. It is still questionable among many of us whether the clearly proven chemical or physiological actions of a drug really are responsible for all its clinical effects. Let's keep this in mind with respect to MER/29.

Whatever else we can say about this drug, as of today, I think we will all agree when we conclude this conference that MER/29 is serving to open up active investigation in an area where long ago it should have been done; namely, on what are the homeostatic mechanisms based which control cholesterol levels in people, whether or not this has anything to do, as, I suppose, we all believe that it does, with atherosclerosis, and what are the pathways of sterol synthesis, and where should they and can they be blocked?

I am certain that much of the information that we will take away with us will not contribute substantially to the profits of The Wm. S. Merrell Company from their sale of this drug. Be that as it may, what have we heard this morning about clinical experiences? We've heard Dr. Kountz and several others attest that this drug seems to lessen anginal attacks in certain patients. Yet we have heard also that it does not lessen anginal attacks in other patients; and if we accept Dr. Russek's report, it does not lessen the evidences of angina on the step test in long-established, well-studied cases of angina pectoris with stable control step test data.

Now, we have no clinical information, except a hint from Dr. Kountz, that this drug may also be effective in lessening the symptomatology of patients with intermittent claudication. As far as I was able to gather, we had no suggestion that it has altered the course of cerebral vascular disease, at least from the standpoint of symptomatology.

Further, it's perfectly clear, from what Dr. Kountz has said—and I can also tell you from what others know—that MER/29 does not prevent the progression of atherosclerotic disease in the periphery, since gangrene may ensue; or in the heart since myocardial infarction may ensue; or in the brain since cerebral vascular accidents will probably ensue in patients on the drug. We must assume that the disease in its essence marches along in people even on MER/29.

This brings us back to the philosophical point that dealing with drugs in ill patients is not the same as dealing with drugs in well persons, and it certainly has no counterpart, in my thinking, or only a very remote one, to dealing with drugs in animals which are kept in cages and are highly bred to be fairly uniform in their physiological and biochemical makeups.

Now, one other thing that came out clinically is: Is there a rigid relationship or any relationship between the clinical improvement that the doctor is interested in and some of the measurements that have been reported? Take the prime one, the cholesterol levels. I could not get it, perhaps you did, that there was a firm relationship between clinical improvement, when it was reported, and the fall in the blood cholesterol. Now, this is a simple thing, so let's establish it or let's throw it out.

Secondly, was the improvement, which was usually stated to occur within 3 to 6 weeks, progressive or did it occur more or less quickly and stabilize? My impression from what was said was that it occurred quickly and stabilized.

Thirdly, does it occur quickly and then stabilize forever, or can it still occur only after months of continued treatment when no early or initial improvement occurred? These are very important questions. There was another suggestion relating to cholesterol level in these clinically observed patients: that it may fall, then it may rise on continuation of the same drug therapy; and then, in



some, if the dosage of the drug is increased there may be a secondary fall, but by no means in all cases. One would then say, why not keep on increasing the dose, and if so, what would happen? Finally, Dr. Leckert said he wasn't sure that the fall that he observed was even due to raising the dose of the drug, that maybe if he had just continued the same dose the fall would have occurred. All of this is evidence that we have not had sufficient experience with this drug to tell all these things. Certainly one can tell what the chronic, long-term effects of a drug may be, good or bad, only by continuing it through a long observation. This takes time.

That seems rather a trite statement, but it's one that I find drug companies reluctant to accept; namely, that you cannot tell what a drug will do after 4 or 5 years of treatment without waiting 4 or 5 years.

The question of some hormonal, humoral or endocrinological change was raised. This question was raised by at least 2 different groups. In Dr. Ford's studies to find some method of evaluating atherogenic and anti-atherogenic procedures or treatments through their effects in simulated stress situations, I think that he persuaded us that this may be a useful method of attack on the whole problem. But just what it means to this question, except for the coagulation changes, was not completely clear to me, and I doubt if Dr. Ford would claim that it is completely clear to him. Again, this is a bias in which he is particularly interested and certainly should pursue.

Most of those who spoke to the point agreed that there is no consistent change in the usual clinical laboratory measurements, such as liver function, renal function, the various fractions of the blood, cellular or chemical, that were significant or consistent except for this relatively consistent lowering of cholesterol. Nobody I have heard has yet given a percentage figure that is "significant." They merely say that their data were not susceptible to that sort of analysis. But we need to know the percentages in cases in which we get a lowering of cholesterol. And in the cases in which we don't get a lowering, what differences are there from those in which we do?

Dr. Steinberg, at the end, and others earlier, addressed themselves momentarily to the idea that we ought to think more about these cases that don't respond. Do certain adjunctive procedures make cases more responsive? The most fascinating suggestions were those of Dr. Estes who brought up that horrible subject, of which I have been guilty so many times, of "combination therapy." The idea that he inserted into the discourse was that perhaps nicotinic acid, which is said to work in some patients, and MER/29 which is said to work in some patients, might possibly work better together than either one does alone. That certainly needs very much more study and is, to me, a very interesting idea.

I think that Dr. Todd did clarify for us that at least as far as she has gone in her studies, she is not convinced that this drug importantly influences the clotting mechanisms. Nevertheless, she would certainly be the first to say that four are too few patients on which to draw any sweeping conclusions.

Coming back to endocrinological side effects, possibly Dr. Blohm cleared up for us an apparent conflict that Dr. Toro mentioned; namely, that some elderly female patients do bleed slightly from the vagina as if there were some estrogenic effect of this drug, by pointing out that even in animals the drug may potentiate the amounts of existing estrogen; and, of course, we know that in human beings estrogens don't all come from the ovaries.

Dr. Corcoran's clinical observations and those of Dr. Leckert showing a reduction in cholesterol levels in 11 of 15 and 4 of 9 of two different groups of patients were somewhat at variance with the observations that Dr. Steinberg showed; Dr. Steinberg was stressing a particular type of study. And yet, I think throughout all of this we have had the suggestion that we aren't really measuring what we ought to be measuring even in our sterol measurements. I am sure we will all be indebted to Dr. Avigan and the other chemical experts who will clarify for us the way in which we should measure these things clinically. Certainly, if I know the statistics, 20 percent is a fairly common



figure for average lowering of the blood cholesterol as measured, and if this is indeed accounted for by the appearance of a new sterol, 24-dehydrocholesterol or desmosterol, then we need to think, as many have suggested, whether this is "good" or "bad," clinically speaking. What are the atherogenic properties of these new sterols which may appear in the blood?

Thus, Mr. Chairman, I think that the morning session by the clinicians has served to emphasize what we don't know. I don't know that the afternoon session is going to answer all these questions, but at least we have the stimulus of knowing what the clinicians don't know. If the afternoon's discourse goes as the morning's has, I think that all of us will have plenty of work still to do, whether in the chemical laboratory, in the electrocardiographic laboratory, or merely in the out-patient department. Thank you.

The Chairman: Thank you very much, indeed. I think that was a very fine, constructive and questioning summary. It emphasizes the statement of the late Dr. Eugene Dubois, that the evaluation of a drug in clinical medicine is an extremely difficult process, usually much more difficult than the experiments that the physiologists and chemists carry out in their laboratories. The final decision may involve hundreds of thousands or even millions of human beings; therefore, it is a major responsibility and cannot be taken lightly.

In order to meditate about this, we will now adjourn.

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## SUMMARY OF CLINICAL SECTION II

By Irvine H. Page

I am sure you do not want me to review what you have already heard this afternoon. You've heard a great deal of interesting work, in case you are in any doubt. I think you all recognize that, in many cases, intellectual bias is showing through the investigator's bloomers, and that this is natural in a field that is so rapidly changing. I should say that the entire symposium was about "par for the course," for meetings on atherosclerosis because the great need for re-evaluation of methods of study becomes so apparent.

I think it is clear, for instance, from all the various studies that great confusion arises from incompletely evaluated methodology, as Dr. Gould pointed out. The methods for cholesterol determination have been notoriously erratic. We found this out by bitter experience in a so-called coordinated study of cholesterol and lipoproteins measured with the ultra-centrifuge. Even in laboratories that prided themselves on their ability to determine cholesterol, many of the measurements were grossly in error; it wasn't enough merely to determine duplicates. What happened was that, from time to time, errors occurred with even reliable technicians. It was not until we were forced to send the cholesterols to Washington that it became apparent how many mistakes could occur. Each one of us naturally defended our own laboratories, and this did nothing to clarify the issue.

So I would strongly urge you to be as objective as possible with your own laboratory; do not warn your technicians that controls are going to be run. Simply put unknowns in the hopper and over a period of weeks and months find out to your chagrin the error of your ways. I think that any figure less than 5 percent is suspicious, because the methods over a long period simply aren't more reliable than that, nor is the human being that reliable.

Another thing that has become increasingly apparent is that you cannot lump all people together according to the variability of their cholesterols. Most people, who have had enough experience, would agree that there are some so-called normal people who have wide swings in their cholesterols, others who exhibit extraordinary stability. What is a control period for one person need



not necessarily be a control for the next. Currently, the whole question of how to study cholesterol levels deserves the white of an egg dropped into it.

The next problem that arises is the degree of reduction of cholesterol level that might be thought to be of value in the prevention of atherogenesis because in the last analysis you face the great emotional problem of suggesting that this drug might be useful in preventing heart attacks. This is most difficult, of course, because nobody, so far as we know, knows the amount of reduction that would be necessary to prevent a heart attack, if indeed it does so. One must use terms like "significant," even "confidence levels" with circumspection, because I am not sure that any of us are confident that if we reduce the blood cholesterol 25, 35, or 40 milligram percent that we will, in fact, reduce the incidence of myocardial infarction.

I would suggest that we hold our fire on the question of tolerance. From a number of the slides we saw it looked as though tolerance was beginning to develop. This has been the bugbear of so many drugs. I know in the example of the anti-hypertensive agents, most of them—if you study them long enough—elicit tolerance, usually just after you have written that they don't. So I would be very careful in accepting the notion that tolerance never occurs. I should suppose that the body would outsmart you, as it usually does, and become refractory as an adaptation. It might adapt by synthesizing more cholesterol as a compensation to overwhelm the blocking agent.

One of the startling things to me during the entire conference was that evidence of serious toxicity was not forthcoming. I had become rather sensitized because the study we made with benzmalacene showed that bromsulphalein retention was occurring in my own liver. I was not amused. I am assured by all of my friends that this is an entirely reversible process. I have not talked to my enemies.

Now, if one includes—and I don't think one currently should—the appearance of desmosterol as evidence of toxicity, this could be one of the most important things coming out of the meeting. I am greatly intrigued by the suggestion that the block to biogenesis is just before the conversion of desmosterol to cholesterol. Of course, there may well be other steroids which accumulate as well. We cannot assume currently that this part of the problem is all solved, and in this I think Drs. Steinberg and Avigan would agree. Whether these intermediates are atherogenic or not is one of the critical questions. We are not so sure as we used to be about the lack of atherogenic qualities of all steroids other than cholesterol. This vista contains many unsolved problems, and we will wait with great interest to see the outcome.

I suppose that one should never tire of stressing the metabolic differences between man and animals. The better results in animals with MER/29 and the less good results in man is a case in point. Heaven knows what this is due to, but there it is. Fortunately, the hypocholesteremic action in man seems clear enough.

I would suggest that in view of the widespread influence of endocrine secretions on steroid metabolism that one should be very careful to watch for the slightest aberrations because over the years these could lead to trouble. On the other hand, so far there is no clear evidence that such changes have appeared yet, and we can only hope that they do not.

I would also suggest that the question of the importance of sterols for permeability in the cellular membrane is one of great importance. For instance, a study might be made with the red blood cell as one of the more useful membranes to see what happens over the long pull when you interfere with sterol synthesis.

Angina—well, we have all been through the cure of angina so many times that we have become cynical, I'm certain. I think all of you remember, as Dr. Rosenman pointed out, that heparin just a few years ago was curing angina. All I can say is, it's probably very fortunate that God cures most angina. The electrocardiographic evidence needs much more careful study before it can be weighed as evidence for the drug.

I think it is clear that this drug is an important one. Whether it prevents heart attacks and atherosclerosis is one thing; but that it is important it seems to me there can be no doubt. It must of necessity compete in the long run with other methods for reducing blood cholesterol. It is fair to say that it, so far, is very much in the running. It has already brought to our attention important changes in mechanism which may have far-reaching consequences in understanding of steroid metabolism as well as possibly—and I emphasize possibly—the mechanisms of atherogenesis. Certainly, a sophisticated audience of this



sort is well aware that by no means all people believe cholesterol is the primary genetic agent involved in atherogenesis.

I can only hope that this drug will join the incense and myrrh group of drugs rather than the mal-de-mer.

In closing, I would like to express my, and I think your, genuine appreciation to The Wm. S. Merrell Company and particularly to President Getman and Dr. McMaster and his associates in putting on what seems to me to have been a very objective and intellectually high-level symposium. The analysis of a vitally important problem has been furthered by the contribution, I think, of an important substance. Thank you.

The Chairman: Thank you, Dr. Page, for your very excellent discussion.

I would like to close this very interesting symposium with one additional comment. If more drugs had been subjected to this kind of review early in their life histories, many mistakes and millions of dollars would have been spared physicians, patients, and pharmaceutical companies. This is the way a new drug should be reviewed, critically and without bias, so that new directions for investigation and evaluation may be pointed out.

*(End of reprint of Proceedings of 1958 Princeton Conference)*

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July 21, 1959. William S. Merrell Company files a New Drug Application under the trade name MER/29.

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September 14, 1959. Food and Drug Administration notifies the firm that the application is incomplete since the data submitted shows a low margin of safety for a drug which would receive chronic use. FDA also suggests that a 1-year oral study in rats and a 3-month oral study in dogs be run, and that in both animal groups one dosage level be selected to produce toxicity.

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*(An Illustrative Letter as Regards Private Consultation With AMA Council on Drugs)*

January 7, 1960.\*

CHRISTIAN WINGARD, M.D., Assistant Secretary, Council on Drugs, American Medical Association.\*\*

LAURANCE W. KINSELL, M.D.,

Director, Institute for Metabolic Research, 2701 Fourteenth Ave., Highland-Alameda County Hospital, Oakland, Calif.

DEAR DR. KINSELL: We should greatly appreciate your serving as a consultant and thereby assisting the Council on Drugs, in its evaluation of the cholesterol biosynthesis inhibitor designated MER/29 by The Wm. S. Merrell Company.

There is enclosed a collection of data, reprints, and summaries of published papers, supplied by the manufacturer. You will render invaluable assistance to the council by reviewing this material and providing us with your assessment and evaluation of the drug, based on the available evidence. We should also appreciate any comments on any personal experience you may have had with MER/29; however, we are *not* requesting that you test this product clinically. Your comments are especially invited concerning the adequacy of the laboratory and clinical data, usefulness, indications and contraindications, and toxicity of the drug; comparisons with other similar drugs would also be helpful.

Your comments will be referred to the members of the council and will serve as a basis for the preparation of a monograph on MER/29 for publication in the Journal of the American Medical Association and subsequently in New and Nonofficial Drugs.

Although you are probably aware that the council abandoned its Seal-Acceptance procedure in 1955, perhaps you will forgive our restating the council's present policy. The council's statements on drugs no longer imply approval, endorsement, or acceptance. Each drug description is designed to provide fair

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\*The date appears first in connection with each exhibit, letter, and other document, as mentioned on p. 824.

\*\*The source appears second, likewise in flush left position.



comment and criticism based on available evidence, whether or not this is considered adequate to establish usefulness. Thus, the monographs may be either favorable or unfavorable.

If it should be inconvenient for you to review the enclosed data and send us your opinion, may we ask that you refer the material to one of your colleagues whom you consider qualified to make such an assessment.

The data need not be returned. However, we should like to request that the unpublished portion of the data be regarded as confidential and that it be destroyed or otherwise prevented from falling into other hands, when you have completed your review.

A postage-free envelope is enclosed for your convenience in transmitting your reply.

May we thank you in advance for your attention to this matter, realizing that we are requesting a not inconsiderable expenditure of time and effort on your part. We shall be most appreciative of your assistance.

Sincerely yours,

CHRISTIAN WINGARD, M.D., *Assistant Secretary.*

January 29, 1960.

LAURANCE W. KINSELL, M.D.

2701 14TH AVE.,  
Oakland, Calif.

CHRISTIAN WINGARD, M.D.,  
*Assistant Secretary, American Medical Association,*  
535 North Dearborn St., Chicago, Ill.

DEAR DR. WINGARD: With regard to your letter of January 7th and the enclosed material relating to MER/29, my thoughts are as follows:

1. MER/29 is an extremely interesting compound which deserves careful evaluation, both from a fundamental and clinical standpoint.

2. On the basis of the material thus far reported, it would seem to me that there is as yet very inadequate evaluation of the effects of this material upon liver function in individuals who have received it over appreciable periods of time. Since the major site of action is in the liver, it would be particularly desirable to have this type of evaluation before considering making the drug available for general clinical application. I would recommend that such studies be carried out by a number of different investigators, and that until this work is completed, the drug should be made available only to well qualified clinical and fundamental investigators.

Sincerely yours,

LAURANCE W. KINSELL, M.D.

(Internal Agency Document)

February 23, 1960.

DIVISION OF PHARMACOLOGY, FOOD AND DRUG ADMINISTRATION

New Drug Branch

Attn: Dr. Talbot

Division of Pharmacology

Triparanol Capsules, MER/29 (Wm. S. Merrell Co.) NDA 12-066

The additional toxicity data submitted by Merrell have been reviewed. The original toxicity data submitted for rats included a 3-week study at 40 milligrams/kilogram/day, a 3-month study at 25 and 50 milligrams/kilogram/day and a 6-week study at 75 milligrams/kilogram/day. The consistent finding in these studies was a marked decrease in weight gain.

The new data include a 9-month study in rats administered 3 and 10 milligrams/kilogram/day in the diet. No significant effects attributable to drug administration were observed with respect to weight gain, food consumption, hematology and pathology. In addition, rats were administered 20 and 40 milligrams/kilogram in the diet for 3 months. Reductions in weight gain of 15-20 percent in the 20 milligrams/kilogram dosage group and 32-40 percent in the 40 milligrams/kilogram dosage group were observed. The food con-



sumption paralleled the body weight response (15 percent less at 20 milligrams/kilogram and 36 percent less at 40 milligrams/kilogram). If the concentration of the drug in the diet was not increased to compensate for the reduced food intake, the actual dosage given to the animals would have been considerably less than stated. The relative weights of the liver, heart and adrenals were significantly increased over control values at both 20 and 40 milligrams/kilogram in both the male and female rats. In the rats receiving 40 milligrams/kilogram, 8 out of 20 animals had grossly visible opacity of the cornea at the end of the 3-month study. There was also an associated conjunctivitis. Several drugs (e.g., more potent narcotics, certain insecticides) have caused this effect in either mice or rats acutely and has been reversible. However, we would consider this observation in a chronic study of a more serious nature and something to be concerned about. Histologic examination of the cornea revealed inflammatory changes.

The company states that an evaluation of the dog studies is difficult because of concomitant, spontaneously occurring diseases in their dog colony with four cases of distemper being diagnosed. Whether the effects described below were due to poor animals, distemper or drug administration would be hard to evaluate. However, it is our opinion that the drug is producing some of the observed effects. Three dogs were administered 10 milligrams/kilogram of MER/29 for 4 months. No effect on the peripheral blood counts were observed and in general the weights of the animals remained constant. However, both of the male dogs in the study showed some inhibition of spermatogenesis upon histological examination.

Six dogs were administered 25 milligrams/kilogram for 6 months. Three of the males dogs died early in the study. They indicated that one died of congestive heart failure secondary to heart worm infestation, and the cause of death of the other two was undetermined due to post mortem changes. Two of the three dogs surviving the study had distended gall bladders but the organs were normal upon histologic examination. In the one male dog surviving the study there was no indication of an effect on spermatogenesis.

Five dogs were administered MER/29 for 3 months at a dosage of 40 milligrams/kilogram/day. Three of these animals died within 6 weeks after the start of the experiment. With respect to the cause of death, they indicated that in the first dog the changes in the liver and massive interstitial hemorrhage are changes consistent with canine viral hepatitis. They indicated that the cause of death of the second animal could have been due to either the bronchial pneumonia, the acute hemorrhagic pneumonia, or hepatic failure secondary to the necrosis and inflammatory response of the liver. Gross examination of the third animal revealed the liver dark and mottled and the entire intestinal tract edematous and hemorrhagic. Histological examination of the liver showed a general ballooning of the parenchymal cells, some disruption of the hepatic cord, areas of coagulative necrosis, and extensive inflammatory response. They indicated that the most likely cause of death in this animal was hepatic failure secondary to chronic inflammatory response and cirrhotic changes in the liver.

In the two dogs surviving the study, no effect was seen in the hematological studies. Cross examination revealed the gall bladders distended and in one of the animals the liver was mottled and there was extensive mesenteric lymphadenopathy. The urinary bladder was very thick and purulent material was present in the urethra. Histological examination revealed some changes in the liver and a reduction in the number of mature spermatocytes in the seminiferous tubules, and a paucity of spermatozoa in the vas. The lymph nodes showed simple hyperplasia.

As you knew the clinical dose of this drug is 250 milligrams daily or about 4-5 milligram/kilograms. We would conclude on the basis of the animal toxicity studies conducted that there is little margin of safety with this drug. Certain changes seen in these animals appear to be due directly to the toxic action of the compound. The inhibition of spermatogenesis in the dog, the effect on the cornea in the rat, the marked reduction in weight gain in the rats at relatively low dosages, all the liver changes, and the deaths of the animals lead us to conclude that this compound is producing toxic effects in the animals at relatively low dosages. We are not convinced that the changes observed in the dogs were due to distemper or hepatitis, particularly since the inclusion



bodies characteristic of these diseases, particularly viral hepatitis, were not mentioned.

We are seriously concerned about the safety of the use of such a drug for reducing blood cholesterol. In the first place, we don't know if a reduction in blood cholesterol really helps the patient. To use a compound that is potentially toxic to produce such an effect is highly questionable. Besides the specific toxic potential of the drug itself, we are worried about the effects of a build-up of desmosterol in the blood. What are the long-term effects of this material in the blood stream? It is certainly an abnormal condition. We do not know that perhaps desmosterol is itself atherogenic?

On the basis of the results of the studies conducted so far, we cannot see the necessity for any further animal studies. On the basis of the studies seen so far we would be opposed to this type of compound being marketed for reduction of serum cholesterol. Of course, the final evaluation of safety must be in the clinical studies. Before we release this drug for general distribution, it is our view that the company should submit results of well controlled extensive clinical studies in which the individuals have received the drug for periods of several years.

E. I. GOLDENTHAL.

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(See official Food and Drug Administration chronology for additional key dates preceding approval of the New Drug Application.)

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April 19, 1960. Food and Drug Administration notifies the William S. Merrell Company that its New Drug Application is made conditionally effective, and that the approval is based solely on evidence of the safety of the drug.



(Promotion Binder Sent to Physicians)

Post-April 1960 (undated).  
Wm. S. MERRELL CO.

# memo

*The Wm. S. Merrell Company, Cincinnati 15, Ohio*

*Department of Medical Research*

MER/29 is now available for your prescription. For the first time it is possible for you to control excess body cholesterol by inhibition of its biosynthesis. This unique action of MER/29, together with data on its safety and clinical benefit, is reviewed in full in the enclosed reference material.

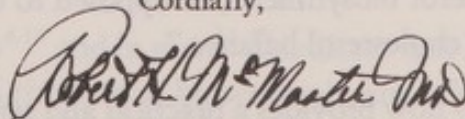
This manual summarizes the discovery and laboratory investigations of more than 4 years, and abstracts the many clinical papers that attest the value of MER/29 in the hands of clinicians throughout the country. The Princeton Conference on MER/29, with Doctor Irving S. Wright as Chairman, summarizes much of this experience, and the précis contained with this mailing can serve as a highly valuable guide to use of this new product in your practice. Proceedings of this conference were issued as a supplement to the May issue of *Progress in Cardiovascular Diseases* and may be reviewed *in toto* there.

MER/29 opens an entirely new avenue to management and understanding of hypercholesterolemia and conditions thought to be associated with it, such as coronary artery disease. You will note that concurrent clinical benefits have accompanied MER/29 therapy in some patients with signs and symptoms of atherosclerotic vascular disease. How consistent these benefits are remains undetermined at this time.

Because MER/29 has been so widely proclaimed an "important drug," it is our intention to keep you fully informed of all aspects of its use. This binder will serve as a convenient repository for all information currently available and expected in the months ahead. From time to time as new published evidence of MER/29 activity and application is available, this will be forwarded to you through your Merrell representative or by mail. We believe that your continuing review of all published experience with this drug can best help you evaluate the role this unique new agent can play in your practice.

If you have any questions or if we can be of any service to you, please do not hesitate to write us.

Cordially,



Robert H. McMaster, M.D.



# Basic Data on MER/29

(brand of triparanol)

MER/29 is a cholesterol-lowering agent which offers an entirely new avenue to the problem of hypercholesterolemia. Because MER/29 is a biochemical inhibitor of cholesterol biosynthesis, it provides a fundamental approach, as these unique features indicate:

MER/29 is the first agent to inhibit *excess* cholesterol formation within the body

MER/29 is the first agent to lower *tissue* as well as serum cholesterol

MER/29 has *specific* action; it has not shown any interference with other vital biochemical processes to date

MER/29 is virtually *nontoxic* and remarkably free from side effects even on prolonged clinical use

MER/29 is the first agent to provide a simple, practical means of lowering cholesterol levels—*no special diet* required.

In almost two years' critical evaluation by eminent clinical investigators, MER/29 has aroused intense interest, not only because of its unique cholesterol-lowering action, but also because of concurrent clinical benefits observed by a number of the groups studying MER/29 in clinical trials. These benefits did not invariably occur, but in some patients there was reduction in frequency and severity of anginal attacks, reduction in nitroglycerine dependence, reversal of ECG abnormalities both at rest and following exercise-tolerance-induced changes, and improved sense of good health and well-being. In addition, a few patients with peripheral vascular disease who were included in these studies reported subjective improvement while on MER/29 therapy. These results have led some investigators to theorize that MER/29 may reduce the cholesterol content of human blood vessels, including the coronary arteries, and actually improve the adequacy of coronary circulation.

The significance of this basic development in the management of hypercholesterolemia and conditions thought to be associated with it can scarcely be overestimated. In a recent 10-year survey by the National Heart Institute into the problems of cholesterol and atherogenesis, it was stated<sup>1</sup>:

"Studies of lipid metabolism have stressed the importance of cholesterol biosynthesis, as opposed to cholesterol intake, in determining cholesterol balance."

MER/29 now provides a practical and safe method of controlling cholesterol biosynthesis in man. Besides its immediate usefulness in the prophy-

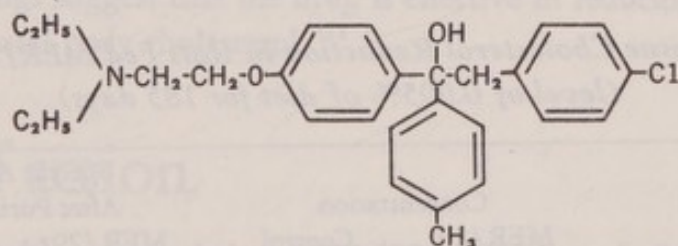


laxis and treatment of conditions suggesting the value of cholesterol reduction, MER/29 is the first clinically available cholesterol-lowering agent offering new insight into cholesterol metabolism.

## Discovery of MER/29

MER/29 was not a chance discovery, but the result of a four-year program planned with the objective of developing a biochemical approach to the problem of excess cholesterol. This program, under the direction of Dr. Thomas R. Blohm, Head of the Department of Biochemistry of the Merrell Research Laboratories, began in 1952 with a thorough study of the mechanisms of the biosynthesis of cholesterol. This study suggested the paths for the Organic Chemistry Department to take in new syntheses, and then the development of a new *in vivo* method for testing compounds of promising configuration.

MER/29, synthesized by Frank P. Palopoli<sup>2</sup> in 1956, is a new chemical entity, triparanol, 1-[*p*-( $\beta$ -diethylaminoethoxy) phenyl]-1-(*p*-tolyl)-2-(*p*-chlorophenyl) ethanol, with the structure:



MER/29 is a white crystalline solid, m.p. 102-4° C., molecular weight 437.98. It is soluble in alcohol, insoluble in water, and slightly soluble in olive oil. Results of the very first assay of this compound showed it to be a potent anti-cholesterol agent.

As the formula indicates, MER/29 is not a hormone, not a vitamin, not an unsaturated fatty acid, nor a plant sterol. It is neither an estrogen nor an estrogen antagonist.<sup>3</sup> Extensive chemical studies involving all possible rearrangements and modifications of this compound, and studies of its component parts, show that MER/29 is an entity whose potency, lack of toxicity and other unusual pharmacological properties appear to be peculiar to this unique molecule.<sup>3</sup>

## Mode of action

Radioisotope studies in animals<sup>4-10</sup> and in man<sup>11,12</sup> indicate that MER/29 produces a partial inhibition of cholesterol biosynthesis, and affects tissue as well as serum cholesterol.



Since acetate is the starting substance for biosynthesis of cholesterol, rats were injected intraperitoneally with sodium acetate-1-C-14, following ten days' administration of MER/29, and sacrificed 30 minutes after injection.<sup>4</sup> Animals which received only the labeled acetate served as controls. Tissue analyses showed that rats given the high dose of MER/29 (25 mg./Kg./day) incorporated only 5.6 per cent as much acetate into liver cholesterol as did control rats; those on the lower dose of MER/29 (7.5 mg./Kg./day) incorporated 25 per cent as much acetate as controls. In the intestine, results were qualitatively similar.<sup>5</sup> It was found that MER/29 does not affect acetate metabolism *per se*, but specifically blocks cholesterol synthesis at a late stage.

In further studies<sup>13,14</sup> it was determined that in rats the specific inhibition in various tissues resulted in a lowering of cholesterol levels in plasma by 62%; in erythrocytes 40%; liver 40%; lung 33%; skeletal muscle 27%; aorta 21%. Levels of brain and adipose tissue, however, were not significantly affected. Similar results have been obtained in an experiment in which dosage of MER/29 was based on a percentage of the diet<sup>7</sup>:

*Tissue Cholesterol Reduction in Rats Fed MER/29*  
(level of 0.005% of diet for 185 days)

	Concentration		Specific Activity After Purification	
	MER/29	Control	MER/29	Control
Liver	1.94	2.32	3,520	14,700
Kidney	3.82	4.82		
Intestine	2.05	2.68		
Adrenal	23.5	51.8		
Red cells	1.29	1.64		
Plasma	0.53	0.51		
Carcass	2.04	2.55		
No. of rats	6	4		



## Effect of MER/29 on body cholesterol metabolism in man

Clinical radioisotope studies on conversion of acetate to cholesterol by Hollander and Chobanian<sup>11</sup> indicate not only that MER/29 inhibits endogenous cholesterol in man, but that the total body pool (tissue and serum) of this substance is affected.

In this study, the conversion of acetate to cholesterol was decreased by 36% during MER/29 treatment. The average reduction in the peak activity of cholesterol in four human subjects was 31%.

Results of this study led Hollander and Chobanian to conclude that the apparent "miscible body pool of cholesterol was reduced from 184 Gms. in the control period to 100 Gms. during MER/29 administration.... These findings suggest that the drug is effective in reducing both serum cholesterol and body cholesterol."<sup>11</sup>

## Site of action

Early studies<sup>4,5</sup> suggested that MER/29 inhibition of cholesterol biosynthesis probably occurs at a stage following formation of the 3-beta-hydroxysteroid nucleus, and does not involve activation or oxidative metabolism of acetate.

In later studies the site of action has been further narrowed down to a



step after the formation of zymosterol, which has now been identified by several investigators<sup>6-9,15,16</sup> as the last stage before formation of cholesterol. The intermediate isolated in greatest quantity (and the only one so far identified) is desmosterol (24-dehydrocholesterol).

Bloch<sup>18</sup> has suggested that desmosterol might be a product of cholesterol metabolism rather than, or as well as, a precursor. The nature of this compound is now under study. It seems obvious, from both animal and clinical records to date, that desmosterol is not a toxic substance, since no adverse effects of MER/29 administration have been reported in treatment periods up to 14 months. Indications from animal experiments are that precursors of cholesterol in MER/29-treated animals are excreted in the bile.<sup>19</sup>

## Pharmacological studies

### *Toxicity: Animal Studies*

MER/29 is virtually nontoxic. Given intraperitoneally to mice, the LD<sub>50</sub> is 1600 mg./Kg., and to rats, over 2000 mg./Kg.<sup>20</sup> Orally, the LD<sub>50</sub> in both mice and rats is in excess of 2000 mg./Kg. The chronic toxicity of MER/29 has been studied in the rat, the dog and the monkey. Dosages used have varied from 3 mg./Kg./day (approximating, on a weight basis, the recommended dosage in man) to 25 mg./Kg./day. On the highest dosage, the only significant change from controls was in weight gain (6% below controls in males, 16% below controls in females), probably ascribable to interference with appetite.

### *No Hepatic Damage*

In a large number of animals (rats) put on dosages of MER/29 up to 5.0 mg./Kg./day for 30 days, total liver lipids remained within normal range, though cholesterol content of the liver was reduced. Further, when MER/29 or its metabolites were removed from the total unsaponifiable fraction, the noncholesterol unsaponifiable matter in the liver became the same for MER/29-treated rats and for pair-fed controls. This finding makes accumulation of cholesterol precursors in the liver highly unlikely, at least in the rat.<sup>22</sup>

In a subsequent study, it was also found that, while MER/29 significantly reduces cholesterol content of the bile, it does not affect 24-hour bile volume.<sup>22</sup>

### *No Effect on Adrenal Function*

A most important observation, from a research as well as medical point of view, relates to reduction of adrenal cholesterol by MER/29. In spite



of this, it was found that MER/29 has no effect on adrenal steroid *production* at all, as indicated by tests on monkeys as well as rats (normal plasma corticosteroid levels, urinary steroid levels, plasma corticosteroid response to ACTH).<sup>20-22</sup>

To summarize other hormonal studies briefly: MER/29 has no effect on pituitary, ovary or estrogen target organs in female mice, rats or monkeys; no effect on pituitary, testes and androgen target organs in adolescent or mature male rats.<sup>21,22</sup>

### *Long-Term Experimental Study*

In long-term study,<sup>22</sup> monkeys were paired in accordance with age and weight, and the treated animals were given MER/29 for periods ranging from 7 months (at 40 mg./Kg./day) to 16 months (on 20 mg./Kg./day) —or from 5.5 to 11 times the recommended daily dosage for man.

Treated and control animals showed similar values for these periods in hemoglobin, erythrocytes, hematocrits and leucocytes. Morphology of the peripheral blood and of bone marrow sections of treated animals showed no divergence from the controls.

Histological examinations were made on the following tissues of MER/29-treated monkeys: brain, cord, pituitary, heart, aorta, lung, esophagus, stomach, small and large intestine, liver, pancreas, spleen, kidney, urinary bladder, testes, seminal vesicles, prostate, adrenals, thyroid, bone marrow and lymph nodes. The only variation from normal was a depletion of lipids in the adrenals, as would be expected and, at autopsy, a slight darkening of the adrenals.<sup>22</sup> Adrenal function studies showed no change from normal response to ACTH, as measured by plasma and urinary 17-20 dihydroketosteroids,<sup>20</sup> and there was no detectable change in the animals' response to stress or in survival rate after stress.<sup>22</sup>

## Clinical safety

At the Princeton Conference on MER/29 in which many of the eminent scientists and clinical investigators who had been studying this new agent participated, Dr. Irvine H. Page remarked in his summation:

"One of the startling things to me during the entire conference was that evidence of serious toxicity was not forthcoming."<sup>23</sup>

The investigators attending the Princeton Conference reported on almost 500 patients treated with MER/29, some for more than a year. Three of these clinicians mentioned side effects which included one patient with headache and nausea;<sup>24</sup> two with nausea;<sup>24,25</sup> one with vertigo;<sup>25</sup> two with rash and dry skin.<sup>26</sup>



### *Studies on Liver Function*

Since many experimental agents used to lower cholesterol have proved toxic to the liver, the effect of MER/29 on this organ was a primary concern. To date, all tests made by numerous investigators<sup>12,24,26-30</sup> (BSP, cephalin flocculation, prothrombin time, alkaline and acid phosphatase, thymol turbidity, etc.) have given essentially negative results. The tests included those in a number of patients who had been on MER/29 therapy for more than a year. These clinical findings confirm the remarkable freedom from hepatic damage seen in animals even when huge dosages of MER/29 were used. As a precautionary measure, however, periodic liver function tests of persons on long-term MER/29 therapy are advised.

### *Studies on Adrenal Function*

The possible effect of MER/29 on adrenal hormone production and function was an equally important question, since MER/29 administration reduces adrenal cholesterol. Careful studies by several investigators<sup>29,31</sup> indicate that MER/29 has no adverse effect on adrenocortical function, as determined by excretion of 17-ketosteroids. In a representative study, no significant changes in the resting levels of the ketosteroids nor in responsiveness following stimulation with corticotrophin were observed after six weeks' therapy with 750 mg./day of MER/29 (three times the recommended daily dose).<sup>31</sup>



### *Long-Term Clinical Studies*

Investigation of MER/29 at the Mayo Clinic<sup>27</sup> included studies of three patients on high dosages (3.0 Gm., 3.0 Gm., and 1.0 Gm. per day, respectively) for 14, 4½ and 4½ months, respectively. "No toxic symptoms were reported except that one patient complained of dry skin; whether or not this was related to MER/29 therapy is not clear. No other abnormal physical findings were noted. Laboratory tests included urinalysis, enumeration of erythrocytes and leukocytes, differential leukocyte count, enumeration of platelets, determination of hemoglobin, erythrocyte sedimentation rate, blood urea, blood sugar and blood bilirubin, and sulfobromophthalein test of liver function. These tests were performed prior to MER/29 therapy and after several (5 to 8) months of therapy. No toxic effects were observed in these patients. One of these three patients was a woman aged 28 who ingested 3.0 Gm. of MER/29 daily for 4½ months. She noted no change in her menses, and she became pregnant approximately 2 months after MER/29 therapy was discontinued. She had a normal pregnancy and delivered a normal infant.... As far as toxicity is concerned, I think that I can say that in spite of the large doses we have used, which amount to anywhere from 25 to 50 milligrams per kilogram, that we had no real evidence of toxicity, and I saw these patients frequently over a period of months." In addition to the usual tests, Kountz<sup>30</sup> ran tests of thyroid function, electrocardiograms and chest X-rays, and vaginal cytology was done in women. No serious toxic or side effects were noted in his 103 patients, but one postmenopausal woman reported vaginal bleeding for one day after having been on the drug for four months.<sup>30,32</sup> It has been suggested that MER/29 may potentiate estrogen which is already present in the body.<sup>33</sup> Two male patients reported decreased libido which lasted for only a few weeks.<sup>30</sup> There was occasional false positive albuminuria in some patients.<sup>30</sup>

MER/29 has no appreciable influence on blood clotting, whether or not anticoagulants are used.<sup>31,34,35</sup>

## Metabolism: absorption and excretion

To obtain information on the metabolism and fate of MER/29 itself, animals were given relatively enormous doses (25 mg./Kg./daily), and the accumulation and excretion of cholesterol precursors and of MER/29 were studied.<sup>19</sup>

The object of giving these enormous doses was to determine whether or not there was an accumulation of sterols—precursors of cholesterol



—when an extreme blockade of cholesterol synthesis was produced. On this dosage, cholesterol formation was only about 5 per cent or less of the formation rate in control animals. After 6 days' treatment, the rats were injected intraperitoneally with labeled d,l-mevalonic acid, a cholesterol precursor. Various studies then undertaken indicated both cholesterol and total unsaponifiable matter were reduced in plasma; in liver, lung and spleen, cholesterol was reduced, and unsaponifiable matter was either unchanged or reduced slightly. "Overall, therefore, cholesterol precursors do not appear to accumulate in sufficient quantity to make up the cholesterol deficit entirely."<sup>19</sup>

After oral administration of MER/29 to rats, about 30 per cent of the dose is excreted in the feces within 48 hours, and 7 per cent in urine. The material excreted in urine was not unchanged drug. It is likely that fecal excretion is via the bile since, in rats with bile fistula, 23 per cent of the oral dose is excreted in bile within 24 hours.<sup>19</sup>

## Clinical observations

### *Hypercholesterolemia*

Every investigator of MER/29 has reported reductions in cholesterol to a more or less marked degree. In an early study Hollander and Chobanian<sup>11</sup> reported cholesterol reductions averaging 48 mg. % in 42 of 50 patients. This represented reductions ranging from 20 to 110 mg. % (10 to 55%) from control values. The drop usually began in 5 to 10 days and became maximal in one to 6 weeks.\* Dosages over 250 mg./day (up to 750 mg./day) showed no appreciably greater effect, which helped establish the recommended daily dosage now used.<sup>26</sup> Kountz<sup>30</sup> reported somewhat smaller reductions in 75 private patients, only four of whom

\*In a later report, the authors revised this estimate of maximal effect to "after 2 to 8 weeks."<sup>12</sup>



failed to respond to MER/29 at all. In 19 the cholesterol went down 30-32%, but in the others the drop was 15-20%. However, he had this to remark:

"In some of these individuals we have been able to compare MER/29 with various other forms of therapy such as lecithin, niacin, estrogen and so forth, which had been used previously. We found that MER/29 is more efficient, more uniform in response, and had less undesirable side reactions than any of the other substances we have given."

Included in Kountz's series were an additional 22 hospitalized patients, some with one or more complications including advanced arteriosclerosis, hypertension, angina pectoris, diabetes mellitus, and cerebral arteriosclerosis with complicated cerebrovascular accidents. These have been reported on by Toro.<sup>32</sup> The average serum cholesterol level in these subjects before treatment was 340 mg.%. "At the end of the first month of MER/29 administration there was an average drop of 23 per cent in serum cholesterol; at the end of the second month, a 26 per cent drop; at the end of the third month, a 33 per cent drop." After the end of the fourth month, five of these patients started to show a rise, but when dosage of MER/29 was doubled (500 mg. daily) the serum cholesterol again dropped.

From the first<sup>11</sup> it was noted that cholesterol reduction on MER/29 therapy appears to be related to some extent to original values, i.e., patients with highest values usually show the greatest decrease. This has been confirmed in more extensive experience, as indicated in the table below which is a compilation of preliminary data from a number of investigators.

*Effect of MER/29 in Hypercholesterolemia*

	Number of Patients	Mean Cholesterol Level		Decrease in mg. %	Per cent Decrease
		Pretreatment	After MER/29		
Patients with cholesterol levels over 250 mg. %	463	324 mg. %	250 mg. %	74 mg. %	21.9%
Patients with cholesterol levels under 250 mg. %	113	216 mg. %	184 mg. %	32 mg. %	14.8%
All patients	576	303 mg. %	240 mg. %	63 mg. %	20.8%

Reporting after 14 months' clinical experience with MER/29, Hollander *et al.*<sup>12</sup> noted also that, in general after experimental discontinuance of MER/29 therapy, "it appeared that the longer the serum cholesterol



level [had been] kept down by MER/29 the longer it took for the serum cholesterol to return to control levels. In a few patients who were maintained on the compound for a fairly long time the serum cholesterol did not recover. It is not clear whether this type of response was spontaneous or was drug induced." On the other hand, several investigators have reported instances where the cholesterol level began to climb toward pretreatment levels during therapy, and did not then respond even to higher dosages. This would appear to be an occasional finding only; at the end of 14 months, Hollander *et al.* state, "At the present time we have no convincing evidence that tolerance to the drug is developing."<sup>12</sup> Gould,<sup>7</sup> who observed some decrease in inhibition of cholesterol biosynthesis in homogenates from livers of rats over a period of 9 days, remarked that he did not believe this represented an "escape" phenomenon, but "part of an adjustment to a lower but constant level of cholesterol in tissues." It might be noted that only 26 patients (out of the total of 576 so far fully reported upon) showed an increase in cholesterol levels on treatment with MER/29.

### *Familial Hypercholesterolemia and Familial Hyperlipemia*

Too few patients with familial hypercholesterolemia and familial hyperlipemia have so far been treated with MER/29 to permit any definite conclusions as to its value in these conditions. It was an early clinical impression that MER/29 alone gave equivocal or negative results in familial hypercholesterolemia. Estes<sup>27</sup> has reported, however, that "in the patients that I have had experience with, MER/29 has brought about some degree of reduction in the cholesterol, but that a combination of MER/29 and nicotinic acid seems to produce a more pronounced effect; that is, using a dose of nicotinic acid which is smaller than what we normally would use produces a similar effect in lowering cholesterol" when combined with MER/29 therapy.

Two patients with familial hypercholesterolemia, one with a myocardial infarction and the other with xanthelasma, were treated with MER/29 by Rosenman and Friedman.<sup>36</sup> In the latter case, serum cholesterol had varied from 284 to 374 mg./100 ml. during a pretreatment period of 22 months and was not affected by administration of corn oil or estrogens. During four months' administration of MER/29 there was a sustained fall from 300 to 246 mg./100 ml. but, the authors point out, this subject had shown a progressive reduction over a 30-month period. In the other patient, fluctuations were so marked before MER/29 administration that results could not be evaluated.

Frantz *et al.*<sup>6</sup> report observations on two siblings with familial hypercholesterolemia, treated with MER/29. In one there was a reduction of



24% in serum cholesterol (as calculated by a method designed to give separate calculations for cholesterol and desmosterol) which was more than replaced by desmosterol. In the other, there was a 38% fall in cholesterol, and only about 40% of this drop was replaced by desmosterol.

### *Atherosclerotic Heart Disease*

The unexpected concurrent benefits of MER/29 therapy in some patients with angina were noted in the earliest published clinical report on this new agent.<sup>11</sup> Similar observations have since been made by a number of investigators, and to date there are on record 29 patients who have shown objective improvement in ECG patterns both at rest and after exercise, 98 who have experienced subjective relief of angina (severity and frequency of attacks), and 126 who have reported a sense of well-being on MER/29 therapy. Many of these patients have greatly reduced dependence on nitroglycerine.

The mechanism of these clinical benefits is still a matter of speculation. One investigator<sup>29</sup> suggests that MER/29 may exert a vasodilating action, though pharmacologically this compound given in large doses produces only slight and transient vasodilating effects.<sup>21</sup> Another group questions this explanation and advances another theory<sup>11</sup>:

"The findings suggest that MER/29 may actually improve the adequacy of the coronary circulation....The slow, rather than the rapid, improvement in angina, and the unchanged blood pressure and pulse rate, do not suggest a direct vasodilating action."

Then, citing reduction of aorta cholesterol in animals, they add: "It therefore is conceivable that MER/29 may also reduce the cholesterol content of human blood vessels, including the coronary arteries."

Whatever the explanation, the effects of MER/29 in certain patients with angina has aroused wide interest, and a number of clinicians are now studying this phenomenon.

The first observation of improvement in angina was by Hollander and Chobanian<sup>11</sup> who noted "striking improvement in exercise tolerance as well as in electrocardiographic abnormalities during exercise in three of nine subjects who received it [MER/29] for from two to four months." Angina had been present in one of these patients for six years and in the other two for less than a year. An additional two patients "appeared to have a 40 to 60%-reduction in anginal attacks during treatment." When MER/29 therapy was withdrawn and placebos substituted, the anginal pain and abnormal ECG patterns reappeared in the three responsive patients.

Among Kountz's<sup>30</sup> patients there were 12 who had had severe coronary disease and 15 others with mild cardiovascular disease with essential hypertension, anginal pains and shortness of breath. Although he does



not go into detail about results in these patients, he notes that "Clinical improvement was observed and also was reported to us by patients. In some instances the anginal pain improved very much."

Corcoran<sup>37</sup> has reported on 5 patients with stabilized ischemic heart disease who were treated for 6 to 12 weeks with MER/29, 250 mg. daily, after 4 weeks on placebos. One patient's resting ECG "definitely improved"; another with fluctuatingly abnormal ECG at the outset "attained consistent normal responses to exercise" during MER/29 therapy. Nitroglycerine requirements decreased in 3 (in one, from 350-400 tablets each 2 weeks to 100-120, after 6 weeks on MER/29). All five patients volunteered that anginal attacks were less severe and voluntarily commented on an increased sense of well-being.

In 3 of 4 patients with ischemic heart disease, Corcoran<sup>37</sup> noted that MER/29 produced sustained improvement in exercise ECG's after some weeks of therapy.

Moyer's group at Hahnemann was among the first to evaluate MER/29,<sup>38</sup> and at the Princeton meeting they were able to report on 15 months' observation in 45 patients with coronary artery disease.<sup>26,39</sup> Among these were 16 with a history of frequent anginal attacks. "Fourteen of these spontaneously stated that their angina disappeared within 2 months of therapy."<sup>39</sup> Electrocardiographic studies "generally showed no significant changes during therapy" except for one man with a persistent coronary insufficiency pattern (ST segment depressions in multiple leads) who had "complete reversion to a normal tracing during MER/29 therapy with associated clinical improvement in his angina."<sup>39</sup> Lisan noted also that within the 15 months of therapy with MER/29 only 2 of the 45 patients had a recurrence of their coronary thromboses and only 1 died (cause undetermined). The two recurrences occurred shortly after a sudden rise in cholesterol to above normal levels. Lisan makes this observation: "It is our opinion that this drug reduced morbidity and mortality rates below those of control series during the first year following coronary thrombosis."<sup>39</sup>

Eighteen patients with angina "which was not already controlled by other drugs or other methods of therapy" were treated with MER/29 by Halperin.<sup>29</sup> Results were "very good" in 6, moderate in 2, and slight in 1. Some other patients thought they had improved but "didn't convince me of it." "I was rather conservative, I think," Halperin remarks on these evaluations. As an example of a "very good" rating, he cited the case of a 68-year-old man who was seldom able to walk two blocks without taking nitroglycerine. After a month on MER/29, this patient visited New York and climbed six flights of office stairs during an elevator strike, taking nitroglycerine only after four flights "although he didn't really



feel enough pain to do so, but he got a little worried." Another patient with "very good" response has been free of pain for about 5 months except "when he goes to see his son at an out-of-town college [and] carries a fifty-pound suitcase...up four flights..."

In discussing his results, Halperin noted that those patients who responded had had angina a shorter time than the others (average 2.9 years as opposed to 5.2 years) and fewer infarcts (average 0.8 versus 1.3), but changes in original cholesterol pattern and response to MER/29 were "identical" in the two groups. He also noted that all six of the patients who responded well showed marked improvement within two weeks, reaching a maximum in a month or six weeks.

In contrast to the investigators cited above, Russek<sup>40</sup> found that "administration of MER/29 in the dosage of 250 mg. daily to a total of 40 patients (26 with angina, 14 with ECG abnormalities) for a period of 3 to 5 months has not disclosed evidence of clinical or electrocardiographic improvement despite significant reduction in blood cholesterol levels in a large segment of these cases. Exercise-electrocardiographic tests using the Master technique failed to disclose consistent improvement in any of the 14 cases studied by this method." Russek notes that this was a "highly selected group of patients" who had been under observation for at least 2 years and some for as long as 10 years, and all were responsive to nitroglycerine.

### *Peripheral Vascular Disease*

The possibility that MER/29 might have beneficial effects in peripheral vascular disease was suggested in Kountz's report at the Princeton Conference.<sup>30</sup> He mentioned five patients, but described results in only one. This was a 71-year-old man who showed great and persistent improvement in ability to walk after MER/29 therapy, despite the fact that there were no objective signs (pulse, sweat test, X-ray) of change in his blood vessel condition.

Since this report, several clinicians are undertaking studies of the effect of MER/29 in peripheral vascular disease, but it is too early to offer any information beyond the suggestion that MER/29 may be tried in such cases.

### *Cerebral Arteriosclerosis*

To date there is no evidence that MER/29 is effective in preventing or relieving symptoms of cerebral arteriosclerosis, beyond a subjective improvement in well-being.



### Indications for MER/29

Indicated for patients with hypercholesterolemia and conditions thought to be associated with abnormal cholesterol metabolism. These include:

coronary artery disease

(angina pectoris and postmyocardial infarction)

generalized atherosclerosis.

### Caution

MER/29 is a new drug which inhibits cholesterol biosynthesis in the body. Since cholesterol plays an important role in the development of the fetus, the drug should not be administered during pregnancy.

Hypercholesterolemia and its associated conditions may require MER/29 therapy over a long period. MER/29 has been shown to be entirely safe in the periods the drug has been studied, but long-term or lifetime effects are unknown. Periodic examination of patients on long-term MER/29 therapy is therefore necessary.

While clinical liver damage has not been encountered, periodic liver function tests may be desirable until more long-term safety data are available. It should be noted that excretion of MER/29 or its metabolites may produce a false positive reaction for albuminuria.

NOTE: The specific site of action of MER/29 is now known to be between desmosterol (reported to be the last precursor in the synthesis path) and cholesterol. Although greater than normal quantities of desmosterol can be qualitatively shown in the livers and blood of animals and the blood of human beings treated with MER/29, reduction of total sterols suggests little, if any, accumulation. The significance of the presence of this substance is unknown and speculative.

### Compatibility with other cardiovascular therapies

MER/29 is not to be considered a substitute for measures ordinarily employed to control anxiety, hypertension, obesity, and other conditions associated with cardiovascular disorders. However, MER/29 is compatible with measures used in these disorders, including anticoagulants, nitroglycerine, and PETN.

### Dosage

One 250 mg. capsule daily, before breakfast.

### Supplied

In bottles of 30 pearl gray capsules.



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(Advertisement)

June 25, 1960.  
WM. S. MERRELL Co.<sup>30a</sup>

The Wm. S. Merrell Company  
announces the availability of

## MER/29

(brand of triparanol)

- ... the first cholesterol-lowering agent to inhibit the formation of excess cholesterol within the body, reducing both serum and tissue cholesterol levels.
- ... no demonstrable interference with other vital biochemical processes reported to date.
- ... convenient dosage: one capsule daily.
- ... toleration and absence of toxicity established by 2 years of clinical investigation.

The following pages report the clinical findings of therapy with MER/29 among patients with hypercholesterolemia and conditions thought to be associated with it, such as

coronary artery disease (angina pectoris, postmyocardial infarction)

generalized atherosclerosis

<sup>30a</sup> Journal of the American Medical Association, vol. 173, No. 8.



## THE FACTS ABOUT MER/29<sup>1-41</sup>

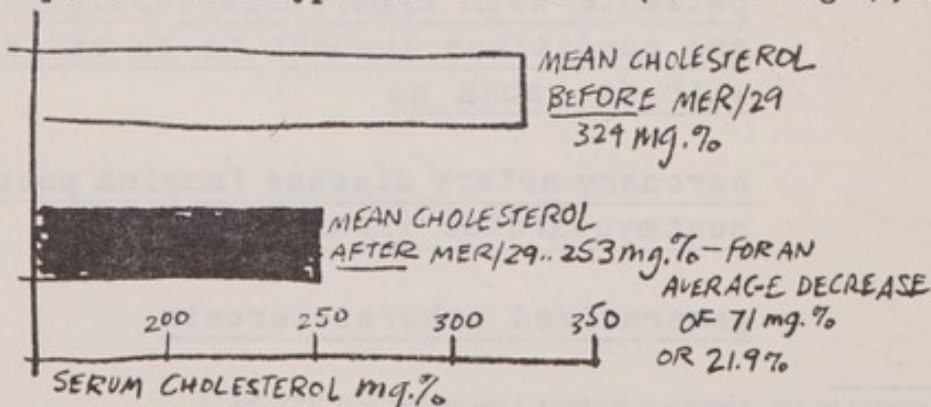
### Fundamental differences between MER/29 and other cholesterol-lowering substances

Cholesterol produced within the body—its biosynthesis—is about three times as great as that obtained from dietary sources. Before MER/29, no method of modifying total body cholesterol production was known. Those measures used to lower cholesterol (unsaturated fatty acids or other dietary measures, vitamins, plant sterols, hormones, etc.) succeeded only in modifying exogenous sources of cholesterol or accelerating its metabolism.

MER/29 is fundamentally different, since it inhibits cholesterol biosynthesis. Thus, MER/29 offers for the first time a method of controlling total body cholesterol content.

MER/29 reduces serum cholesterol in 89%  
of patients, with or without dietary restrictions.  
Radioisotope studies indicate reduction of  
tissue cholesterol as well.<sup>4, 5, 7, 30, 31, 34</sup>

High cholesterol levels are generally considered those above 250 mg. %. Here is a tabular summary of preliminary data on MER/29 therapy in 463 patients with hypercholesterolemia (over 250 mg. %).





Clinical studies show that cholesterol reduction usually begins within two weeks. Maximum effect is achieved in five to eight weeks, and is maintained as long as therapy is continued. The studies of Hollander, Chobanian and Wilkins and those of Kountz found that cholesterol levels were lowered by MER/29 therapy irrespective of diet.

Reduction of total body "miscible pool" of cholesterol has been confirmed by radioisotope studies. Hollander and Chobanian, for example, found that the apparent miscible pool of cholesterol was reduced from 184 Gm. in the control period to 100 Gm. during MER/29 administration.

Studies in animals on MER/29 have shown the following tissue changes: erythrocyte cholesterol levels reduced 40%; plasma cholesterol reduced 62%; liver reduced 40%; skeletal muscle reduced 27%; lung reduced 33%; aorta reduced 21%. Significantly, brain and adipose tissue remained unaffected during the period of observation.

#### Safety and toxicity studies<sup>5, 7, 10, 12, 17, 19, 21-24, 30, 32-34</sup>

MER/29 is well tolerated. In a recent analysis of 576 individual case reports, 165 had been treated with MER/29 for continuous periods in excess of a year. A number had received two to four times the daily recommended dose for as long as 16 months. Side effects were seldom seen, and the incidence of those reported (nausea, dermatitis) was too low for positive correlation with administration of the drug.

In no case has there been clinical indication of toxic effects on the function of any vital organ or system. It should be noted that excretion of MER/29 or its metabolites may produce a false positive reaction for albuminuria.



Clinical observations of MER/29 inatherosclerosis<sup>5, 7, 10, 12, 17-19, 21, 23-25, 28-34, 41</sup>

The lowering of high cholesterol levels is regarded by many as a desirable clinical objective. Moreover, a substantial body of medical opinion implicates elevated cholesterol as a contributor to coronary artery disease and generalized atherosclerosis. Since MER/29 lowers total body cholesterol, can it modify atherosclerotic conditions? While the ultimate answer must await the results of long-term clinical experience, preliminary observations were reported at...

The MER/29 Conference at Princeton

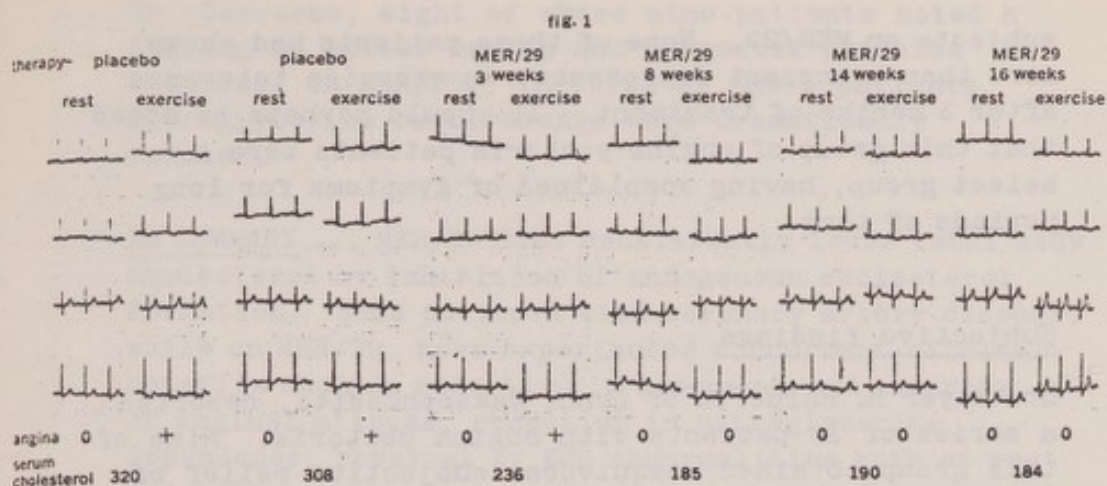
To help find the answer, 18 leading research teams met to discuss the relationship of MER/29 to cholesterol metabolism and atherosclerosis. The conference, moderated by Dr. Irving S. Wright, and summarized by Dr. Konrad E. Bloch, Dr. Robert W. Wilkins, and Dr. Irvine H. Page, was held last December at Princeton, New Jersey.

(The complete transcript of this conference is published as a supplement to the May, 1960, issue of Progress in Cardiovascular Diseases.)

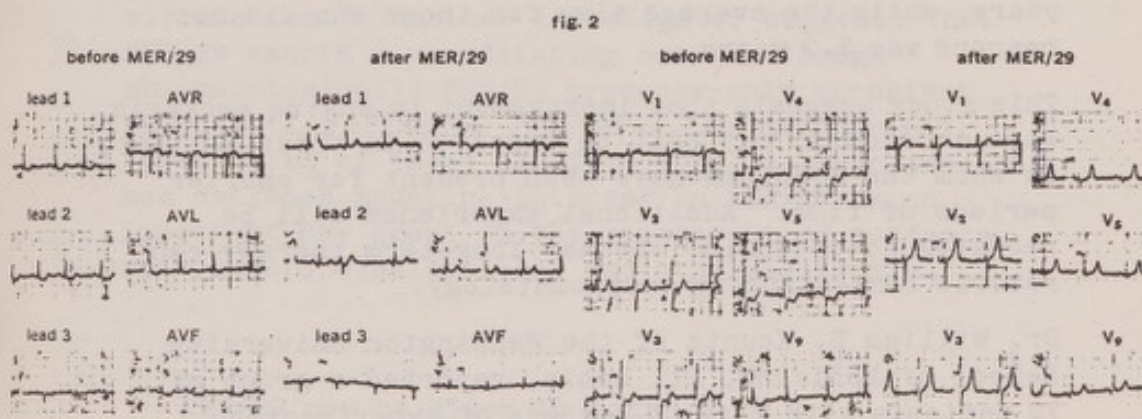
Objective findings

The team of Dr. William Hollander, Dr. Aram V. Chobanian, and Dr. Robert W. Wilkins at Massachusetts Memorial Hospitals, presented Fig. 1. It indicates a reversal of exercise-precipitated ECG abnormalities in a patient with angina pectoris during four months of MER/29 therapy. In all, they reported that three of nine patients showed reversal of exercise-induced ECG abnormalities after three months of MER/29 therapy.





Dr. Philip Lisan of Dr. John H. Moyer's group at Hahnemann Hospital presented Fig. 2. It also indicates reversal of ECG abnormalities in a patient with angina pectoris.



Dr. A. C. Corcoran of St. Vincent Charity Hospital, Cleveland, and Dr. Arthur Ruskin of University of Texas reported similar objective findings. All of these investigators noted that patients offered subjective evidence that they were experiencing a feeling of better health on MER/29 therapy, and that nitroglycerine dependence was diminishing.

Negative data were presented by Dr. Henry I. Russek of Staten Island, N. Y. He reported a study of exercise-electrocardiographic tests in 14 selected



subjects on MER/29. None of these patients had shown more than transient improvement in exercise tolerance after 3 months of treatment. It should perhaps be noted that this group of angina pectoris patients were a select group, having complained of symptoms for long periods of time.

#### Subjective findings

Dr. Meyer H. Halperin of Lynn, Massachusetts, reported a series of 18 patients with angina pectoris. Nine of this group obtained unequivocal subjective relief of symptoms after various periods of therapy with MER/29. An analysis of the duration of symptomatology in these patients indicated that response occurred more frequently when the ischemic heart disease had been present for shorter periods. Specifically, those who responded had had the condition for an average of 2.9 years, while the average time for those who did not respond was 5.2 years.

This study suggests that improvement in angina pectoris, when it occurs, may best be expected in those patients in whom the symptoms have been present for shorter periods of time. Additional experience will be required to determine whether long-term therapy can reverse long-standing symptomatology.

Dr. William B. Kountz of the Washington University School of Medicine, St. Louis, reported a group of 79 patients with varying degrees of hypertension, angina pectoris, diabetes, atherosclerosis or myocardial infarction. "Clinical improvement was observed and was also reported to us by patients. In some instances the anginal pain improved very much."

Similar subjective findings were also reported by



Dr. Corcoran, eight of whose nine patients noted a feeling of better health and increased exercise tolerance on MER/29. In three of these patients, nitroglycerine requirements were dramatically reduced.

IN SUMMARY ... MER/29 does consistently lower total body cholesterol by inhibition of endogenous cholesterol formation. Some patients with coronary artery disease, while on MER/29, have experienced concurrent clinical benefits such as reduction in frequency and severity of anginal attacks, reduction in nitroglycerine dependence, reversal of ECG abnormalities both at rest and following exercise-tolerance-induced changes, and an improved sense of good health and well-being.

The explanation of these clinical benefits is as yet unknown; however, several hypotheses have been advanced. One group speculates that MER/29 "may actually improve the adequacy of coronary circulation." Another investigator suggests that MER/29 exerts a vasodilating action, though pharmacologically MER/29 produces only transient vasodilating effects. Whatever the explanation, observation of these benefits among certain patients has awakened mounting interest in MER/29 as an important new agent in the management of patients with hypercholesterolemia and atherosclerosis.

MER/29 may be given to your patients with hypercholesterolemia and conditions thought to be associated with elevated cholesterol levels, including coronary artery disease (angina pectoris and postmyocardial infarction), and generalized atherosclerosis.



The Wm. S. Merrell Company  
announces the availability of

# MER/29

(brand of triparanol)

... the first cholesterol-lowering agent to inhibit the formation of excess cholesterol within the body, reducing both serum and tissue cholesterol levels.

**Indications:** May be used for patients with hypercholesterolemia and conditions thought to be associated with abnormal cholesterol metabolism. These include: coronary artery disease (angina pectoris and postmyocardial infarction), generalized atherosclerosis.

**Caution:** MER/29 is a new drug which inhibits cholesterol biosynthesis in the body. Since cholesterol plays an important role in the development of the fetus, the drug should not be administered during pregnancy.

Hypercholesterolemia and its associated conditions may require MER/29 therapy over a long period. MER/29 has been shown to be entirely safe in the periods the drug has been studied, but long-term or lifetime effects are unknown. Periodic examination of patients on long-term MER/29 therapy is therefore necessary. While clinical liver damage has not been encountered, periodic liver function tests may be desirable until more long-term safety data are available.

**Note:** The specific site of action of MER/29 is now known to be between desmosterol (reported to be the last precursor in the synthesis path) and cholesterol. Although greater than normal quantities of desmosterol can be qualitatively shown in the livers and blood of animals and the blood of human beings treated with MER/29, reduction of total sterols suggests little, if any, accumulation. The significance of the presence of this substance is unknown and speculative.

**Compatible with other cardiovascular therapies:** MER/29 is not to be considered a substitute for measures ordinarily employed to control anxiety, hypertension, obesity, and other conditions associated with cardiovascular disorders. However, MER/29 is compatible with measures used in these disorders, including anticoagulants, nitroglycerine, and PETN.

**Dosage:** One capsule daily, before breakfast. Each capsule contains 250 mg. triparanol.

**Supplied:** In bottles of 30 pearl gray capsules.

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(Internal Agency File: Memorandum of Conversation and Attachment<sup>30b</sup>)

July 19, 1960.

(No signature or direct indication as to name of preparing officer)

7/19/60

Dr. Pollack  
Conversation re MER-29  
June Amer. Diet Assoc.

Requested FDA to review MER-29  
Forest, Kendall  
Graef  
Kinsell

Seventy-two  
method

In hands of people who know how to use it.  
more toxic in young animals  
Has not been tested on young animals  
MER-29  
Evidence that Desmethyl is  
Oral contraceptive -  
Danger<sup>in</sup> in younger age group

Sterility - male animals sterile - rats  
MER-26 is oral  
contraceptive  
in rats

(Attachment)

## E. F. HUTTON MARKET LETTER

VICK CHEMICAL—VIK—(109 3/4-NYSE) 124 1/2-76

In a recent medical publication, Dr. E. Corday, the chief of cardiology at Cedars of Lebanon Hospital, Los Angeles, was quoted as saying at an AMA Symposium on Hypocholesteremic Drugs, "I have stopped using MER/29 after trying it on 75 patients. Two of these patients have developed hepatitis and two others have marked hair loss and dermatitis." Other panelists did not agree, but such statements retard wide spread use of this new drug. Since the Vick equity has risen sharply because of MER/29, some profit taking is anticipated.

R. I. R.

<sup>30b</sup> Memorandum of conversation with Herbert Pollack, M.D., by an officer of the Bureau of Medicine, Food and Drug Administration. The attachment to the hand-written memorandum of conversation (in the form of a quotation from a financial news letter) was apparently submitted by the visitor.



(Official agency file)

September 9, 1960.

AMERICAN DIABETES ASSOCIATION, INC.,  
1 East 45th Street, New York 17, N.Y.

WILLIAM H. KESSENICH, M.D.

Director, Bureau of Medicine, Food and Drug Administration,  
Washington, D.C.

DEAR DR. KESSENICH: We are writing to you on behalf of Dr. Herbert Pollack, chairman of our Committee on Food and Nutrition.

Dr. Pollack thought you would be interested in the following excerpt from the report of his committee, which was presented to the association's council (governing group) at its recent meeting.

"Your committee would like to call to the attention of this council the fact that MER/29 is now being advertised to the medical profession as a safe drug for the treatment of hypercholesterolemia. The evidence for this is still subject to a good deal of interpretation. It was the committee's opinion that any inhibition of enzyme activity in the body must be viewed over a long period of time before its safety factor can be fully assessed. There is considerable evidence that the precursor to cholesterol accumulates within the body due to this inhibition. The effect of the accumulation of this precursor is completely unknown. This subject is brought to the council's attention with the hope that it can be referred to the appropriate committee for more definitive study."

Incidentally, the council authorized the Committee on Food and Nutrition to continue its study of this matter.

Cordially yours,

J. RICHARD CONNELLY, *Executive Director.*



(An Illustrative Article in the Trade Press)

September 19, 1960  
DRUG TRADE NEWS<sup>27</sup>

DOCTORS TERM TRIPARANOL "IMPORTANT NEW DRUG" FOR TREATING HYPERCHOLESTEROLEMIA, HEART ILL

BOSTON.—Triparanol ('MER/29,' Merrell) is termed "an important new drug," useful in the treatment of subjects with hypercholesterolemia and coronary artery disease, by a group of Boston physicians writing in the September 3 *Journal of the American Medical Assn.*

Its importance is also noted by an editorial in the same issue of the *Journal*, which points out that one of the main objectives in the treatment of atherosclerosis with cholesterol-lowering procedures is to prevent and reduce the accumulation in the arterial wall of cholesterol, a major constituent of atheromas.

Dr. William Hollander and his associates at the Massachusetts Memorial Hospitals report that triparanol significantly reduced serum cholesterol in 71 of 89 subjects with and without hypercholesterolemia. The decrease averaged 45 milligram percent and ranged from 20 to 110 milligram percent, when the drug was given in a daily oral dosage of 250 milligrams. Increasing the dosage to 750 milligrams per day did not appear to have a greater effect, the doctors say.

REDUCTION IS PROPORTIONAL

While the drug depressed serum cholesterol in subjects who had normal as well as high levels initially, the reduction was, in general, roughly proportional to the height of the control serum cholesterol values, the investigators point out.

The fall in serum cholesterol usually occurred after five to 10 days of therapy and was maximal and sustained after two to eight weeks. It appeared that the longer the serum cholesterol was depressed by triparanol, the longer it remained depressed before returning completely to control levels, according to the physicians.

They undertook radioisotope studies of cholesterol metabolism to determine the mode of action of triparanol on serum cholesterol, and these indicated that the drug reduced the total sterol and cholesterol content of the body by decreasing the formation of cholesterol.

The fact that the reductions in serum cholesterol occurred within one week of treatment makes it unlikely that a change in the fat content of the diet was responsible for the hypocholesterolemic effect of triparanol, while the absence of significant weight changes argues against a reduced caloric intake as the cause of the hypocholesterolemic effect, the physicians comment.

The radioisotope studies suggest that the hypocholesterolemic effect of triparanol is due rather to a reduction in total body cholesterol, since the "miscible pool" of cholesterol, as calculated from the disappearance rate of intravenously administered C<sup>14</sup>-labeled cholesterol, was significantly reduced.

The doctors also studied the effects of triparanol on the Master two-step exercise tolerance test in 22 patients with angina pectoris. During the control period, 11 had reproducible anginal pain and abnormal electrocardiographic changes following a given amount of exercise. During triparanol therapy, however, three of these 11 failed to develop angina or ECG abnormalities after the same amount of exercise, but anginal pain and ECG changes reappeared when triparanol was withdrawn.

(Article in the Open—i.e., Professional Literature)

October 1960.  
ELMER E. COOPER, M.D.<sup>28</sup>

CLINICAL EXPERIENCE

I have given Triparanol to 51 patients of both sexes for from 1 to 9 months. Although most of them had overt atherosclerotic disease, five did not. The

<sup>27</sup> Vol. 35, No. 19, pp. 55, 83.

<sup>28</sup> "Decholesterolizing Measures With Clinical Observations on Triparanol (MER/29)," *Texas State Journal of Medicine*, vol. 56, No. 10, p. 778.



usual initial average oral daily dose was 500 milligrams. In three patients with hepatic disease, 750 milligrams was required to effect appreciable reductions. When effective responses were obtained, which occurred most often within 2 to 8 weeks, dosage was reduced to one 250 milligram capsule daily.

The average control cholesterol level was determined from three separate tests taken at weekly to monthly intervals. Many of these control values were the averages of long-range cholesterol determinations taken over months to years prior to treatment. Follow-up determinations during medication were made every 2 weeks. Analyses were done by the same technician using the Bloor colorimetric method. Patients' weights, smoking or drinking habits, dietary desires, physical exercise, and activities were unchanged. Those who were taking various medications previously were permitted to continue their programs unaltered.

Forty-seven of the fifty-one subjects had an appreciable reduction of serum cholesterol ranging from 26 to 195 milligrams per 100 cubic centimeters and percentage drops from 8 to 49 percent of control values were obtained. The overall average drop for the group of 51 patients was 24.7 percent. The percentile decreases were greater in those with the highest initial cholesterol readings.

Compared to our previous decholesterolizing attempts, the results with Triparanol were impressive. The lowered levels obtained were maintained throughout the study with slight variations. Within 2 weeks after medication was discontinued, cholesterol levels rose to control values. Repeated courses of medication caused similar lowering of serum cholesterols.

During the study, routine complete blood counts and urinalyses were taken frequently on each patient. After 2 to 3 months of therapy, transaminase (S.G.O.T.), B.S.P., alkaline phosphatase, urobilinogen and cephalin flocculation studies were performed. These were all unaffected by the drug.

Cooperation and tolerance were excellent. In one instance there was an evanescent erythematous skin rash, and in one patient, nausea, but it was not necessary to discontinue medication. Two women reported thinning of hair while taking 500 milligrams daily and dosage was reduced to await final conclusions on the possibility of this as a side effect. Two patients with angina thought that their attacks were less severe and less frequent. Their electrocardiograms, including tracings made with the Masters test, were unaltered.

#### CONCLUSION

Triparanol has proved to be a more efficient, responsive, predictable decholesterolizing measure with less undesirable side reactions than methods previously reported. Reduction in cholesterol occurs in both the serum and the miscible pool in man. The drug acts by interfering in the end stage of the biosynthesis of cholesterol.

Reports in the literature and my experience with this type of therapy are encouraging. It must be recognized, however, that the long term effects are not known; that the question of tolerance remains to be seen; and finally that we are not yet certain that the drug will prevent heart attacks, strokes, and atherosclerosis.

I am indebted to Dr. Robert H. McMasters, Department of Medical Research, Wm. S. Merrill Co., for his generous help in this project.

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(Official Agency File)

October 10, 1960.

WILLIAM M. KESSENICH, M.D., Medical Director.

J. RICHARD CONNELLY,

*Executive Director, American Diabetes Association, Inc., New York, N.Y.*

DEAR MR. CONNELLY: Thank you for your letter of September 9, transmitting for our information the report concerning MER/29 of your Committee on Food and Nutrition; Dr. Herbert Pollack, Chairman.

We are very appreciative of your interest in this matter, and also of your thoughtfulness in keeping us informed of your activities.

We would indeed be most interested to learn of any additional information which develops from your continued study of this matter.

Sincerely yours,

WILLIAM M. KESSENICH, M.D., Medical Director.



(Article in Independent Professional Appraisal Bulletin)

October 14, 1960.

THE MEDICAL LETTER ON DRUGS AND THERAPEUTICS<sup>20</sup>

### MER/29

Triparanol (MER/29—Merrell) is a new drug promoted as the first safe agent to inhibit body-produced cholesterol. It is offered for use in hypercholesterolemia, coronary artery disease and generalized atherosclerosis. MER/29 is structurally similar to chlorotrianisene, a synthetic estrogen, but it has the unique property of partially blocking the synthesis of cholesterol from its precursor sterol, 24-dehydrocholesterol (desmosterol). Though there is no clear evidence that MER/29 can reverse the deposition of cholesterol or other lipids in atherosclerotic arteries in man, the drug can reduce hypercholesterolemia in many patients.

It has never been established, however, that reduction of blood cholesterol levels prevents coronary artery disease or generalized atherosclerosis, or that it improves the prognosis in these disorders. Nevertheless, the well-established association between abnormal lipid metabolism and clinical atherosclerosis has convinced many physicians of the desirability of reducing blood cholesterol levels in patients with hypercholesterolemia, with clinical signs or symptoms of atherosclerotic disease, or with a bad family history of coronary disease.

*Methods of Reduction.*—Various means of reducing blood cholesterol levels have been used. Dietary measures have included both fat-free diets, and diets in which unsaturated fats (such as corn oil) make up about 75 percent of the total fat intake. These measures are effective but difficult to follow. A variety of drugs have been used, including estrogenic hormones, thyroid or thyroxine analogues, nicotinic acid, beta-sitosterols, and a number of different combinations of concentrates of unsaturated fatty acids in oils. While these drugs are often effective, side effects, sometimes severe, are common.

How MER/29 will fit into this picture is still to be determined. The drug was introduced some months ago after considerable experimental work in animals and limited short-term clinical tests. Most of the published reports on the drug appear in the Proceedings of the Conference on MER/29 (Progress in Cardiovascular Dis., 2:485, May 1960). (For a follow-up report on the experience of one group of participants in the conference see W. Hollander, et al., JAMA, 174:5, Sept. 3, 1960.) These reports indicate that the drug reduces blood cholesterol anywhere from 10 to 55 percent in at least half of patients, with a mean reduction of about 25 percent. Although improvement has been reported in some patients with insufficiency of the coronary and peripheral arteries who received MER/29, the only controlled trial (H. I. Russek, Progress in Cardiovascular Dis., 2:578, 1960) produced no evidence of clinical improvement attributable to the drug in a series of 40 patients with angina.

An important question about the drug arises from the fact that 24-dehydrocholesterol, the precursor of cholesterol, accumulates in patients under treatment with MER/29 (D. Steinberg, et al., *ibid.* p. 586). Dr. Steinberg and his associates ask: "What are the long-term biological effects of 24-dehydrocholesterol and to what extent is it atherogenic?" Until such questions are answered, claims for the safety of the drug cannot be fully accepted.

*Changes in Levels.*—Another question, which applies to all methods of treatment of hypercholesterolemia, arises from the unreliability of cholesterol determinations as guides to effectiveness of a treatment program. Relatively few laboratories are able to determine cholesterol levels accurately. Furthermore, blood cholesterol fluctuates in patients with coronary artery disease (as well as in normal persons), and the fluctuations are wide and unpredictable. They are affected not only by diet, but also by emotional stress and physical activity. Weight reduction alone can depress the blood cholesterol, regardless of the cause of the elevation. Factors such as these indicate the need for controlled trials of cholesterol-reducing drugs, and make valid judgments difficult in the absence of such trials.

Immediate or short-term toxic and side effects with MER/29 were few and slight in the various reported studies. Nausea was uncommon except with large doses, but occasional skin rashes occurred. Although no clear-cut evidence of liver damage was shown, 3 of 28 patients showed an increase in bromosulfo-

<sup>20</sup> Vol. 2, No. 21, pp. 81-83.



phthalein (BSP) retention and a slight increase in alkaline phosphatase (W. Hollander, et al., *ibid.*, p. 637). Some female patients showed cytological estrogenic effects of the drug, and in one elderly patient slight vaginal bleeding occurred for one day. R. G. Gould (*ibid.*, p. 492) suggested that tolerance to the drug might become a problem.

**Dosage**—The recommended dose of the drug is one 250 milligram capsule daily. When reduction of blood cholesterol does occur, it usually begins about 2 or 3 weeks after therapy is started. When the drug is discontinued, there is usually an elevation of cholesterol to previous levels.

To summarize, MER/29 is unique among blood cholesterol reducing agents in its mechanism of action. Short-term studies indicate that it is a relatively nontoxic agent, capable of reducing blood cholesterol in many patients. There is no proof, however, that the drug influences the pathologic basis or the clinical course of atherosclerosis of the coronary or other arteries, or that it is superior to other cholesterol-reducing agents or diets in its effects on blood cholesterol. Because MER/29 causes an accumulation of 24-dehydrocholesterol in the body and because the metabolic effects of this sterol are not known, Medical Letter consultants believe that the drug should still be reserved for experimental trial. If continued studies show that it is both safe and effective over prolonged periods, its convenience will give it an important advantage over dietary methods for many patients. At present the safest method of reduction of blood cholesterol is the use of unsaturated fats for at least three quarters of the total fat intake. But—to repeat—it has not been shown that the reduction of blood cholesterol levels serves any therapeutic purpose. (The cost of MER/29 is about 35¢ per 250 milligram capsule.)



(Advertisement)

November 1960.  
WM. S. MERRELL CO.<sup>30a</sup>

## THE FACTS ABOUT MER/29

**MER/29** *reduces total body cholesterol  
in 8 out of 10  
—and these are the patients  
most likely to benefit*

**your patient with high cholesterol levels...**

MER/29 reduces both serum and tissue cholesterol, irrespective of diet.<sup>1</sup> In 463 patients, the mean cholesterol was reduced from 324 mg.% to 253 mg.%—an average decrease of 71 mg.%.<sup>1a</sup>

**your patient with angina pectoris...**

concurrent benefits have been reported in some patients receiving MER/29. These include decreased incidence and severity of attacks, improved ECG patterns, diminished nitroglycerin requirements, and an increased sense of well-being.<sup>1,4,6-8</sup>

**your patient with postmyocardial infarction...**

while more time is needed to determine the over-all prognostic significance, it has been observed that MER/29 "...reduced morbidity and mortality rates below those of control series during the first year following coronary thrombosis."<sup>4</sup>

**your patient with generalized atherosclerosis...**

atherosclerosis "...has been shown to afflict about 77% of American males as early as in the 20-to-30 age range."<sup>9</sup> With MER/29 you have a new, well-tolerated means of lowering cholesterol—considered "...the *sine qua non* of the atheromatous lesion."<sup>9</sup>

<sup>30a</sup> Journal of the American Medical Association, vol. III, No. 3.



**compatible with other cardiovascular therapies:** MER/29 can be used along with other measures to control anxiety, hypertension, obesity, and other conditions associated with cardiovascular disorders. These include anticoagulants, nitroglycerin, and PETN.

**safety data:** Patients have now been treated with MER/29 for relatively long and continuous periods. In no case has there been evidence of serious toxic effects on the function of any vital organ or system. However, since long-term MER/29 therapy may be necessary, periodic examinations, including liver function tests, are desirable. Side effects (nausea, headache, dermatitis) are rare and have usually been associated with dosages greater than those recommended for effective therapy.

**contraindication:** Pregnancy. Since MER/29 inhibits cholesterol biosynthesis, and cholesterol plays an important role in the development of the fetus, the drug should not be administered during pregnancy.

**supplied:** Bottles of 30 pearl gray capsules.

- 
- ... the first cholesterol-lowering agent to inhibit the formation of excess cholesterol within the body, reducing both tissue and serum cholesterol
  - ... no demonstrable interference with other vital biochemical processes reported to date
  - ... convenient dosage: one 250 mg. capsule daily before breakfast
  - ... toleration and absence of toxicity established by 2 years of clinical investigation

MER/29  
(triparanol)

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*References:* 1. Hollander, W., and Chobanian, A. V.: Boston M. Quart. 10:37 (June) 1959. 2. Oaks, W., and Lisan, P.: Fed. Proc. 18:428 (Mar.) 1959. 3. Oaks, W. W., et al.: A. M. A. Arch. Int. Med. 104:527 (Oct.) 1959. 4. Lisan, P.: Proceedings, Conference on MER/29, Progr. Cardiovasc. Dis. 2: (Suppl.) 618 (May) 1960. 5. Oaks, W. W.: *Ibid.*, p. 612. 6. Hollander, W., et al.: *Ibid.*, p. 637. 7. Halperin, M. H.: *Ibid.*, p. 631. 8. Toro, J.: *Ibid.*, p. 544. 9. Morrison, L. M.: J.A.M.A. 173:884 (June 25) 1960.



*(Official Agency File)*

## United States Government Memorandum

November 3, 1960.

To: Dr. Ralph Smith, NDB-BM.

From: O. L. Kline, DON.

During a visit last Monday with Dr. Pollack, I learned of a report read at the St. Louis meeting of the American Heart Association by a staff member of the Mayo Clinic. This dealt with the effect of 5 gram doses of nicotinic acid used to reduce blood cholesterol. The report indicates that 33 percent of the patients studied developed symptoms of diabetes. It would seem that this needs investigation and if confirmed, would constitute an unsafe use of this substance. Dr. Pollack reiterated his concern about the use of MER/29, also used as a drug to control the cholesterol level of the blood. Dr. Pollack stated that Steinberg has demonstrated an undesirable effect in dogs and that Boyce of Emory University has shown that the trans-aminase content of the liver is significantly affected. I know that he has talked with you on this subject. These comments may be supplementary to his prior discussion.

O. L. KLINE.

*(Official Agency File)*

November 9, 1960.

HERBERT POLLACK, M.D., 70 EAST 77TH ST., NEW YORK, N.Y.

Dr. O. L. KLINE,

*Office of Food and Drug Administration,  
Washington, D.C.*

DEAR LEE: The enclosed advertisement was in my morning's mail. An unscientific presentation of totally inadequate observation from which sweeping conclusions are drawn.

What bothers me most about this is that there is absolutely no mention of the potential toxicity nor the precautions in its administration, nor any mention of the difficulties in serum cholesterol determinations following its use.

Cordially yours,

HERBERT POLLACK, M.D.

*(Enclosed Mailing Piece)*

THE WM. S. MERRELL COMPANY

Division of Richardson-Merrell Inc., Cincinnati, Ohio

DEPARTMENT OF MEDICAL RESEARCH

DEAR DOCTOR: I'd like to tell you about a patient with angina reported on by Dr. Meyer H. Halperin at the Princeton Conference on MER/29, the new agent which reduces the body's production of cholesterol. Or, rather, I'll let him tell you in his own words\*:

"There was one man, about 68 years old, a business executive whom I had followed for several years, and who had angina which was very reproducible under constant conditions of exercise and time of day. He found, for example, when he drove into Boston, parked his car, and had to walk two blocks to the office building where he worked, that if he ever forgot to take a nitroglycerin tablet he wouldn't get very far before he was forcibly reminded about its necessity. That had been going on a long time: at least every morning he had to take nitroglycerin; and four times out of five he had to take nitroglycerin going back to his car at the end of the day, or whenever he happened to walk a little too fast or climb a flight of stairs.

"He was given MER/29, 250 milligrams daily, with the explanation as to the fact that it might be only a placebo. He is a very intelligent patient, Phi Beta Kappa, as a matter of fact, and he entered into the spirit of the thing very well.

"Well, he came back 2 weeks later and told me: 'By golly, if that's a placebo, it's the best doggone placebo I have ever seen.' He hadn't had to use any nitroglycerin at all.

"Two weeks later he came back and said he had had to make a business trip to New York at a time when the elevator operators were on strike. He had to visit an office six flights above ground level. After walking up four flights he

\*Halperin, M. H.: *Progr. Cardiovasc. Dis.* 2: (Suppl.) 631, 1960.



thought he had better take a nitroglycerin tablet, although he didn't really feel enough pain to do so, but he got a little worried.

"This was during the summer and I thought perhaps the weather had something to do with it. I reserved judgment until later in the season to see what happened when the weather got cool.

"Well, his improvement has been maintained. I reminded him every time when he brought back the remainder of his capsules that I might exchange them for a placebo if I so desired, or to change back from a placebo to the true drug. He insisted all the time that he didn't know why or how but if this was placebo, he was doing very well; he hadn't felt that will for 2 years. The improvement has been maintained right into the cold weather that we have had recently in Boston."

This man was 1 of 18 patients with angina treated with MER/29 by Dr. Halperin. He cited this case as one whose response he considered "very good"; in all, 6 of the 18 were so classified, in 2 others the response was "moderate," and in one other, "slight." The other nine showed no response.

An analysis of the cases by factors such as age, cholesterol decrease, number of infarcts, etc. revealed that the only significant difference between patients who responded and those who did not was the duration of angina. Those who responded had had angina on the average only 2.9 years; the nonresponders, 5.2 years.

This experience of Dr. Halperin's appears to be representative of what you may find in some of your own patients with angina. In other words, some patients will report such concurrent benefits (although, in most cases reported so far by other investigators, MER/29 takes longer to bring about such effects—usually 8 to 13 weeks), and most likely these responding patients will be among those with shorter duration of angina.

In addition, as several investigators have reported, occasional patients with ECG abnormalities on the two-step exercise test may show improvement while on MER/29 therapy.

But these subjective and objective benefits from MER/29 are extra dividends, so to speak. The real object of MER/29 therapy is to lower cholesterol levels—as is now widely considered advisable in patients with coronary artery disease and in hypercholesterolemia in general. Although only occasional patients may experience relief of angina and demonstrate ECG changes, 80 to 90 percent of your patients will show reduction of cholesterol levels on MER/29 therapy, and they should understand that this is an important precautionary measure in itself.

If you care to write me about your own experiences with MER/29 therapy of patients with angina and abnormal ECG patterns, I will very much appreciate having this information. We hope that analysis of a large number of cases may reveal further clues about the patients who respond to MER/29 with these concurrent benefits.

Sincerely yours,

ROBERT H. McMASTER, M.D.  
*Department of Medical Research.*

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*(Agency Correspondence)*

December 1, 1960.

FRANK J. TALBOT, BUREAU OF MEDICINE, FOOD AND DRUG ADMINISTRATION  
HERBERT POLLACK, M.D.  
70 East 77th Street,  
New York, N.Y.

DEAR DR. POLLACK: We have for reply your letter of November 9, 1960, addressed to Dr. O. L. Kline concerning a promotional piece for MER/29, a product of William S. Merrell Co.

We are fully in accord with your views as to the offensive character of this promotional literature. There is no convincing evidence that MER/29 is an effective treatment for coronary artery disease and the labeling of the article, including such promotional literature, properly should include information with respect to the limitations of its use, its effects, side effects, and cautions. As you may know, this type of promotion is all too common in the pharmaceutical industry, and recognition of this problem has led us to propose a revision of the regulations under the Federal Food, Drug, and Cosmetic Act that will give us a basis for correcting this type of practice. We are hopeful that the promulgation of these regulations will give us a basis for corrective regulatory actions in the near future.



We appreciate very much the interest indicated by your writing this letter and also displayed in your visit when we discussed reported adverse effects associated with MER/29. We have endeavored to obtain and are continuing to seek any additional information that may be available with respect to either adverse effects or the clinical ineffectiveness of the article and would appreciate any additional information along these lines that you may be able to contribute. We might mention in this connection that we were unsuccessful in obtaining information from Dr. Elliot Corday of Cedars of Lebanon Hospital, Los Angeles, Calif., in substantiation of the reported hepatotoxic effects of the drug.

If we can be of any further service, please advise.

Sincerely yours,

FRANK J. TALBOT, M.D.,  
*Medical Officer, New Drug Branch, Bureau of Medicine.*

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*(Editorial in the Open Literature)*

March 20, 1961.

IRVINE H. PAGE, M.D., editor, *Modern Medicine*.<sup>29b</sup>

#### A DOCTOR'S DILEMMA

It has become generally accepted that elevated blood cholesterol or lipid, if sustained long enough, leads to early atherosclerosis. Examples are the vascular diseases seen with diabetes, nephrosis, hypothyroidism, and familial hyperlipemia. From this it follows that hypercholesteremia is dangerous and should be reduced. But how—diet, exercise, weight loss, or drugs?

Recently, an extremely interesting drug, known as triparanol, or MER/29, has appeared on the market. It is interesting in the sense that it stops the synthesis within the body of cholesterol at the stage just before desmosterol is converted to cholesterol. Desmosterol is a little-known steroid which has so far been identified simply as one of a series of compounds formed on the way from acetate to cholesterol. Whether it has any deleterious effects is not known.

When MER/29 is fed to animals, desmosterol tends to increase and replace some body cholesterol. The cholesterol level in both blood and tissues decreases, though how much is not altogether certain because desmosterol interferes to some degree with the measurement of cholesterol. This drug has been given probably to over 100,000 people, yet no clear evidence of toxicity has appeared so far. This is not to say that toxicity won't appear, and it is of the utmost importance to recognize it if it does. We can expect the usual sensitivities and oddities that occur with any drug in widespread use, but the important thing is to find any toxic action inherent in the drug.

Will this drug prevent or slow the occurrence of atherosclerosis? No one knows. If we admit that a sufficiently high level of blood cholesterol is deleterious, then how much must it be reduced before atherogenesis is slowed or stopped? All we now know is that atherosclerosis is rare in populations with levels of about 180 milligrams per 100 cubic centimeters or below.

This leaves the practitioner with the problem of whether to use this drug or not. Clearly, the evidence on which its use is based is incomplete. The patient with a strongly positive coronary profile is a high risk and may be interested in an experimental approach. Others may feel the same. So, if we recognize that this is a broad experiment in which there is voluntary participation, then the use of the drug can be justified. The great pity is that, with such a large-scale program under way, no study is being conducted to determine its outcome. Atherosclerosis is still a disease that fires few people's imaginations; it only kills more than any other.—I.H.P.

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<sup>29b</sup> Pp. 71-72.



*(Article in the Open Literature)*

April 26, 1961.

RICHARD P. ACHOR, M.D.,

RICHARD K. WINKELMANN, M.D.,

HAROLD PERRY, M.D.<sup>40</sup>

\* \* \* \* \*

## SUMMARY AND CONCLUSIONS

Seven patients experienced cutaneous side effects while being treated with triparanol (MER/29) for hypercholesteremia. Two of these were men, who had clinical ichthyosis, alopecia and loss of hair color. The other five patients were women with pronounced loss of scalp hair; two of them also experienced some loss of body hair. Except for one man, who was taking 250 milligrams of triparanol per day, all patients were receiving 500 or 1,000 milligrams of triparanol daily when the cutaneous effects were noted. All these effects appear to be reversible when use of the drug is stopped or the dose is decreased.

It is suggested that, in susceptible persons, the epidermis, an important location for the synthesis of cholesterol, is affected by triparanol, which is an inhibitor of cholesterol biosynthesis. Patients receiving triparanol should be observed closely for cutaneous side effects, particularly if they are receiving more than 250 milligrams per day.

<sup>40</sup> "Cutaneous Side Effects From Use of Triparanol (MER/29): Preliminary Data on Ichthyosis and Loss of Hair," Proceedings of the Staff Meetings of the Mayo Clinic, vol. 36, No. 9, p. 228.



(Confidential A.M.A. File)

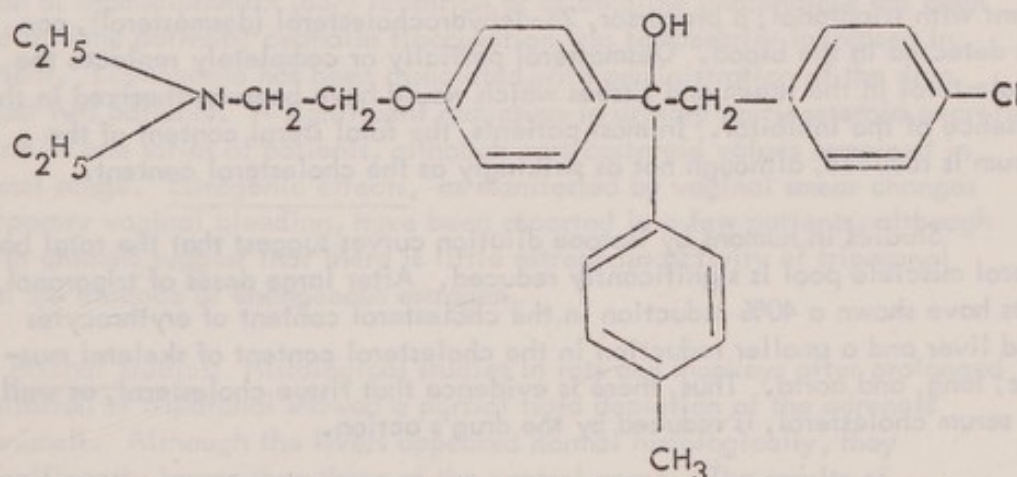
May 17, 1961<sup>40a</sup>

AMERICAN MEDICAL ASSOCIATION, COUNCIL ON DRUGS

TRIPARANOL  
(MER-29)

Evaluated by AMA COUNCIL ON DRUGS --May 17, 1961

Summary of Council Opinion. -- Triparanol, an inhibitor of cholesterol biosynthesis, lowers the serum and total body cholesterol level in the majority of patients to whom it is administered in adequate doses. However, since the role of cholesterol in the pathogenesis of atherosclerosis has not as yet been clarified, and since there is a lack of adequate evidence that the administration of this drug to patients with coronary insufficiency or generalized atherosclerosis has produced a beneficial effect, the use of triparanol must be regarded as experimental. Although serious side effects have not yet been reported in clinical trials, the ultimate consequences of interference with sterol metabolism are unknown; therefore, much longer and more careful studies must be performed before the drug can be considered safe for general or long-term use.

Chemical Formula. --

1-[p-(β-diethylaminoethoxy)phenyl]-1-(p-tolyl)-2-(p-chlorophenyl)ethanol

Actions and Uses. -- Triparanol, a triphenylethylene derivative structurally resembling the synthetic estrogen, chlorotrianisene, produces a significant reduction of serum cholesterol in the majority of patients to whom it is administered. The degree of reduction of serum cholesterol achieved with

<sup>40a</sup> A number of earlier and later confidential bulletins of the Council on Drugs mentioned triparanol, the subcommittee has been informed. On August 13, 1963, Commissioner George Larrick, in response to a subcommittee inquiry, wrote: "We have checked our copies [of the council bulletin—ed.] and find that the issues of February 24, 1960, March 9, 1960, May 17, 1961, May 31, 1961, June 8, 1961, August 9, 1961, and August 16, 1961, contain references to triparanol. The AMA has requested that we treat the information in the bulletins as confidential and if you should need copies of these issues, we would appreciate your directing your request for them to the AMA."



## TRIPARANOL (Continued)

triparanol is approximately the same as that possible with other methods of treatment now in use. The greatest reduction of serum cholesterol is usually seen in those patients who had high initial cholesterol values. The maximum reduction usually occurs after two to eight weeks of therapy, depending upon the size of the initial dose. Discontinuation of the drug results in an increase of serum cholesterol to control values in two to eight weeks in most patients.

In the majority of cases reported, the maximal depression of serum cholesterol that is observed early in treatment with triparanol has been maintained by continued administration of the drug; however, in some patients this depression was temporary, although administration of the drug was continued.

Some investigators claim that treatment with triparanol results in clinical improvement of patients with angina pectoris and in subjective improvement of some patients with peripheral arterial obstruction; other investigators have found no such improvement in their patients. The difficulties inherent in the evaluation of clinical improvement in these conditions are well known, and adequately controlled experiments which would verify or deny these claims have not been performed.

Mechanism of Action.-- It has been demonstrated that triparanol blocks cholesterol synthesis at a late stage in the synthetic pathway. During treatment with triparanol, a precursor, 24-dehydrocholesterol (desmosterol), can be detected in the blood. Desmosterol partially or completely replaces the cholesterol in the serum and tissues which would have been synthesized in the absence of the inhibitor. In most patients, the total sterol content of the serum is reduced, although not as strikingly as the cholesterol content.

Studies in humans by isotope dilution curves suggest that the total body sterol miscible pool is significantly reduced. After large doses of triparanol, rats have shown a 40% reduction in the cholesterol content of erythrocytes and liver and a smaller reduction in the cholesterol content of skeletal muscle, lung, and aorta. Thus, there is evidence that tissue cholesterol, as well as serum cholesterol, is reduced by the drug's action.

Serum cholesterol determinations in humans after triparanol therapy may be misleading, for the drug's action causes cholesterol to be replaced to a variable degree by the precursor, desmosterol, a compound which is about one-half as chromogenic as cholesterol as established by standard colorimetric



## TRIPARANOL (Continued)

cholesterol determination methods. Thus, the true serum cholesterol content will be lower than that reported by the methods in use at present, but the total sterol content will be higher than the reported value.

Since the role of cholesterol or other sterols in the pathogenesis of atherosclerosis has not as yet been clearly delineated, the value of cholesterol-lowering agents in influencing the course of atherosclerosis also remains to be proven. Animal feeding experiments have shown that sterols other than cholesterol may be atherogenic. Nothing is known of the possible atherogenic properties of desmosterol, which is found in increased amounts in the serum after administration of the drug. Desmosterol is very similar to cholesterol in its physical and physiological properties. Until there is evidence to the contrary, the most reasonable hypothesis is that the two sterols are approximately equipotential in their theoretical atherogenicity.

Side Effects.--

Clinical Studies: In clinical trials with this drug, nausea, vomiting and mild erythematous skin rashes have been reported; other cutaneous side effects (loss of hair, change in hair color, dry skin, and ichthyosis) have occurred in patients given a dose of 500 mg. or more of triparanol daily. A temporary elevation of bromsulphalein (BSP) retention or of alkaline phosphatase has been reported in some patients; cephalin flocculation was temporarily increased in one patient. Leukopenia has been associated with administration of the drug in at least two patients. A significant reduction in urinary corticosteroid excretion was found in one series of patients, although corticosteroid values remained in the normal range. Estrogenic effects, as manifested by vaginal smear changes and temporary vaginal bleeding, have been reported in a few patients, although studies in animals suggest that there is little estrogenic activity of triparanol alone in the absence of endogenous estrogen.

Animal Studies: Histological studies in rats and monkeys after prolonged administration of triparanol showed a partial lipid depletion of the adrenals in all animals. Although the livers appeared normal histologically, they were significantly larger than those of the control group. The results of hematological studies in rats were normal except for the development of reticulocytosis.

In one study, dogs were given four to six times the usual human dose of triparanol daily; death, apparently due to hemolytic episodes, occurred in all the animals within three months.

Route of Administration.--Oral.



## TRIPARANOL (Continued)

Dosage.--The usual dose is 250 mg. daily.

Precautions.--Since cholesterol plays an important role in the development of the fetus, triparanol is contraindicated during pregnancy.

The use of this drug should be considered experimental, and it should be administered only to those patients with unusually high serum cholesterol values and serious atherosclerosis.

Since the effects of long-term administration to patients are not known and since there is evidence that hepatic and endocrine function may be disturbed by the drug, periodic liver function tests and hematological evaluations should be performed, and the physician should be aware of any other side effects which may occur.

Preparations.--

Capsules 250 mg.

Commercial Source.--

The Wm. S. Merrell Company.

Year of Introduction.--

1960

This monograph will be included in the 1962 edition of the Council on Drugs' annual publication, New and Nonofficial Drugs.



*(Letter to Editor in the Open Literature)*

August 19, 1961.

HOWARD T. BEHRMAN, M.D.<sup>41</sup>

## DRY SKIN AND ALOPECIA

**Question.** About 8 months ago a 57-year-old man had an attack of angina pectoris. After he had taken 20 milligrams of pentaerythrityl tetranitrate 4 times daily and 250 milligrams of triparanol daily for 3 or 4 weeks, the pain disappeared. He feels well, but for the past 4 months he has complained of dryness of the skin and has lost about half of the hair all over his body except his beard. His eyebrows have lost their color and his hair seems to be fading. He stopped taking all medication 3 months ago, but the dryness of skin and loss of hair continues. What is the most likely cause, and what treatment is recommended?

MACK ROBERTS, M.D., *Monticello, Ky.*

**Answer.** Two recent articles (Achor, R. W. P., Winkelmann, R. K.; and Perry, H. O.: *Proc Mayo Clin* 36:217, 1961; and Cooper, E. E. *Texas J. Med* 56:775, 1960) have noted the alopecia-inducing potential of triparanol (MER/29). In addition, ichthyotic skin and loss of hair color have been reported. As pentaerythrityl is not known to have this effect, the cause of this patient's condition is probably the triparanol. Discontinuing the drug should result in eventual hair regrowth and loss of the other side effects.

HOWARD T. BEHRMAN, M.D.

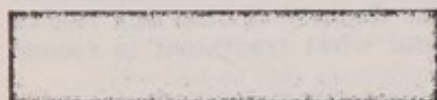
<sup>41</sup> Correspondence, *Journal of the American Medical Association*, vol. 177, No. 7, p. 534.



(Advertisement)

September 1961.  
WM. S. MERRELL Co.<sup>41a</sup>

after 3 years' clinical experience:  
here is what we now know about MER/29 and

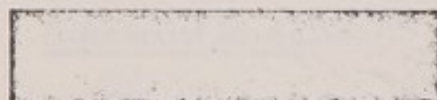


We know that MER/29 lowers cholesterol in 8 out of 10 patients, even without dietary restrictions. In 576 patients studied by various physicians, average cholesterol levels dropped from 303 mg. % to 241 mg. % — an average decrease of 62 mg. %.

We know that MER/29 reduces total sterols in both blood and tissue.

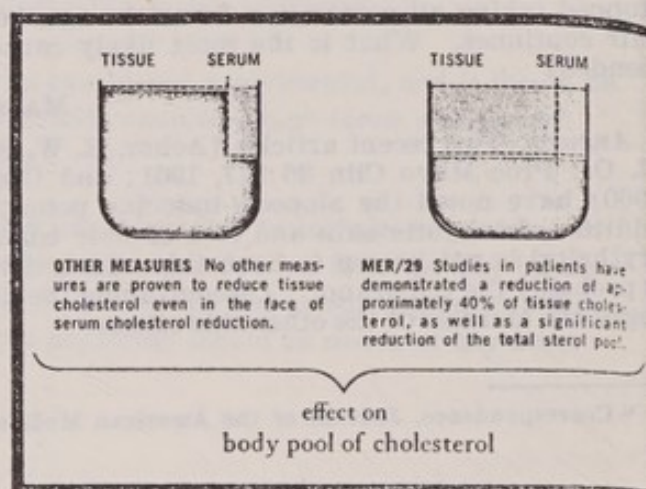
We know that MER/29 does this by inhibiting the body's own production of cholesterol.

We know that its use in over 300,000 patients re-affirms the safety margins established in early laboratory and clinical data.



We know that, in some patients, concurrent clinical benefits attend the use of MER/29. Published papers on MER/29 therapy to date report improvement in 50 of the 79 anginal patients reported in these studies, and comparable results are being obtained in similar studies now in progress. Among the other benefits reported are:

- decreased incidence and severity of anginal attacks
- improved ECG patterns
- diminished nitroglycerin dependence
- increased sense of well-being



"During triparanol [MER/29] therapy there was a definite improvement in the electrocardiographic tracings in response to exercise in 3 of 11 subjects with angina pectoris."  
—Hollander, W., et al.: *J.A.M.A.* 174:5 (Sept. 3) 1960.

"Nitroglycerin requirements decreased in 3 [of 5 out-patient] patients, including the patient showing electrocardiographic improvement....Three [of 4 private male patients], after a lapse of some weeks, showed improvement in exercise electrocardiograms, which was sustained but not further improved in subsequent observations."  
—Corcoran, A. C., et al.: *Progr. Cardiovasc. Dis.* 2:(Pt. 1) 576 (May) 1960.

"Of the 45 patients with coronary artery disease followed for 1 year, 16 had a history of frequent anginal attacks. Fourteen of these spontaneously stated that their angina disappeared within 2 months of [MER/29] therapy....In one patient...with persistent coronary insufficiency pattern (ST segment depressions in multiple leads), there was a complete reversion to a normal tracing during MER/29 therapy with associated clinical improvement in angina."  
—Lisan, P.: *Progr. Cardiovasc. Dis.* 2:(Pt. 1) 618 (May) 1960.

<sup>41a</sup> American Journal of the Medical Sciences, vol. 242, No. 3, No. 1073.



# ...what we are learning about atherosclerosis

It has become generally accepted that elevated blood cholesterol or lipid, if sustained long enough, leads to early atherosclerosis."

Page, I. H.: *Mod. Med.* 29:71 (Mar. 20) 1961.

Epidemiologic studies show that low cholesterol levels are associated with low incidence of atherosclerosis and coronary artery disease.

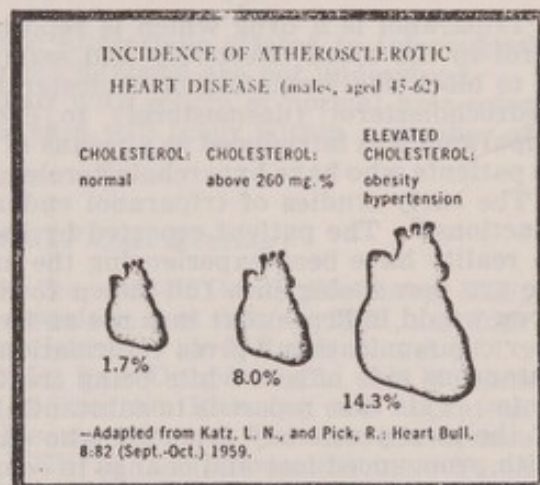
On the basis of such studies, Stamler has said: "...a 15 to 20 per cent reduction in mean serum cholesterol levels alone might be associated with a 25 to 50 per cent reduction in coronary disease incidence rates in middle-aged men."

Stamler, J.: *Am. J. Pub. Health* 50:(Pt. 2) 14 (Mar.) 1960.

Despite our knowledge of the action, benefits and safety of MER/29, much remains to be discovered about the basic concept of cholesterol-lowering therapy. In this, MER/29 is comparable to the well-accepted use of anti-hypertensive agents: we know they lower blood pressure, but we cannot prove that lowering blood pressure will also lower morbidity or mortality. Yet few physicians hesitate to use these agents. The possible good is too great to ignore.

It is with MER/29. No one can yet be certain that sustained lowering of total body sterols

will prevent or alter atherosclerosis. But the current evidence strongly supports this concept.

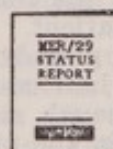


will prevent or alter atherosclerosis. But the current evidence strongly supports this concept.

Perhaps that is why an increasing number of physicians are now prescribing MER/29. They wish to assure their hypercholesterolemic, coronary artery disease, and atherosclerotic patients this reasonable hope.

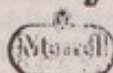
It is a decision facing every physician.

Complete bibliography and prescription information on request.



Still available... write for your copy of this full-length report.

# MER/29



The Wm. S. Merrell Company  
Division of Richardson-Merrell Inc.  
Cincinnati, Ohio / Weston, Ontario



*(Article in the Open Literature)*

September 11, 1961.

HAROLD O. PERRY, M.D.<sup>42</sup>

R. K. WINKELMANN, M.D.

RICHARD W. P. ACHOR, M.D.

## COMMENT

Triparanol is a drug which is reported to lower the concentration of cholesterol in the blood effectively and safely for long periods. Its principal action is to block the formation of cholesterol by preventing the conversion of 24-dehydrocholesterol (desmosterol) to cholesterol. For this reason, the use of triparanol was introduced as a means of reducing the concentration of cholesterol in patients who have hypercholesterolemic states.

The early studies of triparanol endorsed its almost complete lack of adverse reactions.<sup>43</sup> The patient reported by Estes<sup>44</sup> "who complained of a dry skin may in reality have been experiencing the mildest form of an ichthyotic state which we are now seeing in a full-blown form. Our own initial experience with this drug would indicate that it is not as free of side effects as was thought. A former communication<sup>45</sup> gives information on seven patients who have experienced cutaneous side effects while being treated with triparanol for hypercholesterolemia. This case report is in substantial agreement with the case records of two of the men previously reported who experienced clinical ichthyosis of the skin with pronounced loss and change in color of the hair of the scalp and body.

The dosage of triparanol taken by this patient was the recommended amount, namely 250 milligrams daily. Of the two male patients previously reported, one had taken up to 1000 milligrams per day, the second, 250 milligrams per day. Thus, experience with this patient would further suggest that undesirable cutaneous effects may occur when usual dosages of the drug are given and that overdosage is not the sole reason for these effects.

As in the case of one of the previously reported patients, the present patient experienced the cutaneous changes following an interval in which the drug had not been taken. This spatial relationship suggests that the blocking of the synthesis of cholesterol is associated with the inhibition of physiologic effects for normal development of hair and skin for some months.

Including the patient in the present report, the three patients so far encountered who developed ichthyosis, change in color of the hair, and loss of hair have been male patients. Five patients in whom hair loss alone developed were female. At this time it is impossible to explain the more severe involvement in the male patient.

Follow-up study of the two patients previously reported revealed that normal growth of hair, as well as normal coloration, was restored after several months. Thus, although side effects appeared following cessation of administration of the drug in the present patient, it can be expected that these changes are reversible and that there will be a reversion to a normal situation after a lapse of several months.

Since synthesis of cholesterol also takes place in the skin, we have assumed that the synthesis-blocking action of triparanol occurs in the skin as well as in the liver and that this is responsible for the changes which have been manifested clinically as ichthyosis. Precisely how interruption of synthesis of cholesterol affects hair growth and color is less well understood. It seems clear that these effects should be interpreted as physiologic side effects and not as toxic effects or allergic reactions in the usual appreciation of these reactions. The element of idiosyncrasy may be most important.

<sup>42</sup> Read at the meeting of the Southern Minnesota Medical Association, Austin, Minn., "Complications in the Use of Triparanol (MER/29)," reprinted in *Minnesota Medicine*, vol. 45, No. 5, June 1962, pp. 599-600.

<sup>43</sup> Proceedings of the Conference on MER/29 (Triparanol). *Prog. Cardiovasc. Dis.* 2:485-648, 1959-1960.

<sup>44</sup> Estes, J. D.: Clinical Experience With MER/29, an Inhibitor of Cholesterol Synthesis. *Prog. Cardiovasc. Dis.* 2:564-570, 1960-1960.

<sup>45</sup> Achor, R. W. P., Winkelmann, R. K., and Perry, H. O.: Cutaneous Side Effects From Use of Triparanol (MER/29): Preliminary Data on Ichthyosis and Loss of Hair. *Proc. Staff Meet., Mayo Clin.* 36:217-228 (Apr. 26) 1961.

(EDITOR'S NOTE.—Footnotes to the texts of articles in the open literature are reprinted intact from the original articles, as above, except for numbering changes.)



Although we are concerned with the side effect of alopecia in patients who receive triparanol, an early report by Toro<sup>46</sup> indicated that two female patients who were given the drug began to exhibit excessive growth of hair. This paradoxical reaction between these two groups of patients is difficult to explain.

#### SUMMARY

A patient is reported who experienced ichthyosis, loss of hair, and change in color of the hair following use of triparanol (MER/29). This represents the third patient reported by us who had these specific findings associated with the administration of triparanol.

These changes are regarded as physiologic alterations related to interrupted synthesis of cholesterol, although the exact mechanisms are not understood.

It is anticipated that normal growth of hair with return of normal hair color and a reversion to soft, supple, and pliable skin will occur within a number of months in the patient described.

#### *(Summary of Internal N.I.H.-F.D.A. Meeting)*

(September 27, 1961.—A meeting is held in the office of Daniel Steinberg, M.D., National Heart Institute. Present are his associate, Joel Avigan, M.D., and four representatives of the Food and Drug Administration staff, Irwin Siegel, M.D., Deputy Medical Director, John O. Nestor, M.D., New Drug Division, and William Weiss and Jerome Deutschberger, Bureau of Program Planning and Appraisal.

(At the meeting, Dr. Steinberg discusses his experimental findings; in response to inquiry, he questions the usefulness of MER/29 in clinical medicine. For a chronology of Dr. Steinberg's earlier and subsequent correspondence and contacts, see exhibit 128, p. 922.)

#### *(Internal Agency Document)*

October 24, 1961.

J. DEUTSCHBERGER, Bureau of Program Planning and Appraisal, Food and Drug Administration.

Dr. Frank J. Talbot, New Drug Division, BM.

J. Deutschberger, Bureau of Program Planning and Appraisal.

NDA 12-066, MER/29, The Wm. S. Merrell Co.:

We have examined NDA 12-066, MER/29, as it was submitted to us on Sept. 1, 1961. We have in addition examined supplementary data submitted by the Wm. S. Merrell Co. on Sept. 11, 1961. The latter are data that representatives of the Merrell Co. offered to forward to us during the course of our meeting on June 29, 1961.

As you requested, we have particularly examined the applications in relation to the proposed new brochure, on which we have the following comments:

1. Under title "Advantages," it is stated in the brochure: "Serum cholesterol response in 8 of 10 patients. Serum cholesterol depression by MER/29 averages more than 20 percent below pretreatment levels in at least 80 percent of patients."

So far as we are able to determine, this statement is totally unwarranted and is an excessive overclaim. We find, in the data submitted by the company, reports of the responses of 1,047 individual patients to MER/29 therapy. At doses ranging from 100 milligrams daily to 1½ grams daily (and in one case, 5 grams), for varying periods of time on therapy ranging from 1 to 20 months, only 433 (41 percent) of these patients had drops in their serum cholesterol levels of 20 percent or more below their pretreatment levels.

The bulk of the results we cite are developed from the data submitted on Sept. 11, 1961. In the original submission, there is a total of 134 patients for whom there are control serum cholesterol readings and readings subsequent to MER/29 therapy. Of these, only 60 (45 percent) had drops in their serum cholesterol levels of 20 percent or more below their pretreatment readings.

Of an additional 26 patients reported in the original submission by Drs. Leckert, McHardy, et al., only 9 (35 percent) had a lowering of 20 percent or more subsequent to MER/29 therapy.

<sup>46</sup> Toro, Jaime: Evaluation of the Administration of MER/29 to a Group of Institutionalized Patients at the St. Louis Chronic Hospital: A Preliminary Report. Prog. Cardiovasc. Dis. 2:544-547, 1959-1960.



2. Under "Advantages," the brochure reads: "Low toxicity. Recommended doses of MER/29 have not affected the vital organs or systems after 3 years of continuous clinical use."

We should note parenthetically that if the 3 years referred to in the brochure means 3 years for individual patients, we have found data only up to a maximum of 20 months for the individuals in the material submitted by the company.

We note, in reading through the papers that accompany the submission, that there is some statistical misinterpretation of data relating to toxicity. We believe that it may be worthwhile for you to consider these data.

In his paper, "The Effect of Usual Doses of Tripanarol on Adrenocortical Function," Dr. R. V. Ford states: "Although there is a trend toward a reduction of steroid excretion (table 1), this trend is not statistically significant."

The trend of which Dr. Ford writes may well reflect a real effect. It is unlikely that Dr. Ford could demonstrate statistical significance even if the adrenocortical function was affected, because he studied few patients. This study is ineffective in detecting moderate adrenocortical effects of the drug.

Similarly, in an interdepartmental memo, dated May 31, 1961, Dr. H. H. McMaster of the Merrell Co., comments to Dr. F. J. Murray on the subject of MER/29 used in conjunction with anticoagulation therapy: "Dr. Irving S. Wright and his group have conducted at the New York Hospital a double-blind crossover experiment on 19 patients on long-term anticoagulation therapy. The observed changes were not regarded by Dr. Wright or by us as significant statistically \* \* \*."

From Dr. McMaster's report of Dr. Wright's study, we would assume that an effect is more likely than not.

In connection with the toxicity of the drug, we point out that essentially the same error is made in the approach to the interpretation of the animal studies done by the Merrell Co. These studies are treated as if they show no effect, on the theory that the differences between test and control animals are not statistically significant.

We believe that the experiments do show an adverse effect on test rats, and we attach hereto graphs to demonstrate that the relative organ weights (organ weight/body weight ratio) of rats is affected by the drug. This is the same conclusion that Dr. Goldenthal, Division of Pharmacology, reached and reported prior to the time the application became effective (see report vol. 2). Apparently, Drs. Megirian and Vos of Pharmacology concurred in Dr. Goldenthal's opinion.

The change in organ weight/body weight ratio is due primarily to the reduced growth rate of the animals on the drug. From the analysis of the data offered by the Merrell Co., we assume that the change in organ weight/body weight ratio is of greater medical importance than absolute organ weight change.

3. Under "Effects in the Hypercholesterolemia of Diabetes," it is stated in the brochure that of all patients with diabetes mellitus reported to date, 94 percent have obtained significant serum cholesterol response to MER/29. This appears to be a considerable overstatement, and apparently is obtained solely from the results of Bendersky, who achieved a response in 28 (not, as is stated in the brochure, 29) of 30 patients ( $28/30=93\frac{1}{3}$ ).

However, if we include all diabetic patients along with Bendersky's, we have seen reports of treatment for 58 diabetics. Of the 28 patients reported by Hauntz, Cornatzer, and Luper, Ruskin, Hollander and Chobanian, and Kountz, the proportion obtaining significant results is well under 94 percent. We cannot give precise figures because we know only that some 15 of these obtained a response while 6 did not. On the basis that at least 8 of the 56 diabetic patients did not obtain significant results, at least 14 percent of patients did not achieve significant responses. We might add that the criteria set forth by Hauntz and by Rivin for a "significant" cholesterol response may very well not have been met by Bendersky's patients.

4. We are unable to evaluate the significance of the brochure statement on the appearance and significance of desmosterol, given in "Clinical Results." The proposed brochure reads "Total sterol reduction in patients on MER/29 therapy averages 15 to 20 percent, but the cholesterol alone is decreased more than 20 percent."

Since we did not find an average decrease of more than 20 percent in cholesterol levels, we are inclined to doubt this latter statement. Grouping patients by their initial (control) cholesterol levels, we found that changes were as follows:



*Control levels, milligrams, 1 percent*

	199 or less	200 to 249	250 to 299	300 to 349	350 to 399	400 or more
Number of patients.....	32	133	325	317	154	85
Average percent change per patient.....	-2	-12	-14	-19	-19	-18
Percent of patients obtaining a 20-percent reduction.....	19	30	33	48	56	49

For the entire group of 1,047 patients, without regard to their initial cholesterol levels, there was an average change of -16.0 percent of cholesterol level after MER/29 therapy.

Dr. Daniel Steinberg, National Heart Institute, has offered us a formula for determining total sterol changes, valid if the Liebermann-Burchard method is used to determine cholesterol levels subsequent to MER/29 therapy. Using this formula (and assuming the Liebermann-Burchard method), the total sterol reduction for a 16-percent cholesterol reduction would be between 10 percent and 11 percent.

The following table uses the cholesterol levels of two large groups reported in the American Journal of Medicine and in the Journal of the American Heart Association. It gives, in addition, the average percentage change per patient after MER/29 therapy, related to the initial cholesterol levels of patients:

Initial cholesterol level (mg. 1 percent)	Cumulative distribution, cumulative percentage of patients with cholesterol levels equal to or less than highest listed value		Average percent change per patient after MER/29 therapy
400 or more.....	<sup>1</sup> 100.0	<sup>2</sup> 100.0	-18
350 to 400.....	97.5	98.3	-19
300 to 350.....	91.3	96.5	-19
250 to 300.....	78.1	86.0	-14
200 to 250.....	41.1	40.4	-12
200 or less.....	8.1	12.3	-2

<sup>1</sup> Distribution of cholesterol levels in 273 men with a history of myocardial infarction—"Serum Lipids and Coronary Heart Disease," Lowry et al., American Journal of Medicine, April 1957, pp. 614-615.

<sup>2</sup> Distribution of new events in cooperative study on lipoproteins, etc., in "Circulation," Journal of American Heart Association, October 1956, vol. XIV, No. 4, pp. 735-736.

*(Agency Correspondence)*

October 25, 1961.

EVERETT HULLVERSON.

HULLVERSON, RICHARDSON & HULLVERSON,  
St. Louis, Mo.

FOOD AND DRUG ADMINISTRATION,  
Washington, D.C.

GENTLEMEN: I have a client who gave me a history of having taken MER/29 which is a product that is supposed to inhibit the production of cholesterol and is manufactured by the William S. Merrell Company, Division of Richardson-Merrell, Inc., Cincinnati, Ohio. This lady developed a very severe skin condition shortly after she began taking this product about 6 months ago. This condition is still with her and she also lost all of her hair.

She went to Mayo Clinic for treatment for this condition, not having any idea what was causing it, where she was informed it was due to taking MER/29. This lady also suffers sharp pains in her muscles and has some difficulty with her vision, all occurring since the taking of this MER/29.

I am desirous of getting the constituent elements (the formula) of this product and also of finding out what investigation, if any, was made by the governmental departments of this product and what information they have on the matter.

The doctors at Mayo Clinic informed her immediately when she told them she was taking MER/29 that they had been undergoing some investigation on it because a number of their patients had suffered from the effects of taking it.



The reason for her going to Mayo Clinic was that she had read an article about the investigation going on.

This lady is very seriously injured and we would like to determine what should be done under the circumstances.

Very truly yours,

EVERETT HULLVERSON.

*(Internal Agency Document)*

October 27, 1961.

JOHN O. NESTOR, M.D.

To: William H. Kessenich, M.D., Medical Director.

From: John O. Nestor, M.D., Medical Officer.

Subject: MER/29 Triparanol (NDA 12-066).

Wm. S. Merrell Company, Cincinnati, Ohio—AF 1-542, NDA 12-066.

After a thorough reviewing of the contents of NDA 12-066, consultation with outside authorities, interviews with representatives of William S. Merrell Company, and review of the most recent data submitted by the company on October 26, 1961, I have the following comments.

1. There is no objective evidence that the drug has any effect on either the prevention or alleviation of atherosclerosis and its resulting deleterious effects on humans.

2. It has been offered for use on the basis that it lowers blood and body cholesterol and that this in turn prevents or decreases atherosclerosis and its associated deleterious effects. No one has demonstrated that lowering blood cholesterol reverses or inhibits the development of atherosclerosis in humans. This is outlined in the official view recorded in the Federal Register on December 10, 1959.

3. The William S. Merrell Company has made unsubstantiated claims for the effectiveness of Triparanol in lowering blood cholesterol levels and this is reflected in their labeling. In fact, latest available data indicated that it does not significantly effect blood cholesterol levels in the hands of the Mayo Clinic group.

4. Overwhelming evidence has accumulated to demonstrate that MER/29 (Triparanol) produces severe adverse reactions and toxicity in both animals and humans. Much of this evidence was available in the NDA when it was made effective. Much of it has accumulated since.

5. Serious toxic effects in humans include (1) cataracts, (2) diminished libido, (3) impotence, (4) loss of hair, (5) change in color of hair, (6) ichthyosis, and (7) the depression of production of adrenal cortical hormones which are so important in resistance to stress and shock. There have also been suggestive reports of liver damage (fatty metamorphosis).

6. In experimental animals Triparanol has prevented ovulation and conception as well as producing defective offsprings in those that did conceive.

7. The William S. Merrell & Company has withheld from us some of this evidence of serious toxicity in animals and humans which has been in their possession for months.

8. The entire NDA plus the new information given to us by the company representatives on October 26, 1961, is being referred to the Division of Pharmacology for immediate review and comment.

9. Since Triparanol produces serious toxic effects in humans and since this drug has not been conclusively demonstrated to have any material clinical benefit consideration should be given to immediate suspension of this NDA as the potential benefit is not warranted by the definite risk. It should be clearly noted that the company knowingly has withheld certain pertinent information relating to these severe toxic reactions.

10. The physicians of the country should be alerted to this situation immediately.

JOHN O. NESTOR, M.D.



*(Internal Agency Document)*

October 30, 1961.

JOHN O. NESTOR, M.D.

## MEMORANDUM OF MEETING

Wm. S. Merrell Co., Cincinnati, Ohio—AF 1-542, NDA 12-066.

Present: Richard Achor, M.D., Mayo Clinic.  
Kenneth Berge, M.D., Mayo Clinic.  
Robert McMaster, M.D., William S. Merrell & Co.  
John O. Nestor, M.D., Division of New Drugs, FDA.

Date and place of meeting: 8:30 A.M., Americana Hotel, Miami, Florida, October 22, 1961.

Subject: To discuss adverse reactions to MER/29 with special reference to the eyes.

1. Dr. Achor has observed two cases of posterior subcapsular lens cataracts which developed several months after therapy with MER/29 was discontinued because of severe skin and hair changes, specifically thinning of hair and color changes and ichthyosis. He has been unable even to confirm a significant lowering of blood cholesterol.

2. Dr. Achor and Dr. Berge both expressed the opinion that the drug should only be available for investigation and not for general use.

3. They suggested that all medical investigators on this drug be contacted immediately and warned to look for eye changes.

4. They further suggested that FDA adopt a policy of requiring that any medical investigator who signs a form agreeing to investigate a drug should be required to send a duplicate of the report of his results to FDA. They think that many reports never get to FDA under the present circumstances.

5. Both Dr. Achor and Dr. Berge indicated willingness to appear and testify in support of any move to remove MER/29 from general use on prescription.

JOHN O. NESTOR, M.D.

*(Agency Correspondence)*

November 7, 1961.

FOOD AND DRUG ADMINISTRATION.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,  
FOOD AND DRUG ADMINISTRATION,  
Washington, D.C.

HULLVERSON, RICHARDSON & HULLVERSON,  
Attorneys at Law,  
722 Chestnut St., St. Louis, Mo.

Attention: Everett Hullverson.

GENTLEMEN: This replies to your letter of October 25, 1961, in which you request certain information on MER/29 manufactured by the William S. Merrell Company, Division of Richardson-Merrell, Inc., Cincinnati, Ohio.

The generic name for MER/29 is triparanol and its chemical name is 1-(p-(b-diethylaminoethoxy) phenyl-1-(p-tolyl)-2-(p-chlorophenyl) ethanol.

This product is a new drug which has been represented by the manufacturer as efficacious in the treatment of coronary artery diseases and generalized atherosclerosis as well as for other conditions thought to be associated with abnormal cholesterol metabolism. We are enclosing a copy of a brochure on the product prepared by its manufacturers which gives further information, including a brief discussion about possible side effects.

The New Drug Application covering MER/29 became effective April 25, 1960, but since the data given in the New Drug Applications must be held confidential, we regret we cannot provide further information.

Sincerely yours,

VAN W. SMART,  
Assistant Director.

Division of Regulatory Management, Bureau of Enforcement.



*(Article in the Open Literature)*

November 11, 1961.

COUNCIL ON DRUGS, AMERICAN MEDICAL ASSOCIATION.<sup>46a</sup>NEW DRUGS AND DEVELOPMENTS IN THERAPEUTICS<sup>47</sup>

## Council on Drugs' Digests

Triparanol (MER/29) (trī pār' ā nōl) is a triphenylethylene derivative (1-[p-β-(diethylaminoethoxy)-phenyl]-1-(p-tolyl)-2-(p-chlorophenyl)ethanol) which can inhibit synthesis of cholesterol in the body. This block occurs at the final step in this process, resulting in the accumulation of desmosterol, the immediate precursor of cholesterol, in blood and presumably in tissues.

Triparanol has been used orally to reduce hypercholesteremia in patients with coronary insufficiency or generalized atherosclerosis. However, since their cholesterol is replaced partially by desmosterol, which is very similar to cholesterol physiologically and pharmacologically, more clinical evidence is required to prove that these patients benefit from the use of triparanol. Because desmosterol produces a lower reading than does cholesterol in certain colorimetric techniques for determination of blood cholesterol, such assays may yield lower total sterol values than are actually present. The investigations performed on patients with angina pectoris are not convincing in view of the difficulties in determining the efficacy of drugs in this disease. Carefully controlled clinical studies on the use of triparanol in atherosclerosis will have to be continued a longer time before any conclusions on its clinical effectiveness can be reached.

*Adverse reactions* to this drug, which have not been reported to be of a dangerous nature to date, consist of nausea, vomiting, skin rash, dry skin, ichthyosis, loss of hair or its pigmentation, vaginal smear alterations, temporary menstrual bleeding, transient increase in bromsulphalein retention, elevated plasma alkaline phosphatase, and leukopenia. Nevertheless, since cholesterol is a precursor of many steroid hormones, careful and detailed observations will be required to insure that serious endocrine disturbances will not occur. For example, recent experimental studies have demonstrated that this drug can reduce significantly the production of certain adrenocorticoids in normal subjects. Because cholesterol is an important constituent of body cells, including erythrocytes, the present clinical studies have not been pursued long enough to insure that multifarious and serious alterations may not occur, especially on prolonged therapy.

Triparanol is contraindicated in pregnancy.

It is the opinion of the council and its consultants that all patients receiving triparanol be maintained under the carefully controlled conditions of clinical investigations and that the only indications for its use at present should be severe atherosclerosis or hypercholesteremia unresponsive to other types of therapy such as diet, nicotinic acid, or polyunsaturated oils.

*Commercial source.*—MER/29. The Wm. S. Merrell Co.

*(Internal Agency Document)*

November 13, 1961.

JOHN O. NESTOR, M.D.

To: William H. Kessenich, M.D.

From: John O. Nestor, M.D.

Subject: Memo of meeting.

MER/29 (Triparanol) William S. Merrell Company, Cincinnati, Ohio.

NDA 12-066

AF 1-542

1. Eyes—Cataracts, corneal opacities.
2. Hair—Loss of hair, thinning and changes in color and texture.
3. Skin—Ichthyosis, urticaria, drying, scaling, and itching.
4. Reproduction—Impotence, loss of libido, reduced spermatogenesis. Prevention of ovulation and conception. Abnormal offspring. Vaginal smear alterations, temporary menstrual bleeding.
5. Adrenals—Reduced production of adrenocorticoids with associated diminished ability to respond to stress.
6. Blood—Hemolytic anemia. Leukopenia.
7. Liver—Fatty metamorphosis. Transient increase in BSP retention.
8. G.I.—nausea and vomiting.

JOHN O. NESTOR, M.D.

<sup>46a</sup> See pp. 881-884 for the evaluation of MER/29 which had been prepared by the AMA Council on Drugs 6 months earlier.

<sup>47</sup> Journal of the American Medical Association, p. 574.



November 19, 1961. FDA meets with members of the firm to discuss scattered reports of cataracts associated with MER/29.

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(Article in Trade Publication)

November 20, 1961.

F-D-C REPORTS—THE PINK SHEET.<sup>48</sup>

MER/29 Regulatory Status was fingered by AMA Council on Drugs monograph in JAMA Nov. 11 which said that the council and its consultants believe the drug should be used only on patients being "maintained under carefully controlled conditions of clinical investigation." By questioning MER/29 efficacy, the AMA council confronted the Food and Drug Administration (FDA) with a regulatory decision on whether it should shift its attention away from the side effects and focus on the much-harder-to-handle efficacy matter. If FDA followed its traditional procedure, it has passed the buck to Merrell for the initial decision on whether the next step will be "voluntary" or "regulatory."

AMA based its skepticism on MER/29 clinical efficacy, in part, on a key research finding by an NIH group, i.e., "cholesterol is replaced partially by desmosterol." Since the two are "very similar," AMA said, "more clinical evidence is required to prove that these patients benefit" from MER/29 ("F-D-C" Oct. 29).

Merrell has proof that MER/29 does reduce total sterols in the body, but AMA questioned the actual amount of the reduction and its value. NIH-ers and FDA-ers no doubt have been in consultation since they are sister agencies in the same Gov. dept.

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(Drug Warning Letter)

December 1, 1961.

WM. S. MERRELL CO.

DRUG WARNING—MER/29 (TRIPARANOL)

DEAR DOCTOR:

In cooperation with the U.S. Food and Drug Administration, we are writing to inform and caution you concerning adverse effects, including some unpublished reports, associated with the use of MER/29 (Triparanol). Although comparatively few serious clinical injuries have been reported to date, their possible significance is emphasized by findings from animal studies.

**Cataracts.**—Four cases of cataracts in humans are reported in patients who have received MER/29. One of these cases occurred in a patient receiving the recommended dosage of 250 milligrams of MER/29 daily. Cataracts and corneal opacities have also been produced with MER/29 in animals. Slit lamp examinations are necessary for early detection of developing cataracts. For this reason such examinations are indicated prior to and periodically during therapy. Before this problem came to our attention, approximately 1,000 persons being treated with MER/29 were patients of ophthalmologists. Most of them have had careful eye examinations, including use of the slit lamp, before and during drug therapy. Results on these patients will be reported to you as soon as they are available.

**Hair Changes.**—There have been many cases of hair loss, either baldness or thinning of hair, changes in hair color and texture, and loss of body hair. Such hair changes may be related to the skin changes discussed below as well as to the eye changes described above. It is recommended that MER/29 therapy be discontinued promptly at the first evidence of hair or skin changes to minimize progressive effects possibly including eye injury.

**Ichthyosis and Other Skin Changes.**—There are reports of skin reactions ranging from dryness, itching, and scaling to severe exfoliation, and ichthyosis. Some of these changes were also associated with hair loss and cataracts. It is recommended that MER/29 therapy be stopped immediately if such skin changes occur.

**Depression of Adrenocortical Function.**—Adrenocortical function depression as shown by reduced output of adrenal steroids has been produced by MER/29 in animals, and in man at high dosage levels. This effect has not been ruled out in humans at recommended dosage levels. Appropriate precautions should be observed if MER/29 is employed in patients with suspected borderline adrenocortical function or in patients who are subjected to stress.

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<sup>48</sup> Vol. 23, No. 47, pp. 19-20.



**Other Adverse Effects.**—Other adverse clinical effects reported include 4 possible cases of leukopenia and scattered cases of abnormal liver function tests, impotence, diminished libido, vaginal smear alterations, nausea, vomiting and urine test changes simulating proteinuria. At a level of 25 milligrams/kilograms per day of MER/29 deaths have occurred in some dogs within 35 days, with liver damage in some animals. It has caused abortion and prevented conception in rodents, diminished spermatogenesis in dogs, stopped egg laying in chickens, and was assumed to cause acute intravascular hemolytic episodes in some dogs in one study.

The side effects of all types reported to us to date total substantially less than one percent of the patients treated. This includes a number of patients who have been treated with MER/29 in clinical research studies for continuous periods of more than a year, including a few in excess of 3 years.

In view of all reports concerning adverse effects, it is recommended that MER/29 be used only in patients who can be maintained under very close supervision and frequent observation. Dosage should never exceed 250 milligrams per day.

Further studies are underway to assess more fully the incidence and seriousness of adverse effects, with a view to a re-evaluation of the conditions and indications for use of MER/29. We will appreciate any information you may contribute from your clinical experience with MER/29.

Sincerely,

CARL A. BUNDE, Ph. D., M.D.,  
*Director of Medical Research.*

*(Letter to Editor and Response in the Open Literature)*

December 2, 1961.

CARL A. BUNDE, M.D.<sup>49</sup>

#### MER/29 AND LOSS OF HAIR

To the Editor:—Two patients have been observed recently with an unusual complication following the use of MER/29. A report of this side effect has not been discovered by me in the available literature. Both patients, white females, aged 70 years, noted the onset of generalized heavy loss of hair from the scalp upon starting this medication. There was no evidence of any local disease of the scalp, either before or during this period of time. No other cause of the severe hair loss was known. The medication had been given for several months before these patients informed me of the hair loss. About half of their hair was lost during this time. After drug administration was discontinued, one patient reported 80 percent decrease in hair loss. The other patient states that the hair loss has continued. Up to the present time, there has been no regrowth of hair in either patient.

EDWARD S. KOZIOL, M.D.,  
2010 Wilshire Blvd., Los Angeles.

*The above comment was referred to the pharmaceutical manufacturer, and the following reply was submitted.*—ED.

To the Editor:—This is hair loss of a more severe degree than has previously been reported, but lesser hair thinning has been reported in the Proceedings of the Mayo Clinic for April 26, 1961. Doses in these patients were higher than recommended, and that possibly accounts for the high incidence; 7 patients were reported. Several times during oral presentation of research on MER/29 or during discussion of these papers, occasional hair loss has been mentioned. The usual experience has been regrowth when the drug was discontinued. The new literature and labeling for MER/29 state, "Isolated reports have been received of nausea, vomiting, temporary vaginal bleeding, dermatitis, and thinning of the hair."

CARL A. BUNDE, M.D., Ph. D.,  
*Director of Medical Research, The Wm. S. Merrell Company, Cincinnati.*

<sup>49</sup> Correspondence, Journal of the American Medical Association, vol. 178, No. 8, p. 967.



*(Article in Trade Publication)*

December 4, 1961.

F-D-C REPORTS—"THE PINK SHEET"<sup>50</sup>**MERRELL-FDA DISCUSSIONS ON FUTURE OF MER/29 RESULT IN SENDING "DEAR DOCTOR" LETTER TO ALL MDs WARNING AGAINST SIDE EFFECTS**

A "dear doctor" letter warning against all reported side effects and contraindications for the use of Merrell's MER/29 was put into the mails on a midnight-Fri. (Dec. 1) deadline, Merrell's President Frank N. Getman told "The Pink Sheet." The letter was cleared by the Food & Drug Administration (FDA) last week after a lengthy series of conferences between Merrell and Govt. MDs.

The future of the drug was at stake in the Merrell-FDA conferences, and the regulatory discussions ran the full range—from no action to stiffer labeling and a "dear doctor" letter to "voluntary" removal from the market to forced removal by suspension of the New Drug Application (NDA) in a legal proceeding that could be contested.

FDA's acceptance of a "dear doctor" letter in lieu of removal from the market indicates Govt. thinking that the potential efficacy—benefits—of the drug outweigh the risks inherent in the side effects, as long as MDs are fully informed.

The drug's close call is pointed up by the Amer. Medical Assn.'s (AMA) Council on Drugs monograph, published in the Nov. 11 AMA Journal. The council said the drug should be used only on patients being "maintained under carefully controlled conditions of clinical investigation." (F-D-C Oct. 29 & Nov. 20.)

**MER/29 Sales \$9.1 Mil. In Fiscal 1961, Merrell Discloses**

A Merrell announcement on the letter to MDs, distributed for publication today (Mon. Dec. 4), disclosed that sales of the product ran at \$9.1 mil. for the fiscal year ending last June 30. The announcement said:

"William S. Merrell Co., div. of Richardson-Merrell, has just mailed a letter to doctors summarizing all side effects of any nature from MER/29 that have been reported to Merrell. These total substantially less than 1 percent of the more than 300,000 (patients) to whom its anti-cholesterol drug, MER/29, has been prescribed since its introduction June 1, 1960.

"The letter was developed in cooperation with the Federal Food & Drug Administration to alert the doctor and bring him up to date on reported side effects and contraindications for MER/29 and to guard the medical profession in its use of this drug.

"MER/29 was the largest prescription product of Richardson-Merrell during the last fiscal year ended June 30, 1961. However, because Richardson-Merrell has a number of other specialty products of substantial size, MER/29 accounted for less than 6 percent of consolidated sales and a somewhat higher percentage of consolidated income.

"MER/29 was developed by Merrell after nearly 10 years of research and has the unique ability of inhibiting the body's own production of cholesterol. Many leading heart specialists are convinced that high cholesterol levels are directly related to atherosclerosis and other heart illness. MER/29 was selected as the most significant advance in medical therapy in 1960 through a poll of physicians conducted by Medical Research Digest."

Richardson-Merrell's net sales in fiscal 1961 totaled \$151.5 mil. (F-D-C Sept. 25), and 6 percent of this would be about \$9.1 mil. Six percent of the company's \$17 mil. net after taxes would be about \$1 mil. A \$9.1 mil. volume in the first year after MER/29's introduction would have accounted for 13 percent of Richardson-Merrell's 1961 pharmaceutical sales of \$69.9 mil.

Disclosure of MER/29 sales and an approximation of its contribution to Richardson-Merrell's profits were obviously designed to counteract "The Street's" anticipated reaction to the news that a "dear doctor" letter had been sent. Rich-Merrell stock hit 107 the week ending April 7 of this year, then trailed off down through the 90's to a low of 84 on July 4.

It bounced back quickly into the 90's, closing 2 weeks later at 93¾, and remained above 90 ever since—except for 2 weeks, Sept. 8 closing 89 and Sept. 15 closing 87¾. From there it climbed steadily to 103¼ on Oct. 20 and to a

<sup>50</sup> Pp. 24-25.



peak for the year at 107 $\frac{3}{4}$  on Nov. 17. It was off 4 $\frac{3}{4}$  the next week, and last week it was off 7 $\frac{3}{8}$  to 95 $\frac{5}{8}$ .

MER/29 grew in its introductory year "to become both the Nation's most-widely prescribed anti-cholesterol drug and also our largest selling ethical products," Rich-Merrell said in its annual report issued the latter part of Sept. Pharmaceutical marketing men had calculated that MER/29 had a chance to become a \$25-mil. a year product.

*"Full Disclosure" Letter Includes Animal Research Findings and Warnings*

Merrell's "full disclosure" letter to M.D.'s discusses certain animal research findings, and contains warnings that the drug should be discontinued if certain specific conditions develop in the patient. The warnings against major side effects cover ichthyosis, hair loss, cataracts, and decreased adrenal function at high dosage, as well as others of less serious import.

Revision of the MER/29 labeling will follow at a later date, and there were indications that considerable crossing of "T's" and dotting of "I's" remains to be accomplished.

MER/29 got major headlines and favorable press play in the Washington newspapers on Nov. 28, just about the time a decision was being reached, as the result of a report made to the D.C. Medical Society meeting by Dr. William Hollander of Boston Univ.

*(Article in Financial Newspaper)*

December 7, 1961.

WALL STREET JOURNAL.<sup>51</sup>

ADVERSE SIDE EFFECTS INCREASING AS MORE NEW DRUGS HIT MARKET

PATIENTS REPORT HAIR LOSS, SKIN SCALING; PHYSICIANS TOLD TO WATCH MER/29 USE

(By a Wall Street Journal Staff Reporter)

NEW YORK.—A spate of unexpected adverse side effects are popping up among medicines.

Richardson-Merrell, Inc., big drug and chemical maker, earlier this week cautioned doctors in a special letter to watch for possible adverse effects in patients using its new drug, MER/29. The drug is being used to lower the level of a blood fat, cholesterol, in persons with heart disease.

Physicians were told that a small percentage of patients using the drug—"substantially less than 1 percent"—had reported such changes as hair loss, skin scaling and some suggestion of eye damage. The letter was sent to doctors after conferences between the company and the Food and Drug Administration.

DRUG BEING WITHDRAWN

Norwich Pharmacal Co. is in the process of voluntarily withdrawing from the market its germ-fighting drug, Altafur. Doctors, pharmacists and drug wholesalers are being notified to discontinue use of the drug.

The withdrawal comes in the midst of a fight between Norwich and the FDA over side effects of Altafur, which was used to fight widespread infections, particularly those resistant to other drugs. An FDA examiner, in recent weeks, has ruled that the side effects—nausea and vomiting—outweighed the drug's benefits and that Federal approval of the drug's safety should be withdrawn. The company is contesting the ruling and the battle could eventually wind up in the courts.

Last month, McNeil Laboratories division of Johnson & Johnson voluntarily took three of its drugs off the market. The drugs, all of which contained a chemical called zoxazolamine, were used to treat gout and as muscle relaxants. The company told physicians a few cases of hepatitis had been associated with the drug. The question was raised whether the hepatitis was caused by the drugs or by viruses, the concern added. It was recommended that doctors discontinue using the drugs until the question was resolved.

Troubles with drug side effects, while far from common, are not unexpected. Drug makers and doctors note that as more new drugs are developed to fight more diseases, the problem of side effects will pop up increasingly.

<sup>51</sup> P. 2.



Many new drugs are highly potent and side effects are expected in a number of patients. Such drugs, however, are able to combat diseases that before were untreatable. An extreme example is anti-cancer drugs which are highly poisonous but are able to prolong the lives of a few patients.

Side effects, however, are drawing increasing attention from doctors, manufacturers and Uncle Sam. Earlier this year the FDA began requiring drug makers to put notices in all drug packages. The notices list not only the drug's use and benefits, but also all information on side effects and conditions under which it should not be used. The FDA also, has been going over applications for clearance of the safety of new drugs far more thoroughly.

#### "KICK BACKS" ARE INCREASING

Drug makers recently have reported an increasing number of instances where new drug applications were "kicked back" to companies for additional research on the safety of the drug. Such kick backs are delaying the marketing of some drugs by months, the companies say. An FDA spokesman explains that, while there has been no formal change in FDA strictness on clearance of new drugs, the agency has an expanded staff and is able to go over the applications more thoroughly than in the past.

Drug makers do considerable research on the effectiveness and safety of the drugs, in both men and animals, before the drugs are marketed. They also keep close track of the drugs after they are marketed for any evidence of unexpected side effects. In some instances, side effects will appear in such rare instances—one out of every 1,000 patients, for example—that they do not become evident until the drug is in wide use.

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#### (Letter to Editor and Response in the Open Literature)

December 9, 1961.

BETTY Jo TRICOU, M.D.<sup>52</sup>

#### TRIPARANOL

*Question.* A patient who has used triparanol for about a year developed fine kinky depigmented hair which fell out in bunches. The skin became dry, scaly, thin, and tender. In 4 months, after discontinuing triparanol, there has been no change. The serum cholesterol level is 135 milligrams per 100 milliter, whereas it was 190 milligrams 2 months after starting triparanol. Will the skin and hair revert to normal? Is triparanol stored in the body in amounts sufficient to exert an effect long after being discontinued?

M.D., Idaho.

*Answer.* Achor, Winkelmann, and Perry (Proc. Mayo Clin. 36:217 (April 26) 1961) reported 7 cases of hair loss in patients taking triparanol. Two of these developed severe ichthyosis. The authors believed that these effects were probably reversible, but improvement was not noted until 3 or 4 months after cessation of triparanol therapy. It is also of interest that the serum cholesterol values were low in these patients for at least 2 months after the discontinuation of triparanol. In most patients who have responded to triparanol with a reduction in cholesterol, there is a return to pretreatment serum cholesterol values in 2 to 8 weeks.

The very limited data available on absorption and excretion of triparanol indicates that there is probably very little storage of the drug, but the drug acts by producing a metabolic block at the last step in cholesterol biosynthesis—the reduction of desmosterol to cholesterol. The presence of this metabolic blockade is always accompanied by the accumulation of desmosterol in the serum. It would be of interest to determine the serum desmosterol level in the patient described, to see whether the metabolic blockade persists. (See the statement by the Council on Drugs on triparanol JAMA 178:574 (Nov. 11) 1961.)

BETTY Jo TRICOU, M.D.

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<sup>52</sup> Correspondence, Journal of the American Medical Association, vol. 178, No. 10, p. 194.



*(Article in Trade Publication)*

December 11, 1961.

F-D-C REPORTS—THE PINK SHEET<sup>53</sup>

## IN BRIEF

\* \* \* *Smart P.R.*: Merrell's press release on MER/29 "dear doctor" letter blunted impact of news that would have seemed hotter \* \* \*

*(Article in Medical Newspaper)*

December 18, 1961.

MEDICAL TRIBUNE.<sup>53a</sup>

## WARNING ON POSSIBLE SIDE EFFECTS OF TRIPARANOL SENT TO PHYSICIANS

## Medical Tribune—World Wide Report, Washington Bureau

WASHINGTON, D.C.—A letter has been issued informing physicians of the side effects of triparanol, marketed as an oral drug to reduce blood cholesterol. The letter, prepared in cooperation with the U.S. Food and Drug Administration, was sent by the manufacturer, Wm. S. Merrell Co., Cincinnati.

John L. Harvey, Deputy FDA Commissioner, told Medical Tribune the purpose of the letter was twofold: to put physicians on notice that certain side effects have occurred in a relatively few cases, and to "smoke out" additional information from physicians on their own experience with the drug. The FDA official emphasized that "the total number of cases [of side effects] was quite small when compared to the tremendous use being made of this drug."

Four patients, three of whom took doses in excess of the daily level recommended by the manufacturer, evidenced cataracts, the most significant finding observed to date. Commissioner Harvey cautioned that it was difficult to establish a cause and effect relationship. He pointed out that the letter emphasized the need for slit-lamp examinations of patients suspected of eye changes as well as the importance of holding the dose rigidly to the 250 milligrams recommended per day.

## LESS THAN 1 PER CENT

He noted that other side effects observed or reported since the beginning of the use of the drug included skin rash, urticaria, ichthyosis, alopecia, and changes in pigmentation of hair. The letter issued by the manufacturer stated that "the side effects of all types reported to us to date total substantially less than 1 percent of the patients treated." According to the company's statement, this included patients receiving the drug in clinical research studies for continuous periods of more than a year and a few given it for more than 3 years.

*(Editorial in the Open Literature)*

December 23, 1961.

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION.<sup>54</sup>

## CHOLESTEROL-LOWERING AGENTS

Diets and drugs that lower the serum cholesterol level are believed to be highly desirable as one means of preventing atherosclerosis. G. C. Chiu<sup>55</sup> has made a comprehensive review of the mode of action of many of the cholesterol-lowering chemical agents, which have been extensively studied clinically. They include unsaturated fats, sitosterol, niacin, thyroid hormones and their analogues, and triparanol.

A shift from an unprescribed mixed diet to a rice diet which is free of cholesterol and fats causes a sharp fall in the serum cholesterol, but this is a monotonous diet, and it is hard to adhere to for any length of time. The use of rela-

<sup>53</sup> Vol. 23, No. 50, p. 26.<sup>53a</sup> P. 1.<sup>54</sup> Editorial, vol. 178, No. 12, pp. 1158-1159.<sup>55</sup> Chiu, G. C.: Mode of Action of Cholesterol-Lowering Agents, Critique of Facts and Theories, Arch Intern Med 108:717-732 (Nov.) 1961. (Original footnote—ed.)



tively unsaturated fats such as corn, safflower, cottonseed, peanut, or fish oils also reduces the serum cholesterol. In order to obtain a significant lowering of the concentration, however, at least 50 percent of the saturated fats (butter, lard, coconut oil, or hydrogenated vegetable oils) in the diet must be replaced by unsaturated fats. The cholesterol-lowering effects of such a change in diet has been ascribed to (1) higher net unsaturation of dietary fats and increased excretion of cholesterol, (2) increased supply of polyunsaturated fatty acids (linoleic, linolenic, and arachidonic) and decreased endogenous formation of cholesterol, and (3) higher intake of sitosterol, which is contained in vegetable oils and which prevents absorption of cholesterol, plus decreased intake of cholesterol, which is contained in animal fats.

Without dietary manipulations, reduction of hypercholesteremia can be obtained by taking 15 cubic centimeters of 20 percent aqueous suspension of sitosterol before meals or by using the other aforementioned drugs. In contrast to cholesterol, sitosterol, which is closely related to cholesterol chemically, is poorly absorbed from the intestine. The minute amounts which are absorbed do not accumulate in the body but are excreted through the bile and feces. No side effects of sitosterol have been noted. Sitosterol forms nonabsorbable mixed crystals with cholesterol in the intestine. It also may compete with cholesterol for esterification or for absorption. By these mechanisms it interferes with the absorption of dietary cholesterol and endogenous cholesterol, which is chiefly formed in the liver and excreted through the bile to be partly reabsorbed from the intestine (enterohepatic circulation).

Niacin, which is part of the vitamin B complex, when given in large amounts (3 to 6 grams a day) also reduces the serum cholesterol. Flushing, burning sensation of the skin, and itching occur at the start of therapy and usually subside after a few days. Abnormal hepatic function and decreased glucose tolerance have been observed in some patients. Nicotinamide, which rarely, if ever, produces these side effects, has no effect on serum cholesterol. Decreased cholesterol synthesis, a shift of cholesterol from the serum to liver, and other hypotheses have been advanced to explain the cholesterol-lowering action of niacin. The subject is still controversial.

Thyroid hormones have long been known to reduce serum cholesterol and to increase the basal metabolic rate (BMR). The latter effect makes the hormones unsuitable as a cholesterol-lowering agent in patients with normal thyroid function. Recently, various thyroxin analogues have been under clinical investigation and found to reduce serum cholesterol with little or no increase in BMR, but anginal attacks occurred in some patients who had coronary artery disease and who were treated with these analogues. The cholesterol-lowering effect of thyroid hormones has been shown to be unrelated to an increase in the metabolic rate. The best explanation is that the hormones, and presumably their analogues, cause cholesterol elimination to exceed cholesterol synthesis.

Triparanol, a relatively new drug, reduces the cholesterol content not only in the serum but also in the tissues. This action is due to an inhibition of cholesterol synthesis. The immediate precursor of cholesterol is desmosterol. Triparanol blocks its conversion to cholesterol. This blockage leads to a diminution of cholesterol but an accumulation of desmosterol in the serum and tissues. Since the 2 sterols are closely related in chemical structure, further work is warranted to determine whether desmosterol is as atherogenic as cholesterol. In the initial clinical studies, no side effects of triparanol were noted. Recently, Achor et al.<sup>56</sup> reported ichthyosis, change in hair color, and loss of hair in 7 of 19 patients receiving the drug. The side effects appeared at the daily dosage of 250 milligrams in 1 patient and of 500 or 1,000 milligrams in 6 patients. The side effects disappeared in a few months after the medication was discontinued or the dosage reduced.

No conclusive evidence has yet been obtained that atherosclerosis in man can be prevented or cured by lowering the serum cholesterol level. It seems a medically sound approach, however, to reduce hypercholesteremia, since it is implicated as an important factor in atherogenesis. The substitution of unsaturated for saturated fats in the diet should be prescribed and, if necessary, one of the aforementioned drugs may be tried.

<sup>56</sup> Achor, R. W. P.; Winkelmann, R. K.; and Perry, H. O.: Cutaneous Side Effects from Use of Triparanol (MER/29): Preliminary Data on Ichthyosis and Loss of Hair, *Proc. Mayo Clin* 36:217-228 (Apr. 26) 1961.



(Article in Weekly News Magazine)

December 25, 1961.  
NEWSWEEK.<sup>56a</sup>

#### WORTH THE RISK

During the past 18 months—spurred by evidence linking high blood cholesterol levels to heart attacks—some 300,000 Americans have been taking, on doctors' orders, an effective anti-cholesterol pill. Last week the manufacturers of the pill, MER/29, issued a warning: The drug *may* cause cataracts.

In a letter to all licensed physicians, Dr. Carl A. Bunde of the William S. Merrell Co. of Cincinnati reported cataracts in 4 patients taking the drug. Two of them took more than the recommended dosage; no definite relationship between MER/29 and cataracts is established. Yet the possible significance of the cases, Dr. Bunde said, "is emphasized by findings from animal studies."

Should people stop taking MER/29? "The number of cataract cases does not justify withdrawal," said Dr. Irvine H. Page, heart researcher of the Cleveland Clinic Foundation. Cardiologists generally agreed: If MER/29 reduces heart attacks, it is worth the risk of cataracts.

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March, 1962. FDA receives a report from an ex-employee of the firm to the effect that a monkey study reported by the firm has been falsified. An investigation is begun.

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(Internal Agency Document)

April 3, 1962.

J. Deutschberger, Bureau of Program Planning and Appraisal, Food and Drug Administration

#### UNITED STATES GOVERNMENT MEMORANDUM

To: Dr. John O. Nestor, Bureau of Medicine.

From: J. Deutschberger, Bureau of Program Planning and Appraisal.

Subject: NDA 12-066, MER/29, Wm. S. Merrell Co.

We have examined the supplement to NDA 12-066, MER/29, and we have the following comments:

It appears to us that the most meaningful data contained in the supplement are summarized in table 1, exhibit E. The Wm. S. Merrell Co. has managed to collect information about 415 patients who were treated with MER/29 by ophthalmologists. Of these patients, 293 had slit lamp examinations prior to the start of MER/29 therapy. These 293 patients are the only ones for whom it may be said that there are baseline data adequate to permit an evaluation of eye changes while on therapy.

In the group of 293 patients who had baseline slit lamp examinations, 89 (30.4 percent) had cataracts prior to the start of therapy. The average age of these patients was 68.3 years. The figure 30.4 percent is a prevalence figure for this group—and the patients who had cataracts were at risk for, so far as we know, an average of 68.3 years.

The remaining 204 patients had no cataracts at the time of the baseline examination. In a short time on therapy (the average length can be determined from an examination of the case reports, and is probably about 1 year), 22 (10.8 percent) developed cataracts. This is an incidence figure, with the length of time at risk, so far as we know, only a year or so.

While incidence and prevalence data are not comparable, it would appear to us that the incidence of cataracts in MER/29 patients is extremely high. If, for example, in the group of 293 patients with baseline slit lamp examinations, 89 had developed cataracts in the 10 years immediately prior to MER/29 therapy, the average yearly incidence for these 10 years would be only 3 percent.

We understand that it is extremely difficult to obtain incidence data on cataracts. We have been informed that the National Health Survey has compiled data on the prevalence of cataracts in the United States. These data are unpublished, and are confidential until publication, but will be available to FDA on request.

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<sup>56a</sup> Section on Medicine, p. 53.



April 10, 1962. FDA makes an inspection at the William S. Merrell Company in Cincinnati. Animal data on monkeys is obtained which differ from that submitted in the original New Drug Application.

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April 12, 1962. Representatives of the firm, in a meeting with FDA, agree that the drug should be withdrawn from the market.

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April 16, 1962. Firm submits to FDA a letter requesting suspension of the New Drug Application.

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*(Internal Agency Document)*

April 16, 1962.

FOOD AND DRUG ADMINISTRATION.

*(Memorandum of Conference)*

NDA 12-066

Present: Mr. J. Harvey, Dr. Kessenich, Dr. Siegel, Dr. Nestor and Mr. D. Hansen, FDA; and Mr. Silliman, Mr. Mintener, Richardson-Merrell Corp. (Wm. S. Merrell).

Date: April 16, 1962.

Subject: MER/29.

Subsequent to a request for an appointment with Mr. Harvey sought on April 12 by Mr. Mintener, the visitors were received at 10:00 a.m. in Mr. Harvey's office.

The purpose of the visit was to submit a letter indicating the intention of the Wm. S. Merrell Co. to withdraw from the market MER/29 (triparanol). The Merrell representatives submitted a letter to the Food and Drug Administration requesting suspension of their NDA for this drug. They also submitted their proposal for the mechanics of withdrawing this product from the market which included a letter of notification addressed to physicians, pharmacies, hospitals, etc. The proposed letter to physicians as initiated by the firm was found to be unsatisfactory to the Food and Drug Administration. Following the discussion of the various points that we felt should be brought to the attention of the medical profession as well as the concern of the firm about the various aspects of liability involved in an action on their part, it was agreed that additional efforts to develop a satisfactory letter would be undertaken by FDA as well as the firm and that a subsequent meeting would be held later the same day, April 16. It was agreed then that the Merrell representatives would meet in the Bureau of Medicine with representatives of that Bureau at 1 p.m., April 16.

WILLIAM H. KESSENICH, M.D.,  
*Medical Director.*

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*(Internal Agency Document)*

April 16, 1962.

FOOD AND DRUG ADMINISTRATION.

*(Memorandum of Conference)*

NDA 12-066.

Present: Mr. Silliman, Wm. S. Merrell Co.; and Dr. Kessenich, Dr. Siegel, Dr. Nestor, and Mr. D. Hansen, FDA.

Date: April 16, 1962—1:00 p.m.

Subject: MER/29.

Mr. Silliman was advised that after considerable discussion and deliberation a letter to physicians which would be satisfactory to FDA should be somewhat as follows:

"Dear Doctor:

"In cooperation with the FDA, Merrell has decided to withdraw MER/29 from the market. It is recommended that you have your patients discontinue use of MER/29. We are today asking all hospitals and retail pharmacists as well as other possible outlets to return immediately their total stock of this drug.

"This decision is based on additional reports of clinical side effects of the kinds reported to you in our letter of December 1, 1961."



Mr. Silliman indicated that he was unable to accept such a letter without prior consultation with other principals of his firm, including the insurance carrier for the firm's products. He was given a copy of the Food and Drug Administration comments and indicated that he would notify us as to their decision later in the day.

WILLIAM H. KESSENICH, M.D.,  
*Medical Director.*

*(Internal Agency Document)*

April 17, 1962.

FOOD AND DRUG ADMINISTRATION.

*(Memorandum of Conference)*

Present: Mr. Silliman, Wm. S. Merrell Co.; and Dr. Wm. Kessenich, Dr. I. Siegel, and Dr. Nestor, FDA.

Date: April 17, 1962—10 a.m.

Subject: MER/29.

Mr. Silliman submitted a revised proposal of a letter to be sent to physicians incident to the withdrawal of MER/29. After considerable discussion a further revised draft was developed as follows:

"Dear Doctor:

"This letter is to inform you of the Merrell decision to withdraw MER/29 (triparanol) from the market. We are today, with the cooperation of the Food and Drug Administration, asking all hospital and retail pharmacies as well as other possible outlets to return immediately their total stock of this drug.

"This decision is based on additional reports of side effects of the kind reported to you in our letter of December 1, 1961, some of which have occurred at usual dosage. It is recommended that you have your patients discontinue use of MER/29.

"As you probably know, Merrell has had and will continue to have an extensive research program in cardiovascular disease. MER/29 has been one important phase of this effort. The work on this compound by us and many others has made contributions to basic knowledge in this field.

"We would appreciate any data you may be able to furnish us concerning your own past experience with this drug. Such data are most useful when supplied in case history form.

"Sincerely yours,

"FRANK N. GETMAN."

This draft letter was considered satisfactory by the Food and Drug representatives and subsequently was read by phone to Mr. Harvey who likewise considered it acceptable.

Mr. Silliman again wished to confer with his concern and with the insurance carriers. He indicated that he would call back concerning their decision on this letter.

A press statement was issued by the firm on April 16. This was carried in the Wall Street Journal on April 17 and no doubt will be carried elsewhere.

It made reference to the proposed letter to physicians which we found objectionable and did not issue. There were two principal points which we felt to be in error: 1. That no problems were encountered with the recommended use of the drug, and 2. that no new evidence had developed since the warning notice of December 1961. We believe the above letter corrects these points.

WILLIAM H. KESSENICH, M.D.,  
*Medical Director.*



(Article in Financial Newspaper)

April 17, 1962.

WALL STREET JOURNAL.

# RICHARDSON-MERRELL IS WITHDRAWING DRUG USED ON HEART PATIENTS; SIDE EFFECTS CITED

(By a Wall Street Journal Staff Reporter)

NEW YORK—Richardson-Merrell Inc., New York, announced it is withdrawing from the market its widely used anticholesterol drug, MER/29, because of controversy over its side effects.

The company mailed a letter to more than 230,000 doctors, to hospitals and to pharmacies, asking for immediate return of unused supplies of the drug.

"Continuing research and clinical experience has raised some questions concerning the possibility of an unacceptable incidence of side effects," the letter said. "This experience has not established that MER/29 is unsafe when used as recommended. However, out of an abundance of caution, we have determined that the sale of triparanol (MER/29) should be discontinued until all possible controversy is put to rest."

## STOCKHOLDERS NOTIFIED

At the same time, the company wrote stockholders, noting that MER/29 accounted for "less than 6 percent of consolidated Richardson-Merrell sales and a somewhat higher percentage of consolidated income" in the fiscal year ended last June 30. It said sales of the drug have fallen in recent months, but that increases in other products have "more than offset" the sales and earnings loss from the MER/29 decline.

Richardson-Merrell common stock closed on the New York Stock Exchange yesterday at \$84 a share, off \$5.25 from Friday's closing price. The company disclosed withdrawal of MER/29 yesterday morning.

## DRUG INTRODUCED IN 1960

MER/29 was introduced in May 1960, an agent to lower the level of cholesterol, a fatty substance in the blood, in certain heart patients. Cholesterol is a suspected, though unproven, cause of arteriosclerosis, in which arteries harden and become clogged. This often leads to heart attack.

Controversy over the drug became public last December when the company wrote doctors to describe harmful side effects reported in "substantially less than 1 percent" of patients treated. The side effects included four cases of eye cataracts, as well as baldness, skin reactions, and possible cases of leucopenia, serious disorder in which the white blood cell count is reduced.

A Richardson-Merrell official said "there is no particularly new evidence" since the December letter that motivated the withdrawal. He added that the decline in sales since December, plus the controversy among physicians, were major reasons for the action.

Company officials declined to say whether the Food and Drug Administration, the Federal drug policing agency, had played a role in the withdrawal of MER/29. The FDA, for some time, has taken a dim view of the side effects of the drug. In its December letter, Richardson-Merrell noted the warning was being sent out "in cooperation with the Food and Drug Administration. \* \* \*" It's understood, however, the FDA did not formally or officially demand that the drug be withdrawn from the market.

After its introduction in May 1960, the drug quickly became a leading product of Richardson-Merrell. A year ago, the company called it a major factor in an 18-percent gain in profit in fiscal 1961. It was the company's largest selling prescription drug and was advertised by the company as "the Nation's most widely prescribed anticholesterol drug."

Richardson-Merrell earned \$17,025,139, or \$2.86 a common share, on sales of \$152 million in the fiscal year ended last June 30.



(Editorial in the Open Literature)

April 1962.

THOMAS J. KIRBY, JR., M.D.<sup>57</sup>

The recent warning issued by the manufacturer<sup>58</sup> about the danger of the development of cataracts after the use of triparanol (MER/29), and the publication of an account of such a hazard in a widely circulated medium,<sup>59</sup> have caused considerable concern to members of the medical profession.

The writer has been reluctant to present a formal account of his clinical observations of the use and effects of this agent because to date his data lack statistical weight. Still, the effect of the warning of the manufacturer and other comments on this drug inevitably cause the question of responsibility to patients, to general physicians and to ophthalmologists to assume prime importance.

The present statement of views on the use and effects of triparanol will be followed by a paper detailing the writer's experience with the agent.

Undoubtedly, the news of the untoward effects of this drug has stimulated or will stimulate further investigation by other observers. If the first clinical findings are substantiated, an early report will help to protect patients and their physicians. Conversely, if the observations in question prove to be merely coincidental, an early report will help to disprove the allegations directed at the drug at present.

In October 1961 the manufacturers of triparanol were notified that two patients had cataracts which were believed to be complications of triparanol therapy. This warning and the consequent news report were the results of discussions between the manufacturers and members of the Food and Drug Administration of the Department of Health, Education, and Welfare. The news report to the effect that four patients were seen at the Mayo Clinic in whom cataract developed after triparanol therapy is incorrect.

Achor, Winkelmann, and Perry<sup>60</sup> reported the cutaneous side effects caused by triparanol (MER/29) on April 26, 1961. Two reports of moderately severe loss of hair, changes in the color of the hair, and ichthyosis were given. Milder reactions of five other patients were discussed. In the present editorial the ophthalmologic observations in the two patients who exhibited moderately severe cutaneous reactions will be considered.

Early in the course of the ichthyosis of these two patients blepharoconjunctivitis developed, with meibomianitis as part of the ectodermal disease. Their vision was normal and routine ophthalmoscopic examination revealed no changes in the lenses. The blepharitis remained troublesome for several months, during which time the skin and hair were returning to normal. Both patients complained of blurred vision 8 months after the onset of the ichthyosis.

The first patient reported immediately for re-examination. The vision was slightly less than 20/20 in each eye. The vision on previous examinations had been recorded as 20/15 or 20/20+. Posterior subcapsular cataracts with milder anterior subcapsular opacities were seen in each eye. The cataracts resembled an early form of irradiation cataract. The patient's general health was good; he was 37 years old. There was no disease other than the idiopathic hypercholesterolemia. No drugs other than triparanol and nicotinic acid had been taken. Treatment with nicotinic acid had been discontinued in December 1959, 4 months before the use of triparanol was started in April 1960. The family history was negative in respect to presenile cataract. There was no history of exposure to irradiation or toxic environmental factors. A tentative diagnosis of complicated cataract was made.

The second patient lived at a distance from the Mayo Clinic; a change of glasses prescribed and fitted in his home city did not help the blurred vision. At the time of his re-examination at the Mayo Clinic the vision with glasses was 20/30 in the right eye and 20/25 in the left eye. Posterior subcapsular cataracts and lesser anterior subcapsular opacities were seen in each eye. A complete review of the patient's history caused the examiner to hesitate to make a tentative diagnosis of complicated cataract. In addition to cardiovascular disease of 8 years'

<sup>57</sup> "Cataracts As Complications of Treatment with Triparanol," Editorial (published in correspondence section) *Archives of Ophthalmology*, vol. 67, pp. 543-4.

<sup>58</sup> William S. Merrell Company, Cincinnati, Ohio. (Original footnote appears here and in the following two items—ed.)

<sup>59</sup> "Drug Firm Cautions MD's on Anti-Lipid Agent," *Medical World News* 2:34 (Dec. 22) 1961.

<sup>60</sup> Achor, R. W. P.; Winkelmann, R. K.; and Perry, H. O.: "Cutaneous Side Effects from Use of Triparanol (MER/29): Preliminary Data on Ichthyosis and Loss of Hair," *Proc. Staff Meet., Mayo Clin.*, 36: 217 (Apr. 26) 1961.



duration, for which the patient had taken many drugs, diabetes mellitus had been present since May 1959. Even if the fact of his taking of many drugs were disregarded, the fact that he was 56 years old and the presence of diabetes were enough to cast doubt on the diagnosis of complicated cataract. Nevertheless, this patient was one of the two reported to have moderately severe changes in the hair and ichthyosis after therapy with triparanol. Since it had been observed that cataracts had developed in the first patient, the same possibility could not be ignored in respect to the second patient.

The eyes of seven more patients who had some degree of changes in the hair or skin after therapy with triparanol were examined. Six patients (five women and one man) had experienced only loss of hair or mild dryness of the skin. Cataracts had not developed in any of these six patients. One man had ichthyosis and moderately severe changes in the hair, but no blepharitis. Cataracts had not developed in his eyes to the time of this report (9 months after the diagnosis of ichthyosis).

Ophthalmologists certainly appreciate the difficulties and hazards attendant upon the diagnosis of complicated cataract. The diagnosis of complicated cataract in a young person afflicted with a disease which is known to produce cataract can be relatively safe or, at least, such a diagnosis seldom would be questioned. However, if the patient has reached the middle or later years of life, the diagnosis of true complicated cataract can be questioned or debated. The dilemma is compounded when the cataractous changes are located primarily in the posterior subcapsular area. We try to distinguish between complicated cataract and senile posterior subcapsular cataract by means of several objective comparisons. As clinicians we should like to have available more definite, objective means of distinction, but the history remains a very influential factor.

It is interesting to note that the two patients who had cataract also had persistent blepharitis and meibomianitis during the period in which disease of the skin was present, whereas cataract has not developed in the other patient without blepharitis.

The common embryologic derivation of the lens, skin and glands of the eyelids, epithelium of the conjunctiva and cornea (all from surface ectoderm) opens an avenue for speculation or study. Unfortunately, the conjunctiva and cornea in this particular group were not stained for slit-lamp study during the ichthyosis.

Does the formation of cataract in these cases, if valid, represent merely the reaction of one ectodermal structure to a toxic disease of another ectodermal structure, or would the cataract form as the result of the individual reaction of the lens itself to a drug? What possible analogy could there be between the altered cholesterol synthesis of the skin and the formation of a cataract?

On the basis of knowledge of dinitrophenol, irradiation and electric cataracts, the delayed formation (8 months) of cataract in these two patients would not detract from the diagnosis.

The lack of formation of cataract in others who experienced mild changes in hair and skin also suggests differences in individual susceptibility.

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(Internal Agency Document)

May 7, 1962.

PHYSICIANS IN BUREAU OF MEDICINE, FOOD AND DRUG ADMINISTRATION

(Confidential—Administrative)

MEMORANDUM

To: Professional Staff Members—Division of New Drugs, Division of Veterinary Medicine.

From: Dr. Kessenich, Dr. Smith, Dr. Durbin.

Subject: Wm. S. Merrell Co. NDA's.

W.H.K. [Signed initials]

As you may know, we have recently obtained evidence that the Wm. S. Merrell Co. falsified data submitted as part of the New Drug Application for MER/29. In view of this we cannot consider the information submitted by this firm as reliable without thorough verification. Accordingly, we are requesting, pending further notification, that all applications and supplements submitted by this firm, including any that may now be pending, should be promptly referred to Dr. Smith for special handling.



We understand that the Wm. S. Merrell Co. is a subsidiary of the Richardson-Merrell Co., Inc. (formerly the Vick Chemical Co.) which also has as subsidiaries or divisions the following (Oct. 1960 data): National Drug Co., Walker Laboratories, Inc.; Hess & Clark; Jensen-Salsbery Labs., Inc.; J. T. Baker Chemical Co.; Lavis Company, and Drugs and Chemical Inc. We do not know whether or not the unreliability of data submitted by the Wm. S. Merrell Co. is characteristic of the operations of these related firms. Since, however, we cannot reasonably assume their reliability, we are also requesting that any applications or supplements received from any of these related firms be referred to Dr. Smith or Dr. Durbin (veterinary drugs) for special handling.

This memorandum will be amended to furnish a current list of Richardson-Merrell subsidiaries as soon as this information is obtained.

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May 22, 1962. Formal order is issued by Food and Drug Administration suspending the New Drug Application for MER/29.

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(Article in the Open Literature)

July 14, 1962.

COUNCIL ON DRUGS; AMERICAN MEDICAL ASSOCIATION<sup>61</sup>

TRIPARANOL (MER/29)

*Withdrawn in April 1962 because of reports of untoward reactions, including cataracts, falling hair, skin reactions, and possible cases of leukopenia. (An orally administered inhibitor of cholesterol biosynthesis, the use of which had been judged investigational. Evidence that its administration to patients with coronary insufficiency or generalized atherosclerosis had been beneficial was inadequate. Much longer and more careful studies had been deemed necessary before it could be considered safe for general or long-term use. It lowered the level of serum and total body cholesterol in most patients by blocking the final step in the biosynthesis. Attention had been called to the fact, however, that desmosterol, its immediate precursor, which accumulated in consequence, is very similar to cholesterol, both pharmacologically and physiologically. The reminder had also been given that the role of cholesterol itself in the pathogenesis of atherosclerosis is as yet not clear.)*

Commercial Source: The Wm. S. Merrell Co.

Reference: N.N.D., 1962, p. 616.

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(Article in the Open Literature)

July 28, 1962.

ROBERT C. LAUGHLIN, M.D.,

THOMAS F. CAREY, M.D.<sup>62</sup>

\* \* \* \* \*

COMMENT

It seems likely that in both the cases presented the development of the cataracts was attributable to triparanol. The opacities were identical and of a very unusual appearance in both patients. The lens opacification was morphologically different from the usual senile or metabolic cataract, and was similar to that seen in other cataracts caused by toxicity. It is interesting that both patients developed cataract shortly after discontinuing triparanol. We shall not attempt to discuss the possible metabolic factors involved in production of the lens opacities. The fact that both patients developed cataracts shortly after discontinuing triparanol brings up the question as to whether the stopping of the drug contributed to the cataract development.

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<sup>61</sup> "Drugs Evaluated by the Council on Drugs During 1961." Journal of the American Medical Association, vol. 181, July 14, 1962; reprinted in Second Annual Therapeutic Number, Council on Drugs 1962, p. 56.

<sup>62</sup> "Cataracts in Patients Treated With Triparanol," Journal of American Medical Association, vol. 181, No. 4, p. 130.



## SUMMARY AND CONCLUSIONS

Two cases histories are presented in which the patients developed cataracts rapidly, with progressive loss of vision, shortly after discontinuing triparanol. One patient had been taking the drug for 18 months and the other for 15 months. It seems probable that triparanol was responsible for the lens opacities in both cases.

*(Personal Correspondence From a Private Physician)*

August 3, 1962.

LAURANCE W. KINSELL, M.D.<sup>63</sup>

THE INSTITUTE FOR METABOLIC RESEARCH,  
HIGHLAND-ALAMEDA COUNTY HOSPITAL,  
Oakland, Calif.

THE HONORABLE JOHN F. KENNEDY,  
President of the United States,  
Washington, D.C.

MY DEAR MR. PRESIDENT: In your recent news conference I understood you to say that you plan to increase the personnel of the Food and Drug Administration by 25 percent in an effort to prevent occurrences such as those relating to the recent drug toxicity problem.

I would like to respectfully suggest that a quantitative increase in personnel is not necessarily an answer to any type of problem. A few years ago some of us were asked by the Food and Drug Administration as well as by the Committee on Drugs of the American Medical Association for an opinion with regard to the drug triparanol (MER/29). The chief question was whether it should be released for general clinical use by physicians. I stated, in totally unequivocal terms, that I felt that the drug should not be released; that it was a potentially dangerous drug until proven otherwise; and that for a long time it should be used only under the most carefully controlled conditions. Other "experts" gave nearly identical opinions. The Food and Drug people chose to disregard this advice and permitted the manufacturer to make the drug available for general clinical use. As you are perhaps aware, the drug was withdrawn from the market within the last few months because of disastrous consequences attendant upon its use. All of this could have been avoided.

Quality, not quantity, determines an effective organization. I believe that the crux of the problem which faces the Food and Drug Administration is an inability to get hold of a sufficient number of capable people on a full-time basis. I would therefore like to suggest that serious consideration be given to the creation of advisory committees in a number of different areas. These would include highly capable scientists. In the case of drugs and nutrients, for the most part the membership should be made up of clinical investigators; that is, people with medical degrees who are actively engaged in research in the specific areas involved. Needless to say, their recommendations should have "teeth."

Let me know if I can be of any help with regard to the above.

Very sincerely,

LAURANCE W. KINSELL, M.D., *Director.*

*(Newspaper Articles)*

August 7, 1962.

BARBARA YUNCKER<sup>64</sup>

## UNITED STATES PRESSES PROBE OF HEART DRUG SALES

*(By Barbara Yuncker)*

The uproar over thalidomide has obscured the legal and medical controversy over another drug which many experts say has done even more harm in the United States.

<sup>63</sup> A copy of the above letter to the President was received by Senator Humphrey in June 1963 in connection with the subcommittee's inquiry to Dr. Kinsell on June 7, 1963 (see p. 919).

<sup>64</sup> New York Post, p. 2.



It is triparanol—trade name MER/29—a synthetic compound to lower cholesterol, put out by the William S. Merrell Co., the same firm which sold thalidomide in Canada and sought to sell it here.

MER/29 is believed to have caused cataracts in scores of persons and certainly has caused skin disease and loss of hair in thousands. It was first tested in humans in 1958, marketed in 1960, and withdrawn as unsafe in April 1962.

At the request of the Food and Drug Administration, a Federal grand jury is now investigating whether the company broke the law in its 1959 marketing application. This is the first time the FDA has ever exercised its legal power to ask the Justice Department to look into a case in which the FDA has reason to believe a firm has lied in its application, submitted rigged research, or withheld information it is required to supply.

#### ANIMAL EVIDENCE

MER/29 illustrated the tricky terrain the drug industry is exploring and the quagmires into which the average doctor and his patient often follow.

The Post has documents which show the drug was sent out to be tested in humans on very scanty animal evidence. Experts are convinced it was dumped into general use and widely promoted without any evidence that its intended effect had therapeutic values. And the company has systematically ignored another effect which some specialists consider potentially very dangerous: the appearance of a fatty acid not normally present in human blood.

Triparanol was developed in the wake of growing evidence that high blood cholesterol is linked to fatty deposits in the arteries and thus to the heart disease death rate.

The broad and intense hunt during the late 1950's was for a pill with three qualities: one which would lower blood cholesterol, in itself do no bodily harm, and not create other harm by whatever process through which it cut cholesterol. By early 1958 Merrell thought they had it.

#### FDA APPROVAL

The substance was named MER/29 and rushed into the tests in a race to market it ahead of possible competitors. In 1959 Merrell applied to sell it for prescription use. The FDA was satisfied it was safe early in 1960 and the promotion campaign was on, citing "the remarkable record of efficacy, lack of serious toxicity, and rarity of side effects."

The Journal of the AMA did sound a caution in January 1961, but sales climbed briskly. By July 1961, more than 300,000 persons had got the drug and the firm had grossed well over \$9 million with it; MER/29 was Merrell's biggest seller, although it had quickly become clear that loss of hair, changes in hair color, and disfiguring skin ailments were being caused in what the company now says was less than 1 percent of cases.

By the fall of 1961, possible eye damage was brought to the FDA's attention.

In December, after disputatious conferences at FDA, Merrell sent all doctors a warning citing four "associated" cases of cataract, "many" cases of hair loss and skin damage, probable reduced output of adrenal hormones—plus liver damage in dogs and sexual effects in test animals.

#### TAKEN OFF THE MARKET

The FDA wanted to order the drug off the market then but Merrell indicated it would fight such a move in court if necessary. Government attorneys didn't feel they had enough "new" evidence to win in court.

By April 1962, with the quietly developing thalidomide disaster as backdrop, Merrell, in "cooperation" with the FDA, decided to take MER/29 off the market, still protesting the eye damage was unproved.

In a recent report sent FDA and a few doctors on request, Merrell reveals 71 "possibly associated" cases of human cataract (fewer they say than might be normally expected). Even more significant, they report that experiments (at what time they do not state) showed high dosages of MER/29 would produce cataracts in every dog tested.

Sometime after April, the FDA called in the Justice Department.

Under present law the company has to tell FDA everything it knows while its application is pending but is not required to reveal any bad news it gets after a drug has been cleared.



August 8, 1962.

BARBARA YUNCKER<sup>65</sup>

### HOW THE "WONDER" HEART DRUG WAS RUSHED TO THE MARKET

(By Barbara Yuncker)

The rush to get to market with MER/29—the "wonder drug" to lower blood cholesterol—was so intense that *outside* doctors were asked to try it in their patients for a whole variety of ailments before the company had any results in its own clinical trials to guide them.

With the cholesterol scare providing the climate in which mass sales could be expected to await the first effective agent to reduce cholesterol, the William S. Merrell Co. offered the drug for human testing only a few months after synthesizing it and after limited animal trials.

The June 1958 invitation, sent to an unrevealed number of doctors, was couched in what the company itself called a "very preliminary confidential medical brochure." This is a document revealing in ways the company did not perhaps intend.

The *activity* of triparanol (MER/29) in lowering blood cholesterol was demonstrated in just 27 rats on two different doses, contrasted to 13 "control" rats not given the drug, plus three treated and three control monkeys.

The evidence of *safety* was derived from unstated numbers of mice and rats. The brochure said mice could not be given doses large enough to kill half of them. Three monkeys were also studied.

#### ACTING IN HASTE

Although drug houses routinely do some clinical (i.e., human) trials at home base before sending the drug out, such was Merrell's haste that the brochure conceded data on the effects and the safety in man "have not yet been collected."

Nevertheless, Merrell "confidentially" and apparently confidently told the doctors that MER/29 was "indicated for all conditions associated with hypercholesteremia [high blood cholesterol] and excessive secretion of cholesterol in the bile." Specifically it was suggested for "arteriosclerosis, coronary heart disease, hypertension [high blood pressure] and cholelithiasis [gallstones]."

Although MER/29 was withdrawn this year as unsafe, there was nothing in the 1958 brochure which caused the company to insert any alerts or contraindications, although specialists have since pointed out that some of the early animal effects should have suggested some cautions at least.

August 9, 1962.

BARBARA YUNCKER<sup>66</sup>

### HIDDEN DANGERS CITED IN SALE OF HEART DRUG

(By Barbara Yuncker)

Whatever the Justice Dept. decides about possible legal violations involving MER/29, the withdrawn cholesterol-lowering drug, experts agree there are hidden and potentially grave dangers in these two unanswered questions:

Why did the William S. Merrell Co. promote the drug for broad general long-term use before there was any proof that lowering cholesterol has therapeutic value?

Why did the company omit in its publicity the fact that the drug cuts blood and tissue cholesterol only by putting another fatty acid, desmosterol, into the blood?

"Desmosterol does not appear spontaneously in the blood of man and its long-term effects are unknown," commented Drs. David Blankenhorn and Oliver Kuzma, of California, in last October's *Metabolism*. Other experts fear it may deposit more fat in the arteries than cholesterol is suspected of doing.

#### KNOWN IN 1959

This tampering with normal metabolism was known to the firm at least as early as 1959 (months before marketing), when leading Government scientists

<sup>65</sup> New York Post, p. 4.

<sup>66</sup> New York Post, p. 2.



told a symposium put on by Merrell that the drug worked by stopping cholesterol production in the liver at the last precholesterol stage, thus releasing a precursor, desmosterol, into the blood instead.

Dr. Daniel Steinberg, of the National Institutes of Health, stated then—and left open—these significant questions: "What are the long-term biological effects of 24-dehydrocholesterol (desmosterol) and to what extent is it a therogenic (fat-depositing)?"

According to another specialist: "This is the scariest kind of thing imaginable. Who knows yet what it's doing? If ever a drug should have remained experimental, MER/29 is it!"

It was tested all right—broadly and beyond control—for two years in hundreds of thousands of men and women whose doctors were bombarded by blurbs that it was effective and safe. (Some of the patients might have been interested, too, in a suggestion, omitted from those blurbs but revealed in Merrell's animal tests that "sexual frustration \* \* \* might result from impaired adrenal function.")

Doctors could have been alerted, despite the company's selective reticence, by The Medical Letter, an independent drug evaluation service. It cited the desmosterol evidence in October 1960 and said:

"Until (Dr. Steinberg's) question are answered, claims for the safety of the drug cannot be fully accepted \* \* \*. It has not been shown that the reduction of blood cholesterol serves any therapeutic purpose." (However, only about one doctor in 10 takes Medical Letter.)

#### BRIEF CAUTION

There was a brief general caution in the January 1961 new drug listing in the Journal of the AMA followed in November by: "All patients receiving triparanol should be maintained under carefully controlled conditions of clinical investigations."

In Physicians' Desk Reference for 1962—the average doctor's drug bible—the company warned it shouldn't be given to pregnant women "since cholesterol plays an important role in the development of the fetus" but continued to urge general use and said nothing about desmosterol. In April it was withdrawn.

Merrell says it would have made the 35-cent pill prohibitively expensive to have entered into large human trials before marketing.

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August 9, 1962. John L. Harvey, Deputy Commissioner, Food and Drug Administration, concedes<sup>66a</sup> that MER/29 should never have been allowed to go on the market in the United States. Mr. Harvey states in an address before an American Bar Association group that by mid-November 1961 "the administrators and lawyers agreed with the scientific view that the drug should be removed from the market." But he states, "The Government could not yet prove that the drug was unsafe in the dosage recommended in the labeling." FDA, he said, knew then of only 4 cases in which patients receiving MER/29 had developed cataracts. "FDA was unable, in the absence of new data and in the absence at that time of proof that the application contained untrue statements, to correct the situation." In the speech, Mr. Harvey states that "the product was used for another 4½ months before clear evidence of lack of safety made it possible to get it out of the hands of physicians."

<sup>66a</sup> See pt. 2, exhibit 64, p. 383.



(Letter to and Furnished by a Private Physician)

August 21, 1962.

RALPH A. DUNGAN, SPECIAL ASSISTANT TO PRESIDENT JOHN F. KENNEDY.

DR. LAURANCE W. KINSELL,  
Director, The Institute for Metabolic Research,  
Highland-Alameda County Hospital,  
Oakland, Calif.

DEAR DR. KINSELL: The President has received your letter. Your comments and suggestions have been fully noted, and you may be assured that your interest in writing and your kind offer to be of service are appreciated.

Sincerely,

RALPH A. DUNGAN,  
Special Assistant to the President.

(Article in the Open Literature)

October 1962.

THOMAS J. KIRBY, JR., M.D.,  
RICHARD W. P. ACHOR, M.D.,  
HAROLD O. PERRY, M.D.,  
R. K. WINKELMANN, M.D.<sup>67</sup>

\* \* \* \* \*

#### SUMMARY

In the 2 patients reported with the triad of loss of hair, change in color of the hair, and ichthyosis after therapy with triparanol (MER/29), cataracts also developed subsequently. Both patients had blepharitis with meibomianitis during the course of the ichthyosis. The cataracts resembled those usually considered to be complicated or secondary cataracts. The youth, negative family history, repeatedly negative results of physical and laboratory examinations, and the characteristics of the cataract substantiate a clinical diagnosis of complicated cataract in the first patient. The age (56 years) plus the diagnosis of diabetes leaves the diagnosis of complicated cataract open to question or argument in the second patient.

Cataracts have not developed in 7 patients with milder cutaneous reactions to triparanol nor in 9 patients with no cutaneous reactions to triparanol.

Further observations of these and other patients who have had triparanol therapy are needed to reach definite clinical or statistical conclusions. The authors prefer to have obtained more statistical evidence for or against the implication of triparanol, but the warning by the manufacturer and the publication of an account of such a hazard in a widely circulated medium have forced them to make a preliminary report.

T. J. KIRBY, M.D., *Mayo Clinic, Rochester, Minn.*

#### ADDENDUM

Since submission of this paper we have seen another patient with cataracts which developed while he was being treated with triparanol. The patient was a 6-year-old boy with familial hypercholesterolemia and xanthomatosis of the skin. A brother of this patient died in childhood of coronary occlusion.

The treatment with triparanol, 250 milligrams per day for 15 months, then reduced to 250 milligrams every other day for 5 months, was successful in lowering the blood cholesterol. The xanthomas of the skin disappeared within the first 10 months of treatment. By the 15th month of treatment, marked ichthyosis had developed, and the hair of the scalp, eyebrows, and eyelashes was much lighter. At this time vision was 20/25 in each eye (E chart), and the lens of each eye was clear to both ophthalmoscopic and slit-lamp examination. The color of the hair returned to normal, and the ichthyosis improved greatly on the reduced dosage.

The eyes were reexamined in the 20th month of treatment (5 months after ichthyosis developed). The vision was 20/30 in each eye (E chart). There were stippled crystalline deposits in the corneal epithelium of each eye and anterior and posterior subcapsular lens opacities in each eye. The opacities had a fish-net configuration.

<sup>67</sup> "Cataract Formation After Triparanol Therapy," *Archives of Ophthalmology*, vol. 68, p. 489.



(Release to the Press)

October 4, 1962.

Senator HUBERT H. HUMPHREY.

SENATOR HUMPHREY CONDEMNS "SHOCKING" CHRONOLOGY ON MER/29<sup>67a</sup>

Senator Hubert H. Humphrey (D. Minn.) characterized as "shocking" the history of Food and Drug Administration decision-making on a cholesterol-lowering drug, MER/29.

The official chronology was made available to Senator Humphrey, as Chairman of the Senate Subcommittee on Reorganization and International Organizations, at his request.

"FDA has given only a cursory account of the history on this New Drug Application," Senator Humphrey said. "Even this limited account represents a sharp indictment of the FDA itself—its laxity, its tardiness in seeking to remove the drug from the market, its failure to protect the public interest."

Expert observers have reported confidentially to the subcommittee that the MER/29 history is a "tragedy of errors." "No one has yet made an accounting of the toll in human suffering which this drug has taken," Senator Humphrey stated.

Humphrey called attention to the fact that the National Institutes of Health has been supporting considerable research on cholesterol-lowering substances.

"The FDA scientist in charge of the New Drug Application never consulted with NIH before the drug went on the market, nor did NIH initiate such consultation. After it was on the market, a second FDA reviewer did conscientiously seek expert NIH advice," Senator Humphrey said.

"Before the Senate and House Appropriations Committees, NIH has frequently pointed with pride to its considerable studies in cholesterol-lowering research. But it never took the initiative of working as a team with the Federal agency responsible for reviewing cholesterol-lowering drugs."

Humphrey said that expert observers have told him that "one of the most significant aspects" of the FDA chronology is that on March 28, 1960, FDA requested comprehensive information from the company as to patient reactions. Yet, less than a month later, before the data came in, it suddenly cleared the New Drug Application on a "conditional" basis. The observers wonder why "FDA cleared the drug so fast without receipt of the requested information." The only data which came in during the interim was information on hepatic function which, at least, some observers regarded as very inconclusive.

The official chronology will be published as one of more than 70 exhibits in the subcommittee volume, containing the transcript of the August 1-9 hearings.

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(Letter to Editor and Response in the Open Literature)

October 20, 1962

RICHARD W. P. ACHOR, M.D.<sup>68</sup>

## TRIPARANOL AND CATARACTS

*Question.* I have 2 patients who have developed cataracts following cessation of triparanol therapy. Is cessation of administration the triggering mechanism in these cases; in other words, would the cataracts have developed if therapy had been continued?

ROBERT FRIEDENBERG, M.D., Albuquerque, N. Mex.

*Answer.* This question is similar to that proposed in the comment portion of a recent article entitled "Cataracts in Patients Treated With Triparanol" by Laughlin and Carey (JAMA 181:339 [July 28] 1962). Although information concerning triparanol-induced cataracts is limited, a number of carefully observed patients have developed cataracts while treatment with the drug was being continued. In addition, other patients have maintained their usual vision for many months after stopping therapy with triparanol and before the formation of lens

<sup>67a</sup> Release H 10-5-62.<sup>68</sup> Journal of the American Medical Association, Correspondence, vol. 182, No. 3, pp. 198-199.



opacities. Cataracts have also been found to form during uninterrupted treatment with triparanol in experimental animals (dogs and rats). Consequently, the cessation of administration of triparanol should not be considered the cause of cataract development; rather, it is the drug which has furnished the toxic stimulus. What cannot be answered is whether stopping triparanol therapy may accelerate, at least for a time, the progression of lens opacities in some patients.

Available information and experience concerning patients with triparanol-induced cataracts permit some tentative observations which may be useful as a frame of reference. The age of the patient, the dose of triparanol, and the duration of treatment are not critical factors in the development of cataracts. The course of triparanol-induced cataracts has been relentlessly progressive with eventual severe disability requiring surgical correction. However, the progression is often erratic and there may be periods of quiescence followed by bouts of rapid worsening.

RICHARD W. P. ACHOR, M.D.

*(Article in the Open Literature)*

November 1962

HAROLD O. PERRY, M.D.

R. K. WINKELMANN, M.D.

RICHARD W. P. ACHOR

THOMAS J. KIRBY, Jr., M.D.<sup>62</sup>

\* \* \* \* \*

SUMMARY

The triad of ichthyosis, loss of hair, and change in color of hair is reported as a configuration of findings that may follow the administration of triparanol. The fact that such changes occur even when the usual recommended dose of the drug is taken, the peculiar predilection for males with an incomplete development of findings in female patients, and the apparent involvement of even the very young are emphasized.

The possible development of cataracts in patients with changes in the skin and hair is to be remembered.

Thus the condition of patients receiving triparanol should be evaluated by slit-lamp examination at intervals during such therapy.

ADDENDUM

Since the preparation of this manuscript, additional observation in case 3 reveals that this child also, in addition to the patients in cases 1 and 2, has now developed bilateral cataracts which have progressed to maturity.

*(Article in Financial Newspaper)*

May 14, 1963

WALL STREET JOURNAL<sup>70</sup>

ATTORNEYS FORM GROUP TO GATHER DATA FOR USE IN MER/29 LAWSUITS

THEY REPRESENT 150 CASES FILED AGAINST RICHARDSON-MERRELL UNIT THAT PRODUCED THE DRUG

(By a Wall Street Journal Staff Reporter)

NEW YORK.—A group of about 45 lawyers representing clients allegedly injured through use of an anticholesterol drug, MER/29, have united to pool information to help them pursue their lawsuits.

The lawyers have each contributed an undisclosed amount of money to an "MER/29 Information Fund," which will be used to develop information that can be used in all suits against the maker of the drug, the Wm. S. Merrell division of Richardson-Merrell, Inc., New York.

<sup>62</sup> "Side Effects of Triparanol Therapy," American Journal of the Medical Sciences, vol. 244, No. 5, pp. 562-563.

<sup>70</sup> P. 8.



The existence of the group was confirmed by Paul D. Rheingold, a Nahant, Mass., attorney who has been elected trustee of the fund. He said the group had held two organizational meetings recently, one in Chicago and the other in New York.

Mr. Rheingold said the 45 attorneys who have joined the group represent "about 150 cases" involving MER/29. He added that he is aware of about 100 other MER/29 cases pending against the company.

Richardson-Merrell officials declined to comment on the lawyers' group. The company has refused to disclose how many suits have been brought against it as a result of damages allegedly incurred through use of the drug. It has told stockholders, however, that it has liability insurance and doesn't expect the outcome of the suits to have any material effect on the company's financial position.

MER/29, or triparanol, was widely used to lower levels of a fatty substance, cholesterol, in the blood. Some doctors believe that a buildup of such fats leads to heart disease, or atherosclerosis. A year ago, Merrell withdrew the drug from the market because of side effects possibly associated with the drug, including eye cataracts and loss of hair.

Mr. Rheingold said the lawyers' group would pool information gathered from medical literature, medical reports on individual cases, Food and Drug Administration reports and other sources. It may also take sworn statements from individual physicians and FDA officials for use by all attorneys involved, and may hire a pharmacologist to prepare basic data on MER/29.

Mr. Rheingold said that, to the best of his knowledge, Merrell "has settled only a few small cases" involving the drug. He declined to estimate the total amount of damages asked by all clients represented by the attorneys' group. He added that the group was seeking to enlist as members all other attorneys whose clients have brought lawsuits against Merrell involving MER/29.

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(Professional Paper)

May 28, 1963.

LUDWIG VON SALLMANN, M.D., BARBARA GRIMES, B.A., AND ELEANOR COLLINS<sup>62a</sup>:  
Ophthalmology Branch, National Institute of Neurological Diseases and Blindness.

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INTRODUCTION

Recent reports (1, 2) of cataract development in patients treated with triparanol (MER/29) for prolonged periods indicated that experimental work on the possible cataractogenic effect of this drug is needed. Although the action of triparanol on cholesterol biosynthesis had been examined extensively in several species of experimental animals, no systematic studies of its effect on the lens were available. For this reason, an investigation of cataract induced in rats by triparanol feeding was instituted. Biomicroscopic, histologic, and cytologic examinations of the lenses were combined with histochemical techniques in view of the known effects of the drug on lipid metabolism.

METHODS AND MATERIALS

Young male rats of the Sprague-Dawley strain were placed on a stock diet containing 0.1 percent triparanol when their weight was approximately 100 grams.<sup>1</sup> Thirty-eight animals were examined with the biomicroscope at regular intervals. Of these, 11 died of unknown causes and 24 were killed at various time intervals after bilateral cataracts had formed. The eyes were either fixed in Bouin's solution and embedded in celloidin for routine histology; or fixed in formalin, embedded in gelatin, and sectioned on the freezing microtome. Frozen sections were treated with various fat stains. Fresh tissue from cataractous lenses of two rats were examined with phase contrast optics and polarized light

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<sup>62a</sup> "Triparanol-Induced Cataract in Rats," presented before 99th annual meeting American Ophthalmological Society, Hot Springs, W. Va. (by Dr. C. W. Rucker in Dr. von Sallmann's behalf).

<sup>1</sup> The triparanol-treated rats were supplied by Dr. Joel Avigan of the Laboratory of Cellular Physiology and Metabolism of the National Heart Institute.



to compare lipids in the native and fixed states. The lenses of eight eyes were Feulgen-stained and processed for cytologic examination of whole mounts of the lens epithelium.

#### RESULTS

Thirty-four of the 38 rats developed cataractous changes within 10 weeks after triparanol feeding was started. In three animals, lens changes were not seen until 16 weeks, and only one rat failed to develop opacities within the 16-week examination period. Subcapsular silky opacities developed in the posterior cortex, together with typical changes in the anterior which were characterized by a radial arrangement of regularly spaced grey striae reflecting the anatomical distribution of fibers in this portion of the lens (fig. 1).<sup>2</sup> Gapping anterior sutures, faint subcapsular grey patches around the anterior pole, and dendritic or net-like opacities were occasionally seen. Generally, the incipient lesion progressed rapidly to a diffuse involvement of the lens cortex. The biomicroscopic picture of early changes in the rat lens was similar in some respects to that of human cataracts ascribed to triparanol. This similarity was confirmed in the examination of two patients, 41 and 30 years old, admitted to the National Institute of Neurological Diseases and Blindness because of bilateral cataract development following triparanol therapy of 1-year duration. Figures 2a, 2b<sup>2</sup> demonstrate the radial arrangement of fine gray dots observed in the anterior cortex giving an overall feathery appearance. Multicolored crystalline dots were located centrally in the superficial layers. The posterior cortex showed a cupuliform cataract in which delicate striations could be seen. The striate character of the opacities was more conspicuous in the rat lens, but there was little doubt that in both instances it indicated incipient fiber pathology.

Histologic examination of the cataractous rat lenses revealed that the early changes consisted of hydropic changes of fibers in the superficial cortical layers. Later many fibers were swollen, but adjacent fibers in the same layer appeared normal. The irregular distribution of hydropic cells produced a variable mosaic pattern when seen in cross section (fig. 3<sup>2</sup>). With progression of the cataract, swollen fibers disintegrated, and large spaces filled with granular debris were formed. Islands of normal fibers were often spared in areas of advanced destruction. Although the lens epithelium and the bow were well preserved at early stages, more severe cortical damage was accompanied by distortion of the bow and occasional proliferation of the epithelium in the equatorial area of the anterior pole (fig. 4). Examination of Feulgen-stained flat mounts of the lens epithelium indicated that abnormal proliferation occurred earlier in the cataractous process than noted in sections. Y-shaped accumulations of cells were frequently seen in the region of the anterior suture. Mitotic figures and signs of nuclear fragmentation were found at these sites.

The results pointed to primary damage of the lens fibers in the superficial cortex which was in accord with the biomicroscopic findings. The epithelial changes were assumed to occur secondarily, due to cortical damage.

Examination of formalin-fixed frozen sections of cataractous lenses indicated the presence of certain abnormal lipid structures. These structures stained well with Sudan black B in propylene glycol and had the appearance of minute vesicles (fig. 5<sup>2</sup>). They tended either to aggregate in grape-like clusters or to form large multilayered irregular shapes. They were seen throughout the cortex and were not confined to the areas of fiber destruction, but extended to deeper layers of the cortex where fiber pathology was not detectable. Oil red O and Sudan III stained the same structures but only weakly.

Examination of both unstained and stained sections in polarized light demonstrated that Maltese cross birefringence usually was associated with the sites which were Sudan black positive (figs. 6, 7<sup>2</sup>). This type of birefringence characterized cholesterol and nitrogen containing compound lipids as phospho- and glycolipids. Application of the Schultz technique showed the association of cholesterol or cholesterol esters with a number of the lipid structures. Marked staining with Sudan black B, together with the observed Maltese cross birefringence, suggested the presence of phospholipids in addition to cholesterol. A more specific test for phospholipids was therefore attempted. Selected sections were treated with Elftman's controlled chromation procedure. After chromation, the lipid aggregates stained with both Sudan black B or Luxol Fast Blue and with hematoxylin, indicating that phospholipids were a major component of the lipid mixture.

<sup>2</sup> The figures are not reprinted within this volume.



Examination of fresh tissue with phase contrast optics demonstrated clearly that small-, and even medium-sized globules can occur in the cytoplasm of swollen and, also, normal fibers (fig. 11<sup>2</sup>). Aggregated larger forms were seen between fibers and were particularly numerous around regions of fiber disintegration. The sudanophilic deposits in fixed material and the structures noted in fresh tissue with phase contrast were remarkably similar in size and shape (fig. 9<sup>2</sup>).

In conclusion, histochemical examinations of triparanol cataract and observation of fresh material with phase contrast and polarization techniques revealed small sudanophilic vesicular forms which aggregate to larger clusters. These structures lay in normal or swollen lens fibers, or between fibers and appeared to be composed predominantly of phospholipids, cholesterol, and cholesterol esters.

#### COMMENT

Recent studies (3, 4, 5) have established that triparanol acts by blocking the enzymatic reduction of desmosterol (24-dehydrocholesterol) to cholesterol. This block results in a fall in cholesterol levels associated with the accumulation of desmosterol in both plasma and tissue. On the basis of these observations, it is reasonable to assume that in the lens cholesterol biosynthesis is inhibited by the same mechanism, leading to an accumulation of desmosterol. Chemical analysis was not carried out, however, and the lipid stains used in the present study did not differentiate between cholesterol and desmosterol.

It is probable that in triparanol cataract, the small round sudanophilic deposits first developed in the cytoplasm of otherwise normal fibers, although it could not be decided from which part of the fiber the lipid substance originated. Localized destruction of the cell membrane was not seen with the techniques employed in this study, but the accumulation of the characteristic lipid structures between fibers, or in areas where the fiber architecture appeared to be interrupted, indicated that the massive intercellular deposition of lipid material was preceded by disintegration of the fiber membrane. In this context, it is of interest that Scanu, Hawk, and Page (6) observed an increased fragility of red blood cells of dogs on prolonged triparanol treatment. They considered that the lowered cholesterol levels, or the accumulation of desmosterol in the erythrocytes, was potentially injurious to the cell membrane.

More knowledge of aberrant lipogenesis in the cataractous process is necessary before a definite statement on the specificity of the changes in triparanol cataract can be made. In any event, an acquired cataract in man and in rats has been shown for the first time to be associated with a definite change in lipid metabolism.

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6. Scann, A.; Hawk, W. A.; and Page, I. H.: Lethal effect in dogs of prolonged triparanol oral administration. *Arch. Pathol.*, 73: 445, 1962.



*(Subcommittee Correspondence)*

June 7, 1963.

HUBERT H. HUMPHREY, U.S. SENATOR.

LAURANCE W. KINSELL, M.D.,  
*The Institute for Metabolic Research,  
Highland-Alameda County Hospital,  
2701 14th Avenue,  
Oakland, Calif.*

DEAR DR. KINSELL: I was interested to learn that on August 3, 1962, you had written to President Kennedy concerning your early recommendation against "general clinical use" of MER/29.

As you may know, this subcommittee has been making a comprehensive study of Federal drug policy, with particular respect to the Food and Drug Administration and New Drug Applications. Enclosed is the second volume in our series, containing numerous references to MER/29.

I would very much appreciate receiving any and all documentation, which you might be in a position to present, with regard to your and your colleagues' early comments on MER/29, i.e., before approval of the NDA, as well as thereafter.

We are about to send to press an additional hearing-exhibit volume and would like to include in it as complete a history as possible on this drug, supplementing the exhibits in part 2.

Looking forward to hearing from you, I am,

Sincerely,

HUBERT H. HUMPHREY,  
*Subcommittee Chairman.*

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*(Response to Inquiry as to Extent of Claimed Injuries)*

June 11, 1963.

PAUL D. RHEINGOLD,  
Trustee, MER/29 Group:

NAHANT, MASS.

DEAR SENATOR HUMPHREY: I have your letter of June 7, 1963, inquiring about the experience with MER/29 which I have had in my capacity as trustee or clearinghouse for the plaintiffs' counsel handling these cases. I am delighted to be able to be of assistance and I know I speak for the group when I say that, consistent with the paramount rights of the various clients represented, we would like to do all in our means to be of service to your committee. We recognize that prevention is better than litigation and that the best basis for improvement in the ethical drug practice is study of unfortunate happenings in the past.

Unfortunately I cannot tell you exactly how many claims have been filed against the Richardson-Merrell Co. for injury from MER/29; probably that company is the only body in possession of accurate figures. There are, as of this date, 58 lawyers in our MER/29 group, and due to certain publicity our group has received it is growing at about the rate of 1 new member a day. Besides these 58, I know personally of at least 50 more counsel with cases. Many of the 58 in our group have more than 1 case; 2 of the men state that they have upward of 25 cases. I would say, therefore, that our group represents about 150 individual actions, presently.

We are interested, of course, in the total number of claims that will be brought. I feel that well over 1,000 persons have been injured by the drug, but not all will sue, because they suffered only minor, transitory effects, because they have since died, because they do not consider themselves the type that sues, or because they are ignorant of their rights or of the fact that the conditions from which they suffer are due to the use of triparanol. I would venture the guess therefore that before this matter is finished, there will be 500 actions maintained.

As to the type of injuries, the majority of the cases with which I am acquainted involve cataracts (almost always bilateral, usually operable). Since these cataracts may be slow in development, it is probable that not every case that will be has yet appeared. Most of the cataract cases involve what is coming to be regarded as the classical triad of triparanol injuries: cataracts, hair thinning or loss, and skin damage (including ichthymosis, exfoliation, scaling, and itching). Almost all of the noncataract cases involve both of these other reactions. Needless to say, these are the less serious cases and a number of them have already been settled.



In addition to these three main reactions, there have been a large number of other types of reactions allegedly due to ingestion of MER/29, though less often involved. These include liver damage, spleen damage, personality change, diminished libido, impotence, damage to fingernails, sweat glands affected, vomiting and nausea, kidney damage, headaches, loss of normal circulation, pains in various parts of the body, anemia, gastrointestinal upset, ulcerative colitis, diminished adrenocortical function, and fatigue. Some of these, of course, may have only coincidentally occurred with the true reactions to MER/29.

As time passes we may have available more definite statistics. In the meanwhile perhaps there are other areas within the scope and purposes of your committee's work in which we can be of aid. If so, please do not hesitate to call upon us. I appreciate receipt of the first two parts of your hearings and look forward to the future reports of the committee. The material on MER/29 in the material sent is invaluable to our purposes. In a newsletter to all members of our group I have digested those portions most relevant to our cases and I have directed the members to order copies as needed from the GPO directly.

With best wishes,

PAUL D. RHEINGOLD,  
*Trustee, MER/29 Group.*

June 20, 1963.

LAURANCE W. KINSELL, M.D.

THE INSTITUTE FOR METABOLIC RESEARCH,  
HIGHLAND-ALAMEDA COUNTY HOSPITAL,  
Oakland, Calif.

MY DEAR MR. HUMPHREY: Thank you for your letter of June 7.

Enclosed are photostats of two letters, (a) from the Council on Drugs of the American Medical Association, dated January 7, 1960, and (b) from me to the Council on Drugs of the American Medical Association, dated January 29, 1960.

My advice was solicited with regard to MER/29 by staff members of the Food and Drug Administration. My advice to them was essentially the same as that contained in my letter to the American Medical Association. It was perhaps somewhat more forceful. All of this latter interchange was verbal, not written. All of it occurred prior to the approval of MER/29 by the Food and Drug Administration.

I should again like to emphasize statements which I made in my letter to President Kennedy under date of August 3, 1962. Mere increase in numbers of the staff of the Food and Drug Administration and manifold increase in the amount of paperwork required from responsible clinical investigators and responsible members of first-class pharmaceutical organizations will have two predictable effects:

1. The taxpayers will carry an increasing load.
2. There will be a significant and dangerous decrease in the amount of time and effort devoted to the evaluation of new drugs by competent clinical investigators.

Both results will work to the detriment of the public.

I hope that your committee will give some serious thought to erasing completely all of the new regulations with regard to new drugs and will carefully reappraise the entire picture, with reference to emphasis upon the setting up of highly competent advisory committees made up of clinical investigators and pharmacologists.

Very sincerely,

LAURANCE W. KINSELL, M.D., *Director.*



*(Subcommittee Correspondence)*

July 18, 1963

HUBERT H. HUMPHREY, U.S. SENATOR

JAMES V. WARREN, M.D.,<sup>70a</sup>

*President, American Heart Association, Inc.,  
44 East 23rd St., New York 10, N.Y.*

DEAR DR. WARREN: I should like to express an invitation to the American Heart Association to present a statement which might be published by this subcommittee in its forthcoming hearing-exhibit volume on "The Role of a Voluntary Health Organization in Drug Research."

This statement would be useful to the subcommittee in the study which it has been making on "Interagency Coordination in Drug Research and Regulation."

Enclosed, by way of background, is a set of the two volumes which we have issued to date.

As you know, I feel that the American Heart Association is one of the Nation's greatest voluntary health organizations. AHA's medical program, under the supervision of your distinguished medical director, Dr. George E. Wakerlin, offers, I believe, a splendid example of the excellent professional services rendered through a voluntary organization.

The statement which the association might prepare might include answers to any or all of the following questions and comment on any other phase which you and your associates believe would be appropriate:

(1) As a general principle on drug policy, what does AHA believe to be the optimal role which a voluntary health organization should play in connection with:

- (a) research on experimental drugs,
- (b) fostering of careful use of drugs with an effective New Drug Application,
- (c) professional medical organizations, including specialty organizations,
- (d) pharmaceutical companies,
- (e) Federal agencies, such as the Food and Drug Administration and the National Heart Institute?

(2) Would AHA cite illustrative instances of its past experience in any of these connections which might prove useful to the subcommittee's understanding.

(3) Does AHA have any recommendations as to future Federal drug activities, particularly on the part of the Food and Drug Administration?

In the case of question (2) as to specific past instances, I should like to invite AHA comments and possibly documentation with respect to the drug, Triparanol. The subcommittee plans to publish a comprehensive chronology, compiled from both official and private sources, as to what was known, written, published, advertised, said and done on the drug, as of a long series of dates from 1958 through 1962.

Our purpose is to submit to the Congress, to the scientific community and the public as complete a record of the history of this drug, as possible, and exactly as that history unfolded, with actual texts.

If it would not be an imposition and would not violate any confidence, the subcommittee would be glad to receive any AHA letters or other documents which might have substantive value for this chronology, e.g., possibly correspondence by the AHA Committee on Nutrition on proposed advertising which had been submitted on Triparanol.

In the subcommittee's final report, I may say, we will be making recommendations for improvements in certain Federal activities. But we will also respectfully urge nongovernmental organizations to follow certain excellent examples which have been set in drug programs by individual private groups, alone, in cooperation with one another and with Federal agencies.

With respect to cardiovascular drugs and MER/29, the subcommittee's volume 1 shows (p. 285) \$5.6 million in National Heart Institute support of cardio-

<sup>70a</sup> The above letter was acknowledged with thanks by George E. Wakerlin, medical director, American Heart Association, in the temporary absence of Dr. Warren.

The association's forthcoming substantive reply will be printed in a future volume, together with additional information requested or otherwise anticipated by the subcommittee, but not available as of the time the present volume is sent to press.

Within this volume, certain additional comments on MER/29 will be found in two exhibits: (a) Exhibit 172, Miscellaneous Correspondence (pp. 1242, 1243); (b) Exhibit 173, pp. 1256-1257, Background Memorandum, highlighting a few significant issues.



vascular drug research in the 1962 fiscal year. It also shows (p. 294) minimal contact, unfortunately, between NHI and FDA, prior to the approval of MER/29, but helpful contact later on, and overall professional contact at an AHA meeting in Miami in October 1961 (p. 295). A condensed FDA chronology on the drug appears in part 2, pp. 501-504.

In closing, may I express appreciation for the cooperation which the association has always extended to our subcommittee throughout our 5 years of study of medical research and related problems.

Looking forward to hearing from AHA in the next few weeks, I am,

Sincerely,

HUBERT H. HUMPHREY, *Subcommittee Chairman.*

#### EXHIBIT 128

#### MER/29—CHRONOLOGY OF CORRESPONDENCE BETWEEN DANIEL STEINBERG, M.D., OF THE NATIONAL HEART INSTITUTE, THE WILLIAM S. MERRELL CO., OFFICERS OF THE FOOD AND DRUG ADMINISTRATION AND OTHERS

One of the early investigators of triparanol was Daniel Steinberg, M.D., Director, Laboratory on Metabolism, National Heart Institute. Dr. Steinberg and his associates had numerous contacts with the William S. Merrell Co. and, later on, at the invitation of members of the Food and Drug Administration staff with employees of the Bureau of Medicine of this agency. In view of these many activities and contacts, the subcommittee asked Dr. Steinberg to furnish a set of his letters and memorandums with the company, with FDA and others on the subject of triparanol.

In view of the extensive nature of the correspondence and memorandums, it is printed as a separate chronological unit, rather than being incorporated in the overall chronology of the preceding exhibit. It is hoped that by maintaining it separately, the various highly technical issues which Dr. Steinberg and Dr. Joel Avigan reviewed can be studied with greatest clarity by the professional community.

THE WM. S. MERRELL COMPANY.  
*Cincinnati, Ohio, June 6, 1958.*

Dr. DANIEL STEINBERG,  
*National Heart Institute,  
National Heart Institute, National Institutes of Health, Bethesda, Md.*

DEAR DR. STEINBERG: I appreciate very much your kindness extended to me and Mr. Casale when we were in Bethesda. My brief summary of information on MER/29 has been typed, and it is my pleasure to enclose a copy of it as well as a statement of investigator which we would like to have on hand if you are willing to administer this material to animals or to human beings. I know that the provisions of the Food, Drug, and Cosmetic Act are such that we could send material to a Government institution designed for research purposes without the statement of investigator, but we find that the form is a handy thing to keep on file with everybody's mailing address in a place where it is easy to find.

I was particularly encouraged by your suggestion that perhaps you could measure in detail the potential effects of MER/29 on adrenal function. Your suggestion that the feeding of a high cholesterol diet might prevent the development of toxic effects in experimental animals is an extremely interesting one. I am looking forward to discussing this with Dr. Blohm as soon as possible. At that time I will ask him about the inhibition of precursors other than sodium acetate and also the quantitative figures for the carbon dioxide excretion studies.

As soon as the complete description of animal work is available, I will have a copy of it sent. In the meantime, please do not hesitate to raise questions which may come to mind after you have had a chance to review my very brief abstract of the animal work.

Kindest personal regards,

R. C. POGGE, M.D.,  
*Director of Medical Research.*



June 20, 1958.

DR. R. C. POGGE,  
Wm. S. Merrell Co.,  
Cincinnati, Ohio.

DEAR DR. POGGE: I enjoyed your visit here in Bethesda very much and look forward to the next time we can get together. After reading your summary on MER/29 and from our discussions about it, it seems to me to be a very interesting compound indeed. I am enclosing the statement of investigator which you requested.

I am just leaving for a short vacation but next month we could start some preliminary studies in rats if you can make some of the compound available to us. I would like to have your suggestions about initial dosage for patients and any suggestions you may have about parameters that should be followed other than blood lipids.

Sincerely yours,

DANIEL STEINBERG, M.D.,  
Chief, Section on Metabolism, National Heart Institute.

July 15, 1958.

DR. THOMAS R. BLOHM,  
Department of Biochemistry,  
The Wm. S. Merrell Co.,  
Cincinnati, Ohio.

DEAR DR. BLOHM: Thank you very much for your highly interesting brochure on MER/29. The effects of this compound are certainly dramatic and study of its effects in humans as well as further studies of its action in animals seem most worthwhile pursuing. We are starting a group of rats on the compound in order to check specifically the question of effects on adrenal function. To know whether all inhibitors of cholesterol synthesis will inhibit adrenal function or not would be important.

One of the most surprising things to me was the highly significant drop in red blood cell cholesterol levels. Ordinarily this resists changes and does not fluctuate as does the plasma cholesterol level. Do you have any idea as to whether the total sterol content of the red cells is decreased parallel with the decrease in total cholesterol?

As soon as we have some information on the effects of MER/29 we will certainly get in touch with you. Thank you once again for sending us the compound and the highly interesting experimental results you have obtained with it. I think you are to be congratulated on a good job well done.

Sincerely yours,

DANIEL STEINBERG, M.D.,  
National Heart Institute.

THE WM. S. MERRELL COMPANY.

July 28, 1958.

DR. DANIEL STEINBERG,  
National Heart Institute,  
Bethesda, Md.

DEAR DANIEL STEINBERG: I was gratified to hear of your interest in working with our experimental drug, MER/29. We are continuing to explore some aspects of its biochemistry; unfortunately our rather prolonged experiment on sodium excretion effects did not work out due to failure of control animals to behave as expected.

I agree that the reduction of red cell cholesterol is unusual. We have not looked into the possibility of the presence of other sterols in the red cells; however, we now have chromatographic evidence for the presence of a small amount of a noncholesterol sterol-like material in liver of rats treated with MER/29. In the tissues generally, total unsaponifiable matter is reduced less than is cholesterol. As stated in the brochure, high doses produced a pronounced reticulocytosis in rats, which I thought might be related to an inability to achieve red cell maturity due to lack of cholesterol. This might also explain the vacuolated and binucleated lymphocytes found at high doses. I think it might be very interesting to look into the question you raised.



Obviously, there are many interesting ramifications of this type of drug action. I hope that we will eventually be able to investigate the major ones to definite conclusions.

I will, of course, be most interested in your findings. If you need more MER/29, or have questions, please let me know. If we get any more information of interest, I will pass it on.

Sincerely,

THOMAS R. BLOHM.

THE WM. S. MERRELL COMPANY.

July 30, 1958.

DANIEL STEINBERG, M.D.,  
National Heart Institute,  
Bethesda, Md.

DEAR DR. STEINBERG: Your problem of keeping MER/29 in solution in rat serum has not been encountered here, and no one seems to have any particularly good ideas on it. In the heart perfusion experiment, a solution of the citrate was injected into a moving stream of perfusate, which was not recycled, so it is pretty hard to tell what concentration was obtained.

During screening for antihistaminic activity, solutions of the citrate in Krebs-Ringer bicarbonate were prepared up to  $2 \times 10^{-2}$  M, so we know at least that this concentration can be obtained. Usually the proteins of serum enhance solubility, so it is possible that some improvement over this figure can be made. Fundamentally, of course, the problem is that the pKa is such that the unionized form predominates at physiological pH, and that form is pretty insoluble in water. I do not think that trying various salts would help very much.

MER/29 free base is fairly soluble in alcohol, and by adding a concentrated alcoholic solution to your serum you may be able to get a colloidal solution without exceeding a reasonable concentration of alcohol in your system. Propylene glycol and polyethylene glycol are often useful in this way also, and usually do not affect enzymes or tissues very much. Of course, you can't be sure of the actual effective concentration (physicochemical activity) this way, but often the results are surprisingly good.

If you are dealing with a single enzyme, even a dispersing agent such as a Tween can sometimes be used.

I am sorry that I can't provide you with more definite information, but we have not been faced with the problem before. If I get any ideas that work, I will let you know.

Sincerely,

THOMAS R. BLOHM.

November 7, 1958.

Dr. R. C. POGGE,  
Director, Medical Research Department,  
The Wm. S. Merrell Co., Cincinnati, Ohio.

DEAR DR. POGGE: We are writing to acknowledge your recent letters to us and receipt of the quantity of MER/29 which you so kindly sent. We must confess that we have not yet used it in patients but have done considerable work in animals. We do want to try to pick up any possible toxicity in these animals before going ahead with patients.

If you have any newer information on suggested dosage for patients or toxicity, we would of course be glad to hear from you. Despite our caution we still remain most interested in the drug.

Sincerely yours,

DONALD S. FREDRICKSON, M.D.,  
JOEL AVIGAN, Ph. D.

Section on Metabolism, National Heart Institute.



THE WM. S. MERRELL COMPANY,  
Cincinnati, Ohio.

November 11, 1958.

DONALD S. FREDRICKSON, M.D.,  
Section on Metabolism,  
National Heart Institute, Bethesda, Md.

DEAR DON: Thanks a lot for your note of November 7. We have gone up to 3,000 milligrams of MER/29 daily in one patient whose hypercholesterolemia appears to be rather resistant to treatment. Some other patients have been getting 1,000 milligrams daily and some of their blood cholesterol levels have been coming down very pleasantly.

It is my guess that you will not find any abnormalities in the white blood cells of your animals. The point seems to be that we must have run into an epidemic of infectious mononucleosis when we were doing our chronic safety studies, and the percentage of white cells showing the typical changes of infectious mononucleosis was somewhat higher in the treated group than in the control group. Since these animals also had very low blood cholesterol levels, it may well be that a cholesterol deficiency state influences the course of a virus infection undesirably. We probably will not run human blood cholesterol levels down anywhere near that low, so I do not anticipate any difficulty with this possible change in resistance to virus infection.

Kindest personal regards,

R. C. POGGE, M.D.,  
Director of Medical Research.

THE WM. S. MERRELL COMPANY,  
Cincinnati, Ohio.

January 23, 1959.

DANIEL STEINBERG, M.D.,  
National Heart Institute,  
Bethesda, Md.

Dear Dr. STEINBERG: As always in the case of a promising new compound, investigational supplies of MER/29 are inadequate. However, I do expect a modest improvement in the supply situation within a few weeks; and I am anxious to make certain that all investigators who have patiently put up with our shortages early in the MER/29 study have adequate supplies before I offer material to new investigators. Accordingly, I would appreciate it if you would complete the enclosed form in as great detail as possible and return it to me at your earliest convenience.

I am also enclosing an important warning on the false positive reactions for "albuminuria" which occur when MER/29 is excreted in the urine. Apparently, the biuret test is the only one which is satisfactory for the differentiation between albumin and MER/29.

Sincerely,

R. C. POGGE, M.D.

CONFIDENTIAL

#### Special Warning

To: MER/29 INVESTIGATORS.  
Re False Positive "Albuminuria."

One of the clinical investigators has reported that all of his patients receiving MER/29 displayed a low degree of albuminuria. An inspection of this report showed that the albuminuria persisted only as long as the drug was being given and ceased promptly upon discontinuation of administration of the drug. This, and the uniformity of the albuminuric response, suggested that the "albuminuria" might possibly be due to the excretion of the drug in the urine. In order to test this hypothesis, we ran several standard tests for urinary albumin on normal urine to which MER/29 citrate (a soluble salt of MER/29) had been added. Not only did this MER/29-containing urine give positive tests in those reactions for which we might predict a positive response, but also in some for which there was no obvious chemical basis on which to predict a positive reaction. Positive reactions were obtained in the following tests: sulfosalicylic



acid test, heat coagulation test, nitric acid ring test, and the Uristix test (Ames Laboratories, dip stick test). It was expected that a positive test would be obtained with the so-called alkaloidal reagents, such as sulfosalicylic acid, phosphomolybdic acid, ferrocyanide, etc. It was quite surprising to find a positive test with the heat coagulation test, but perhaps this can be explained on the basis of formation of an insoluble salt of MER/29 upon heating, such as the phosphate or urate.

We tried several approaches in an effort to find some means of distinction between true albumin and excreted MER/29 in the urine. First we attempted to extract MER/29 free-base from alkalinized urine. This did not work as well as expected, perhaps again due to the formation of insoluble salts. Finally we hit upon the biuret test, which is a general test for proteins but does not depend upon a precipitation reaction. This test requires a little more attention to detail than most such qualitative tests, and the following directions should be followed closely:

To 5 milliliters of urine in a test tube add 4 milliliters of 10 percent sodium hydroxide solution and mix thoroughly. To this add 2 or 3 drops (no more) of 10 percent copper sulfate, and mix. The presence of albumin is indicated by the formation of a violet or bluish-gray color. MER/29 may give a precipitate but does not give this color, the color remaining a yellowish-green as is obtained with normal urine. A normal (albumin-free) urine should always be run as a control.

Information kindly supplied by—

T. R. Blohm, Ph. D., Biochemical Research, the Wm. S. Merrell Co.

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February 18, 1959.

Dr. R. C. POGGE,  
The Wm. S. Merrell Co.,  
Cincinnati, Ohio.

DEAR DR. POGGE: I must apologize for being so late in replying to your letter of January 23. The delay is in part due to the fact that we have been mulling over the question of whether we wanted to initiate clinical studies of MER/29. At the moment we do not see our way clear to starting any serious clinical investigation with the compound, although we are very much interested in its biochemical effects.

I believe Dr. Avigan has already communicated to you the cholesterol lowering action that we have observed in rats in confirmation of Dr. Blohm's results. Even at low levels (0.005 percent in the diet) the experimental rats do not gain as well as controls. This growth limiting effect is more marked in younger animals. The cholesterol lowering action is dramatic, as you have observed. At 0.038 percent in the diet we have observed a drop in serum cholesterol from 66 to 24 milligram percent in 26 days. However, pair-fed controls only dropped to 58 milligram percent. We have also given the drug subcutaneously and there we got a drop from 61 milligram percent to 24.5 milligram percent. Again the experimental animals gained much less than the controls (29 gram gain versus 73 gram gain). We have found no inhibition of incorporation of C<sup>14</sup>-acetate into total nonsaponifiable lipid and are currently trying to fractionate the nonsaponifiable lipid.

We would be happy to have your comment and we would, of course, like to know what other information you have gathered about the action of this interesting compound.

Sincerely yours,

DANIEL STEINBERG, M.D.,  
National Heart Institute.

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THE WM. S. MERRELL COMPANY.

February 25, 1959.

DANIEL STEINBERG, M.D.,  
National Heart Institute,  
Bethesda, Md.

DEAR DR. STEINBERG: I appreciate sincerely your report of February 18 concerning confirmatory data on the effect of MER/29 on blood cholesterol in experimental animals. I am taking the liberty of passing along your letter of February 18 to Dr. Blohm for his comments.



We have given MER/29 in dosage up to 3 grams daily to human beings without producing any striking manifestations of toxicity. The patient who got 3 grams daily suffered from familial hypercholesterolemia and did not obtain a therapeutic response. In general, the other patients have usually shown a gratifying therapeutic response to MER/29 in daily dosage of 250-750 milligrams. We do not have any very convincing evidence that the bigger doses are more effective than the smaller doses, since we have been studying a limited number of patients in a relatively informal manner. At the moment I have a group of psychotic patients who have been eating a standard diet for many years, taking 250 milligrams once daily and a similar group taking 250 milligrams twice daily. If both of these groups fail to get a satisfactory response, I will conclude that the tentative dose is 750 milligrams daily and study such a dose intensively. If both groups respond well, I will proceed to study 125 milligrams daily in the hope that we can get an effective and economical dose.

Both Dr. Blohm and I are hoping to attend the federation meetings in April, and we would welcome an opportunity of having you join us for lunch and dinner at some mutually convenient time and place to discuss the whole MER/29 problem.

With kindest personal regards,

R. C. POGGE, M.D.

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*Memorandum*

May 20, 1959.

Thru:

Dr. James A. Shannon, *Director, NIH*

Dr. Robert W. Berliner, *Associate Director in Charge of Research, NHI*

Dr. Daniel Steinberg, *Section on Metabolism, NHI*

CURRENT STUDIES OF THE METABOLIC EFFECTS OF MER/29

The Section on Metabolism has been studying the effects of MER/29 on laboratory animals since last summer. At that time Dr. Pogge visited the section with Mr. Casale and we have corresponded subsequently. Dr. Joel Avigan and I have confirmed the observations of Dr. Blohm of the William S. Merrell Co. with respect to the cholesterol lowering properties of MER/29. After 2 weeks of daily subcutaneous injections of 10 milligrams of the drug the serum cholesterol fell from 61 milligram percent to 24.5 milligram percent. When fed at the level of 0.005 percent in the diet for 2 weeks the serum cholesterol levels fell from 63 milligram percent to 22 milligram percent. At these dosage levels, however, the compound has definite toxic properties evidenced by failure to gain weight at a normal rate, scruffiness of the coat and some erudation about the nose. Furthermore, the compound leads to a fall in tissue levels of cholesterol. The initial brochure from the William S. Merrell Co. described observations of abnormal lymphocytes in experimental animals receiving the drug. In summary, the compound is an extremely interesting one with definite cholesterol lowering properties but the toxic manifestations described require further clarification before clinical trials appear to be justified. At the spring meetings some preliminary results of clinical trial at Hahnemann Medical College were reported and it appears that at very low dose levels the compound may be well tolerated.

In the livers of animals receiving the drug a sterol closely related to but not identical with cholesterol accumulates. After injection of radioactive acetate or mevalonate radioactivity accumulates in this sterol. We are currently trying to determine the structure of this compound which may be an intermediate in cholesterol biosynthesis.

I spoke with Dr. Pogge in Atlantic City this spring and asked him to send me data on clinical experience with the compound but I have not received this as yet. It is my impression that the William S. Merrell Co. has placed the drug in several centers for clinical evaluation and that this aspect of the problem is probably well enough covered.

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THE WM. S. MERRELL COMPANY.

June 2, 1959.

DANIEL STEINBERG, M.D.,

*National Heart Institute, Bethesda, Md.*

DEAR DR. STEINBERG: Many thanks for calling with reference to MER/29. I was happy indeed to hear of the excellent subject whom you have available



for therapeutic trial. I am at this time sending 200 of the 250 milligram capsules. The suggested dose is 250 milligrams once every 24 hours; and I would think that the therapeutic response should be detectable within a few weeks.

I am attempting to collect the safety data which is said to exist with reference to the 2 patients who have been on 12 times the dose recommended above for a period of moderately more than 6 months. In terms of total dosage this would be equivalent to 6 years of treatment at the rate of 250 milligrams per day.

With kindest personal regards,

R. C. POGGE, M.D.

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*Memorandum*

June 2, 1959.

Dr. James A. Shannon

Thru:

Dr. Robert Berliner

Dr. Daniel Steinberg.

CORRESPONDENCE WITH DR. R. C. POGGE OF WM. S. MERRELL CO.

I spoke with Dr. Pogge on the telephone yesterday and thanked him for keeping us informed on recent progress with MER/29. Dr. Pogge said that his continuing correspondence has been primarily for the purpose of assessing possible demand for MER/29, supplies of which are somewhat limited at this time.

I assured him of our continuing interest in the compound and asked him to send sufficient material for clinical trial in two or three cases which would be studied intensively. We are particularly interested to see if the unusual sterol that we find in the livers of drug-fed rats accumulates to any extent in the serum of treated patients. We will also study the lipoprotein patterns. Dr. Pogge was very pleased to learn of our plans and agreed that extensive clinical trials already underway would suffice to gather the necessary statistics about the compound.

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THE WM. S. MERRELL COMPANY.

July 20, 1959.

DANIEL STEINBERG, M.D.,

*National Heart Institute, National Institutes of Health, Bethesda, Md.*

DEAR DR. STEINBERG: I want to thank you for taking the time from your busy schedule last week to discuss with me our cholesterol biosynthesis inhibitor, MER/29. We are indeed grateful to you for your continued interest in this compound and you may be sure that we shall keep you informed of our progress with its clinical evaluation.

With the accumulation now of approximately 1 year of clinical experience by a number of eminently qualified investigators, we can be sure that MER/29 is well tolerated and has not caused impaired function of the liver, kidney, hemopoietic system, or other vital organs and systems. With respect to response to the drug in terms of total and combined cholesterol in the serum, there has been a sufficiently large enough group of patients from several different geographic locations in the country that we are able to estimate that 8 or 9 in 10 patients will have a significant and sustained drop. We are also quite convinced that a dose of one 250-milligram capsule administered once daily is adequate.

As I told you, the limited number of cases of familial hypercholesterolemia and familial hyperlipemia which have been reported so far have failed to respond to MER/29 given alone, although concurrent administration of nicotinic acid in sufficient dose seems to be quite effective. I shall be very much interested in learning of your observations in the one such case now under treatment with MER/29 singly at the National Heart Institute. Also, I shall hope that, assuming this patient tolerates the medication satisfactorily without evidence of lack of safety, you will be sufficiently encouraged to expand the clinical use of MER/29.



Within the next few days, I shall write to you again about our plans for a working conference on MER/29 and the inhibition of cholesterol biosynthesis which will be held in Princeton, N.J., on December 16, 17, and 18.

With best personal regards,  
Sincerely yours,

R. H. McMASTER, M.D.,  
*Research Associate.*

P.S.—Thank you for arranging for me to see Dr. Braunwald during my visit at the National Heart Institute. Although he is quite interested in what we have so far learned about MER/29, he told me that it will not be possible to include this drug in his research protocol at the moment.

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THE WM. S. MERRELL COMPANY.

August 3, 1959.

DANIEL STEINBERG, M.D.,  
*National Heart Institute,  
Bethesda, Md.*

DEAR DR. STEINBERG: As a part of the MER/29 clinical development program arrangements have been made to bring together you and the other clinicians as well as the basic scientists who are most familiar with the compound. In order to provide sufficient time for you to accumulate additional experience with MER/29, this meeting has been set for Thursday, December 17, 1959, and will be held in the Princeton Inn, Princeton, N.J.

The conference will open with a dinner meeting at 7 p.m. on Wednesday, December 16. Cocktails will be served prior to the dinner. The bulk of the program is to be arranged for Thursday, December 17, and will consist of presentation and discussion by participants of accumulated data on MER/29. This will be a "working session" without formal audience.

Irving S. Wright, M.D. (professor of clinical medicine, Cornell University Medical College) will serve as moderator of the conference.

As a means of future communication of the conference proceedings, arrangements have been made for the verbatim transcription of all presentations and comments. Each conferee will be given an opportunity to edit his remarks and context. The proceedings will then be published by an acceptable professional journal or academic press.

The Wm. S. Merrell Co. will assume all expenses of your travel to and from Princeton and will provide lodging, meals, and incidentals during the period of the conference. The company will also provide for you a consultation fee of \$200.

In order that we may anticipate the space and other accommodations required for the Princeton conference, it is asked that you complete and return the accompanying form in the addressed envelope provided.

We are looking forward to your participation in what we are sure will be a most informative and stimulating conference in December.

Sincerely yours,

ROBERT H. McMASTER, M.D.

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August 13, 1959.

Dr. ROBERT H. McMASTER,  
*Department of Medical Research,  
The Wm. S. Merrell Co.,  
Cincinnati, Ohio.*

DEAR DR. McMASTER: Thank you very much for your letter of August 3 and your kind invitation to participate in the MER/29 conference.

While we may have enough clinical data to discuss by that time, I think that the best contribution I could make would be to describe instead our biochemical studies on the mechanism of action of the compound. This can be done, I think, in 15 minutes. Should there be any interesting results from the patient studies perhaps I could use an extra 5 minutes to describe them.

My close collaborator in these studies has been Dr. Joel Avigan and if the size of the conference permits I would like very much to have him attend also.

Sincerely yours,

DANIEL STEINBERG, M.D.,  
*National Heart Institute.*



THE WM. S. MERRELL COMPANY.

August 24, 1959.

DANIEL STEINBERG, M.D.,  
*National Heart Institute,  
Bethesda, Md.*

DEAR DR. STEINBERG: Many thanks for your letter of acceptance of August 13 to participate in our MER/29 conference in December. We are expecting that this will be a very instructive session and will look forward to seeing both you and Dr. Avigan at that time. As you have suggested, I am writing separately to Dr. Avigan to invite him to the conference.

I am indeed hoping that you will accumulate sufficient clinical data to justify your taking at least a part of your discussion time to describe your observations. The conference is of course highly weighted on the clinical side but a certain amount of basic work is not only necessary but highly desirable.

With best personal regards,

Sincerely yours,

R. H. McMASTER, M.D.

THE WM. S. MERRELL COMPANY,  
*Cincinnati, Ohio.*

August 31, 1959.

DANIEL STEINBERG, M.D.,  
*National Heart Institute,  
Bethesda, Md.*

DEAR DR. STEINBERG: Many thanks for your kindness not only in making suggestions concerning compounds related to MER/29 which might potentially have some activity but also in going over the experience you have had personally with MER/29. I was quite interested in the changes in cholesterol which occurred in the 52-year-old patient suffering from familial hypercholesterolemia. I did not make a note of the actual numbers or the actual days on which each determination was made. My colleagues have asked me about this patient, and it would be extremely helpful if you could supply me with specific information on the nature of the diet, the duration of time that the patient was on the special diet, the dosage and duration of administration of MER/29, and then also the dates when the different cholesterol determinations were made. Under the circumstances of the test with a standard diet, it did appear as if there were a change in the blood cholesterol which may have been due to the MER/29.

I will talk to my colleagues in the laboratory, and I am sure that one of them will have a comment concerning the possible preparation of compounds related to MER/29.

With kindest personal regards,

R. C. POGGE, M.D.

THE WM. S. MERRELL COMPANY.

October 6, 1959.

DR. DANIEL STEINBERG,  
*National Heart Institute,  
Bethesda, Md.*

DEAR DR. STEINBERG: On my return recently from a combination business trip and vacation Dr. Pogge informed me of your interest in relatives of MER/29. We have synthesized a large number of relatives of MER/29 and have been studying these over a period of years. MER/29 proved to be by far the most interesting compound in the series up until the present time. Some work is being continued, and should we find anything with important activity, we will let you know and will make samples of the material available to you.

We are aware that at least one individual has reported that certain ethanol amines have a hypocholesteremic action when evaluated acutely in animals. We have studied a variety of ethanol amines and have not found any with activity of the type possessed by MER/29. Based on results so far, we have no specific plans for additional work in this direction. If you feel additional efforts might be productive, I would be interested in your thinking and would reconsider the problem of additional work.

Sincerely,

HAROLD W. WERNER, M.D.,  
*Director of Research.*



October 12, 1959.

DR. R. C. POGGE,  
*The Wm. S. Merrell Co.,  
Cincinnati, Ohio.*

DEAR DR. POGGE: When we looked over our data on the patient I discussed with you here in August, we were disappointed to note that there was some downward slope on our baseline cholesterol values. We now have [the patient] back in the house for a repeat trial of the drug. We also have now carried out trials on two other patients and have a fourth patient just starting on the drug. If supplies permit, we would like to have another 100 capsules of 250 milligrams each, since that is the dosage we have been giving to the other patients in the series.

Our attempts to identify the unusual radioactive sterol in the rat livers are progressing slowly. It appears that the samples we have been dealing with have been mixtures of cholesterol with the noncholesterol sterol. However, we are certain that the radioactivity is in something other than cholesterol and we are pursuing various fractionation techniques to obtain the new sterol in pure form.

We will appreciate your cooperation in supplying more drug if it is available.

Sincerely yours,

DANIEL STEINBERG, M.D.,  
*National Heart Institute.*

THE WM. S. MERRELL COMPANY.

December 22, 1959.

DANIEL STEINBERG, M.D.,  
*National Heart Institute,  
Bethesda, Md.*

DEAR DR. STEINBERG: We are deeply grateful to you for your contribution to the proceedings of the Princeton conference on MER/29. It is my firm conviction that we can all look with pride upon not only the development of this important new compound in which you have had so prominent a part, but also upon the unrestrained and critical review to which it has just been submitted.

It is my pleasure to enclose our check in the amount of \$200 as honorarium or consultation fee. Upon receipt of your statement of travel and other expenses incidental to your trip to Princeton from Bethesda, a separate check will be sent.

All of us wish for you and yours a most joyous holiday season and New Year.

Sincerely yours,

R. H. McMASTER, M.D.

December 28, 1959.

Dr. R. H. McMASTER,  
*The Wm. S. Merrell Co.,  
Cincinnati, Ohio.*

DEAR DR. McMASTER: I meant to catch you during the conference to tell you that I had decided it would not be advisable for me to accept your generous offer of an honorarium for my contribution to the MER/29 conference. Because of my Government affiliation and also because I am currently a member of the Metabolism Study Section which may have to pass on grant applications in connection with projects involving your company, acceptance of an honorarium might be misunderstood by some. Therefore, I am returning your check with thanks. My expenses to this meeting were paid by the National Heart Institute.

I enjoyed participating in the conference and I believe it served a very useful purpose in bringing together the people studying MER/29. The new information that we presented at the meeting represented primarily the work of the few weeks preceding the conference and so I had not had time to communicate with you about it before. There are several serious questions raised by these findings. First, we do not know yet whether 24-dehydrocholesterol is or is not atherogenic to the same extent or to a greater extent than is cholesterol. Second, we do not know yet whether 24-dehydrocholesterol has other biochemical effects that might make it unsafe to treat with MER/29. I know that you are, of course, anxious to obtain FDA approval to market the drug but I do not feel that this would be wise in view of the new data.



What are your own thoughts on this matter? Have you any suggestions as to the kinds of information that should be sought in order to clarify the status of the drug?

Again, many thanks for your hospitality and for arranging a valuable conference.

Sincerely yours,

DANIEL STEINBERG, M.D.,  
*National Heart Institute.*

December 30, 1959.

Dr. R. H. McMASTER,  
*The Wm. S. Merrell Co.,  
Cincinnati, Ohio.*

DEAR DR. McMASTER: I wish to thank you for the invitation to the Princeton conference, which I found extremely valuable and interesting. I am also grateful for the opportunity of presenting the results of our study at the meeting, as well as for your kind hospitality.

In view of my affiliation with a Government institution, I find that it would be improper for me to accept a consultation fee or charge the company for travel expenses. I wish to thank you for your offer just the same. Enclosed is your check for \$200.

Best wishes for a happy holiday season.

Sincerely yours,

JOEL AVIGAN, Ph. D.,  
*National Heart Institute.*

THE WM. S. MERRELL COMPANY.

January 7, 1960.

DANIEL STEINBERG, M.D.,  
*National Heart Institute,  
Bethesda, Md.*

DEAR DR. STEINBERG: Thank you for your letter of December 28. We appreciate your remarks about the Princeton conference on MER/29 and are happy that you and the other participants regard it as having been a purposeful, valuable, and successful meeting.

The contributions made by you and Dr. Avigan to the fund of information about MER/29 and its site of action are of great interest. Whether or not accumulation of desmosterol or other sterols in animals will also be true in man and occur in sufficient magnitude to assume clinical importance is unknown. All evidence, basic and clinical, indicates that total sterols are either unchanged or are reduced. In addition, clinical benefit from MER/29 administration in terms of improved coronary artery function indicates that any possible alteration in sterol makeup is at least not harmful.

With respect to untoward biochemical effects other than atherogenicity (or lack of it) of desmosterol or other sterols to be considered in this instance, the animal and clinical safety data are rather overwhelmingly against them. You will recall Dr. J. Earle Estes' experiences with clinical safety of doses up to 3 grams daily of MER/29. Patients in other studies have been carefully followed for periods up to 15 consecutive months on doses of 1 gram per day (four times the recommended dose) without developing toxic symptoms or signs in the usual and often unusual parameters of toxicologic evaluation.

We hope you will continue your basic and clinical research with MER/29. To this end, we will be happy to supply you with quantities of the drug in both bulk and capsule form and we shall appreciate your interim reports as new data come to light.

Sincerely yours,

R. H. McMASTER, M.D.

THE WM. S. MERRELL COMPANY.

January 13, 1960.

DANIEL STEINBERG, M.D.,  
*National Heart Institute, Bethesda, Md.*

DEAR DAN: As you can imagine, we have all been quite busy trying to digest the information which came out of the Princeton meeting, and formulate plans accordingly. I am not at all sure this process has been completed, so I can only tell you what is going through my mind at the moment. \* \* \*



I have been giving a good deal of thought to the problem of desmosterol, and in fact, to the general problem of cholesterol precursors before we knew the identity of the one which accumulates. As I see it, if one wanted to evaluate the atherogenicity of desmosterol in rabbits, several important conditions would have to be established.

1. Absorption would have to be good enough to provide plasma levels of desmosterol comparable to levels of cholesterol known to be atherogenic.

2. These plasma levels would have to be established by accurate, specific analysis for desmosterol in plasma, plus separate analysis for cholesterol levels.

3. MER/29 would be required to prevent the conversion of desmosterol to cholesterol in the animal (we do not yet know whether MER/29 does this in rabbits).

4. Several groups of rabbits should be given cholesterol at different dietary levels so as to provide a sufficient number of "positive controls," i.e., animals with cholesterol levels comparable to the levels of desmosterol in the desmosterol-fed animals.

All of this presupposes that desmosterol can be obtained in sufficient quantity to carry on this type of experiment. At present, this assumes the proportions of a missile program, but perhaps an efficient synthesis can be worked out. We are studying the synthesis problem, and would be grateful for any suggestions.

As to the rabbits, we only know that MER/29 does not reduce LB-positive materials in plasma. This, of course, does not tell us much. We did save plasma from some rabbits against the day when we could chromatograph the sterols. I would be glad to work up the sterols from this plasma and send them to you for chromatography. We don't have our methods worked out yet. Incidentally, if you have an analytical method for desmosterol, I would very much like to know about it, and also about a source of milligram quantities of it. Does Stokes have any?

I am not particularly worried that desmosterol is toxic, since all our toxicology information indicates that there is a really amazing lack of toxicity considering the degree of inhibition produced by MER/29. Of course, the atherogenicity is another matter, and there we have no data, except that monkeys kept on MER/29 at high doses for 16 months showed no lesions in the aorta.

If you have any new information I would appreciate hearing about it, and I will try to keep you informed as to developments here.

Sincerely yours,

THOMAS R. BLOHM.

January 14, 1960.

Dr. R. H. McMASTER,  
The Wm. S. Merrell Co.,  
Cincinnati, Ohio.

DEAR DR. McMASTER: Thank you for your letter of January 7 and for your comments about the possible toxic effects of desmosterol. While I agree that the tests to date indicate no untoward side effects of the drug I cannot help feeling that the presence of a new and unstudied compound in the serum must be carefully evaluated. Perhaps the only way to evaluate it is to continue with long-term studies of the drug in animals and selected patients.

I would like to ask if you could send us several grams of pure MER/29 that we can use in vitro studies. I suppose the capsules contain some filler. Also, if you have made progress on a method for assay of MER/29 in tissues or blood we would be grateful for information you can give us along that line.

Sincerely yours,

DANIEL STEINBERG, M.D.,  
National Heart Institute.

January 22, 1960.

Dr. R. GORDON GOULD,  
Post Office Box 1663,  
Los Alamos, N. Mex.

DEAR GORDON:

\* \* \* \* \*

I did not mean to imply that not a single capsule of MER/29 should henceforth find its way into patients. The animal and patient studies already done



indicate that there is at least no acute toxicity of any magnitude, whether due to the accumulated dehydrocholesterol or any other effects of the drug. I raised the question in connection with the plan to make the drug generally available for practitioners of medicine. Certainly I see no objection to studies even in patients with no limitation on their life expectancy, provided the studies are short-term. \* \* \*

Sincerely yours,

DANIEL STEINBERG, M.D.,  
*National Heart Institute.*

January 22, 1960.

Dr. THOMAS R. BLOHM,  
*The Wm. S. Merrell Co.,  
Cincinnati, Ohio.*

DEAR TOM: Your discussion of the problem of evaluating atherogenicity of desmosterol coincides exactly with our own thoughts on the matter. The problem is difficult but I should think that its importance would warrant the time and effort involved.

We have fed 0.1 percent MER/29 to one rabbit and found much less 24-dehydrocholesterol in the liver than we have found in rats fed similar amounts of MER/29. However, there *was* 24-dehydrocholesterol there, indicating some block in synthesis. The burning question is whether the block in this species is only partial and whether it will be possible to pile in enough MER/29 to prevent the fed 24-dehydrocholesterol from being converted to cholesterol at a rate such as to significantly raise blood levels of cholesterol itself. The ghastly possibility is that one would wind up with a test animal in whose serum there would be excesses of both cholesterol and 24-dehydrocholesterol. You can see that this would make an evaluation of the atherogenicity of 24-dehydrocholesterol difficult.

We do not have any simple analytical method for desmosterol as yet. The synthesis of the ester derivatives and their separation on columns is not too difficult but it is certainly too time consuming and tedious for any large scale study. However, we are working on this problem and hope we will come up with something simpler in the near future and I will let you know as soon as we have it. We only have very small amounts of 24-dehydrocholesterol which we are using as carrier in our isolations. However, there is a rich source of this material in certain marine invertebrates. It may be that a large scale isolation program would be simpler (but by no means simple) than a scientific program. I have written to Idler and Fagerlund to inquire about this possibility and to ask for any small amounts of 24-dehydrocholesterol they may have on hand. If they make some available I will be glad to send you enough material to use as carrier and reference compound.

I agree that the studies already done in animals and in man are reassuring with respect to acute toxicity. My only question is whether, in view of the "foreign" sterols appearing under drug treatment, long term therapy or general use is warranted at the present time.

Sincerely yours,

DANIEL STEINBERG, M.D.

THE WM. S. MERRELL COMPANY.

May 5, 1960.

DANIEL STEINBERG, M.D.,  
*National Heart Institute,  
Bethesda, Md.*

DEAR DAN: It was good to talk to you again. In response to your request, we are sending under separate cover 6 bottles each containing 100 250-milligram capsules of MER/29. These are a reddish-pink color and are the same as those we have sent you previously. In addition, I am sending 24 bottles each containing 30 250-milligram capsules in the pearl-grey color. These are representative of the type of packaging and color which will eventually be marketed. You may wish to use the latter in preference to the former.

Enclosed you will find reprints of the available published basic and clinical data on MER/29. I am also enclosing\* a copy of the paper by Dr. John T. Leckert and his associates from the Browne-McHardy Clinic in New Orleans. This paper was delivered by Dr. Leckert at the Louisiana State Medical Society meeting in Baton Rouge and can be so referenced. Just as soon as a usable

\*Enclosure not reprinted in this volume.



copy of the Princeton conference proceedings is available, I shall see that you receive it.

I have told Tom Blohm of your interesting antifertility studies with MER/29, and no doubt you will hear from him shortly.

With best personal regards,  
Sincerely yours,

R. H. McMASTER, M.D.

THE WM. S. MERRELL COMPANY.

May 12, 1960.

DANIEL STEINBERG, M.D.,  
*National Heart Institute,  
Bethesda, Md.*

DEAR DR. STEINBERG: Events of interest concerning drugs in development should, we feel, be made known first to the investigators whose combined efforts have created the existing basic and clinical information about them. It becomes my pleasure, therefore, to announce to you that MER/29 will become available for prescription use in the United States and Canada on June 1, 1960.

Personally and on behalf of all my associates, I wish to express sincere appreciation of the contribution you have made and are making toward the development of MER/29. I know you will want to share with us justifiable pride in the accomplishment to date, tempered by the realization that the full story of the effect of MER/29 upon cardiovascular disease has not yet been written. We can be grateful also that MER/29 has stimulated new thinking and research in the pathogenesis and treatment of atherosclerosis and its manifestations.

Sincerely yours,

R. H. McMASTER, M.D.

THE WM. S. MERRELL COMPANY.

October 6, 1960.

DR. DANIEL STEINBERG,  
*National Heart Institute,  
Bethesda, Md.*

DEAR DAN: Following our visit to your lab yesterday, it occurred to me that we have some data bearing on the liver triglycerides of rats on MER/29®. These data were collected quite early in our work, and I had almost forgotten them. As you can see in the enclosed reprint\*, we gave rats something in excess of 50 milligrams per kilogram per day of the drug for a month, without any effect on total lipids. Since the great bulk of such lipids is triglycerides, this means that this fraction was not changed significantly.

Obviously something was different between your experiment and ours. It may have been dose, since our toxicology studies indicate that when one reaches a toxic dose, a mild fatty infiltration of the liver is one of the manifestations. Of course diet and a number of other things may have entered into it too.

We all agreed that you presented a very well-organized and interesting seminar, as was also evident from the discussion which was stimulated. \* \* \*

Sincerely yours,

THOMAS R. BLOHM.

THE WM. S. MERRELL COMPANY.

October 7, 1960.

DR. DANIEL STEINBERG,  
*National Heart Institute,  
Bethesda, Md.*

DEAR DR. STEINBERG: I wish to express my thanks for the time you spent with us Wednesday discussing our MER/29. We also appreciated the opportunity to sit in on your excellent seminar.

As discussed with you, we are planning to alter our brochure covering the discussion on desmosterol and the limitation of tests based on the Liebermann-Burchardt reaction. On the basis of our discussion, we appear to be in agreement on three major points. If this is not true, I hope you will correct me. These points are (1) The atherogenicity of desmosterol is unknown. It may be the same as, more than, or less than cholesterol. In the absence of specific data, one may assume it is the same. (2) Desmosterol appearing in the serum of patients

\*Enclosure not reprinted this volume.



on MER/29 therapy levels off and stays constant, representing about 20 percent of total sterols. (3) MER/29 therapy results in 15 to 20 percent reduction of total sterols.

I am forwarding a copy of this letter to Dr. Frank Talbot in view of his interest in this general area.

Best wishes.

Sincerely yours,

F. JOS. MURRAY.

*(Informal Interagency Correspondence)*

October 3, 1961.

DANIEL STEINBERG, M.D.,  
Chief, Metabolism Section,  
National Heart Institute,  
Bethesda, Md.

DEAR DAN: Enclosed are two copies of the latest proposed brochure<sup>1</sup> on MER/29 (triparanol, Merrell). We would appreciate your and Dr. Avigan's review of this material.

Please keep in mind that this proposed brochure is intended for use by the average physician in practice.

Dr. Nestor, Mr. Weiss, Mr. Deutschberger, and I again wish to thank you and Dr. Avigan for your interest in our problem and for the time you gave us at our meeting last week.

Sincerely yours,

IRWIN SIEGEL, M.D.,  
Deputy Medical Director.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,  
PUBLIC HEALTH SERVICE,  
Bethesda, Md.

November 17, 1961.

DR. IRWIN SIEGEL,  
Deputy Medical Director, Bureau of Medicine  
Food and Drug Administration.

DEAR IRWIN: Since you have already talked with Joel, this letter is probably unnecessary but I will put down some specific comments that we had on the brochure you sent.

No. 1—page 2: The evidence for point 3 is tenuous. The statement is presumably based on the work of Hollander and Chobanian. What they have shown is that labeled cholesterol disappearance curves when extrapolated back to zero time indicate a smaller "pool." What is not known is the extent to which labeled cholesterol will exchange with desmosterol in the tissues. If this exchange occurs more slowly than exchange of cholesterol with itself the difference in these curves may not prove that the total body pool of sterols is actually low in triparanol-treated patients.

No. 2—page 2 (point 4): Again the company emphasizes cholesterol levels per se, without at the same time pointing out that desmosterol accumulation causes the depression of total sterols to be smaller.

No. 3—page 2 (point 6): The validity of this statement depends on whether you consider the hair, the skin, the adrenal glands, and the lens of the eye to be "vital organs or systems."

No. 4—page 3 (last paragraph): See no. 1 above.

No. 5—page 7: Our results show much smaller effects on sterol production when both desmosterol and cholesterol production are included.

No. 6—page 8: Here it is implied that desmosterol does not deposit in diseased coronary arteries as rapidly as does cholesterol. This is unwarranted. The lesions in the coronary artery were undoubtedly of very long standing. Cholesterol in the lesion had been laid down over a period measured in years. The net amount of new sterol deposited during triparanol therapy was almost certainly a small percentage of the total sterol present. Consequently one would expect to find only a very small percentage of desmosterol even if both sterols were being

<sup>1</sup> EDITOR'S NOTE.—Neither this nor certain other brochures were available to the subcommittee in time for reprinting within this volume.



deposited at comparable rates during the time that triparanol was being administered. Recent results by Avigan and myself suggest that there is no difference in the rate at which the two sterols are deposited in developing atheromata. A rabbit fed both cholesterol and desmosterol along with triparanol developed gross aortic atheromata. At sacrifice the serum desmosterol accounted for about 30 percent of circulating sterols; the desmosterol in the lesion accounted again for about 30 percent of the total sterol present.

No. 7—page 11: Does the drug only interfere with established pregnancy or does it affect fertility?

I hope these comments will be of help to you. Please don't hesitate to call on us if we can provide you with any further information.

Best regards,

Sincerely yours,

DANIEL STEINBERG, M.D.,

Chief, Section on Metabolism, National Heart Institute.

THE WM. S. MERRELL COMPANY.

November 29, 1961.

DANIEL STEINBERG, M.D., Ph. D.,  
National Heart Institute,  
Bethesda, Md.

DEAR DR. STEINBERG: The enclosed warning letter<sup>2</sup> is being sent to all physicians in the United States who have had or will have occasion to prescribe MER/29. We want to insure that you, as one of the clinical investigators of MER/29, are acquainted with its contents before it is generally received by your colleagues.

Of particular interest is the side effect outlined under "Cataracts." In three of the four cases which have come to our attention, the lens change was described as diffuse punctate opacity formation on the posterior lens surface subcapsular. No ophthalmologic report is available in the fourth case. All changes followed severe dermatitis with loss and color change of the hair and, in all cases, MER/29 in doses ranging from 250 to 1,000 milligrams daily had been continued for some time after first appearance of the dermatitis.

The overall incidence of reported side effects from MER/29 remains gratifyingly low. We are certain that their existence need not interfere with your further use of the drug. We shall, however, welcome comments and reports concerning your own experience with the various side effects mentioned.

Sincerely yours,

ROBERT H. McMASTER, M.D.

December 14, 1961.

Dr. ROBERT H. McMASTER,  
The Wm. S. Merrell Co.,  
Cincinnati, Ohio.

DEAR DR. McMASTER: It is unfortunate that triparanol has been found to lead to the several serious toxic effects that have been reported with chronic treatment. The drug is biochemically "clean" in the sense that its effect appears to be so specific but in view of the adverse effects that can be encountered, and in view of the limited depression of total serum sterol levels, it is doubtful that clinical use is justified over long periods of time.

The second paragraph of your letter of November 29 implies the possibility that the lens changes that have been observed may have been on an allergic basis. As you know, rats that are fed high dosages of triparanol develop complete lenticular opacity with chronic treatment. Since this is not an effect limited to an occasional animal, there is no reason to feel that the effect is an allergic one. Is there any reason to attribute the human lesions to an allergic reaction rather than cumulative effects of the drug itself? Is there any information available to implicate changes in sterol metabolism as a possible contributing factor to the eye changes? It would be particularly interesting to know if chronic treatment at high dosage levels with some of the compounds structurally related to triparanol but of much lower activity in inhibiting cholesterol synthesis would cause cataracts.

<sup>2</sup> EDITOR'S NOTE.—See text of this letter in exhibit 127, p. 895.



We ourselves encountered no toxic effects in the dozen or so patients that we treated but our patients were under treatment for no longer than 3 months at a time. I cannot agree with your conclusion that the side effects "need not interfere with your further use of the drug." In the case of triparanol or any drug used to lower serum cholesterol levels, the acceptable incidence of toxic effects must be as near to zero as possible. There is no assurance that treatment with such drugs is actually conferring a benefit on the patient. Consequently, it is not justifiable to expose the patient to potential damaging effects. Until clinical results become available to give us a basis for evaluating to what extent we improve prognosis by lowering cholesterol levels, we will not be in a position to decide what risks we can take with chemotherapy. We may be morally certain that we are helping the patient but we cannot be scientifically certain. Consequently, it is my feeling that we should be scientifically certain that we are not hurting the patient when we administer drugs in this context.

Sincerely yours,

DANIEL STEINBERG, M.D.,  
*National Heart Institute.*

THE WM. S. MERRELL COMPANY.

December 28, 1961.

DANIEL STEINBERG, M.D.,  
*National Heart Institute,  
Department of Health, Education, and Welfare,  
Bethesda, Md.*

DEAR DR. STEINBERG: Thank you for your letter of December 14.

Your reference to a possible inference that the cataracts may have been on an allergic basis is difficult for me to understand. I have reread the second paragraph of my letter to you of November 30 and am unable to discern such an implication. Also, I am unaware of similar criticism from any others of the several hundred physicians to whom the letter was addressed. It is true that in all cases the cataract development followed severe dermatitis and drug withdrawal by several months. The cataracts may have been related to the skin changes as suggested by the similar pattern of events and the common embryology of the involved structures. The suggested relationship, however, is the same as that of cataracts and atopic dermatitis and is not based on an allergic response. In fact, two of the four patients who developed cataracts had past medical histories which included neurodermatitis. The time sequence alone argues against allergic reaction.

I appreciate your comments about triparanol. You may be sure, also, that I respect your opinion concerning the justification of its clinical use even though it is not shared by those of us who have access to the greater bulk of data and reports concerning the drug or by an impressive number of other experts in this field. Furthermore, I believe any attempt to deprive the fully informed practicing physician of his right to exercise professional judgment in the selection of treatment for any particular patient is not consistent with the accepted philosophy of medical practice in the United States.

Sincerely yours,

ROBERT H. McMASTER, M.D.

March 8, 1962.

DR. THOMAS R. BLOHM,  
*The Wm. S. Merrell Co.,  
Cincinnati, Ohio.*

DEAR TOM: We are continuing with studies of the in vitro action of triparanol and have been able to show that it inhibits the reduction of lanosterol to dihydrolanosterol as well as inhibiting reduction of desmosterol to cholesterol. We are trying to determine whether the same enzyme is responsible for both reactions and for this purpose would like to compare the activities of various inhibitors on the two reduction steps. I know that you have studied a large number of variants on the triparanol structure and I am wondering if it would be possible to have samples of some of these. If the relative activity in inhibiting lanosterol reduction and inhibiting desmosterol reduction paralleled each other it would provide indirect evidence that a single enzyme is involved. On the other hand, if we should find that any of the inhibitors inhibits the lanosterol reduction as well as does triparanol while showing markedly reduced activity on desmosterol reduction this would evidence for the presence of two different enzymes.



We would particularly like to have compounds very similar in structure to triparanol but with markedly reduced activity. Palopoli described the compound in which the methyl and chlorine groups were interchanged and said it had only a fraction of the activity of triparanol. Would it be possible to have some of this material? Knowing what we have in mind I think you can see what we are after and we would be glad to have your suggestions.

Best regards,

Sincerely yours,

DANIEL STEINBERG, M.D.,  
*National Heart Institute.*

THE WM. S. MERRELL COMPANY.

March 27, 1962.

Dr. DANIEL STEINBERG,  
*National Heart Institute,  
Bethesda, Md.*

DEAR DAN: I have not answered your request for analogs of triparanol earlier because I have been trying to "liberate" some of them from other departments which are also interested in them. Finally I requested a resynthesis of the compound which you specifically requested. This should be completed in a month, and I will send it to you then; by that time I should be able to send at least one other compound also.

I think your approach to the problem of the sequence of events in the conversion of lanosterol to cholesterol is very good, and I will be interested to hear what happens. Does triparanol inhibit the lanosterol conversion at the same concentration as required to inhibit desmosterol conversion? Of course you would still need the additional evidence of additional inhibitors. Perhaps we can discuss this at the Federation.

Sincerely yours,

THOMAS R. BLOHM.

#### *Memorandum*

May 1, 1962.

Dr. Knutti, *Director, NHI*

Thru: Dr. Berliner, *Director of Intramural Research, NHI*

Dr. Steinberg, *Chief, Section on Metabolism, NHI*

#### TELEPHONE CALL FROM MR. DONALD GRAY, WITH HOUSE INTERGOVERNMENTAL RELATIONS SUBCOMMITTEE

Mr. Donald Gray telephoned this morning on behalf of Dr. Goldberg to put some questions concerning studies in the Heart Institute on triparanol (MER/29). He asked me to summarize the studies that we had done with the drug. I told him that our interest had been primarily in the biochemical mechanism of action of triparanol and summarized our work that led to the elucidation of its site of action. He asked specifically about any clinical studies done here and I told him that we had carried out short-term studies in a group of 10 or 12 patients for the purpose of establishing whether the mechanism of action in man was the same as that in animals and that our studies had established that it was. He asked if we had observed any toxic side effects and I told him that we had not but that our studies were of short duration, the patients being kept on the drug only as long as necessary to permit the biochemical investigations planned.

He raised the question of whether there was any formal relationship between our Intramural Research Department and the Food and Drug Administration. I told him that I did not know if there was any formal liaison but that I had been telephoned by an FDA representative in the winter of 1959, at which time they were trying to reach a decision about triparanol. At that time we had just very recently made the discovery that desmosterol accumulated under the influence of triparanol but had already shown in one patient that desmosterol did appear in the serum and red blood cells during treatment. I informed the FDA man that we had already established that desmosterol gave a low color-yield in the Liebermann-Burchardt reaction and that this would necessitate re-evaluation of clinical results obtained using this test for cholesterol levels. At that time we could give no estimate of the extent to which desmosterol accumulated and therefore no estimate of the degree to which results reported might be in error.



I told Mr. Gray that we had discussed the effects of triparanol on several occasions with Dr. Irwin Siegel of FDA. Dr. Siegel was aware then of our observations of the toxic effects of *high* doses in experimental animals and we called his attention to unpublished experiments of other investigators who had observed toxic effects.

I explained to Mr. Gray that the question of the value of triparanol hinged to some extent on whether or not desmosterol was as atherogenic as cholesterol. I told him that we had predicted that it would be and quoted our 1960 article read in Milan. And I told him of our recently published results confirming experimentally that desmosterol is deposited in lesions of experimental atherosclerosis as readily as is cholesterol.

Mr. Gray asked if I would send him reprints describing our studies on triparanol and I said that I would be happy to do so. He thanked me for the information and said that he might be in touch with me again if they needed further information.

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,  
FOOD AND DRUG ADMINISTRATION,  
Washington, D.C.

May 24, 1962.

Dr. DANIEL STEINBERG,  
National Heart Institute,  
National Institutes of Health,  
Bethesda, Md.

DEAR DR. STEINBERG: We are investigating the studies conducted on the drug triparanol (MER/29) manufactured by the William Merrell Co., Cincinnati, Ohio. We have learned that some studies on MER/29 were conducted by your section, and that you and perhaps others in your section engaged in correspondence with the William S. Merrell Co. concerning the results.

For official enforcement purposes, we request that you make available to Mr. Tilros of the Food and Drug Administration for review and duplication, if necessary, the files concerning any tests performed by your section on this drug.

If you have questions concerning this request, please contact the writer at code 13 extension 22161. Unless we hear from you to the contrary, Inspector George Tilros, of this Administration, will visit you on May 31.

Sincerely yours,

G. S. GOLDHAMMER,

*Director, Division of Regulatory Management, Bureau of Enforcement.*

(EDITOR'S NOTE.—Handwritten note at bottom of letter):

5/31/62 Discussed with Dr. Berliner. Approval given to turn over correspondence files to FDA representative.

D. STEINBERG.

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EXHIBIT 129

MER/29—CHRONOLOGY PROVIDED BY T. J. KIRBY, M.D., SECTION OF  
OPHTHALMOLOGY, MAYO CLINIC, ON EARLY CLINICAL EXPERIENCE

In the history of MER/29, numerous references appear to the early work by physicians of the Mayo Clinic on this drug. Accordingly, Senator Hubert H. Humphrey invited one of the physicians who had been active in the early clinical cases, T. J. Kirby, M.D., Section of Ophthalmology, Mayo Clinic, to convey a chronology of his and his colleagues' experiences. The chronology follows in the form of a letter to Senator Humphrey. Additional references to contributions by Mayo clinicians will be found in the chronology in exhibit 127.



(Since the materials in exhibit 127 were sent to press, prior to the receipt of the present exhibit, there is a small degree of overlap in references to articles in the open literature.)

MAYO CLINIC,  
SECTION OF OPHTHALMOLOGY,  
Rochester, Minn., July 17, 1963.

DEAR SENATOR HUMPHREY: This letter describes the chronology of triparanol (MER/29) at the Mayo Clinic.<sup>1</sup> Attached are reprints of papers concerning the use of triparanol and the side effects noted.

The first supply of the drug was received in March 1960 for clinical investigation.

On May 10, May 19, and September 13, 1960, reports were sent to the drug company. These reports stated that, due to the small number of patients and the short duration of treatment, no impressions of the drug's effectiveness could be advanced.

*October 27, 1960.*—Report to the drug company: On a 3-month trial basis the MER/29 at a dose level of 250 milligrams daily showed a 6 percent reduction in cholesterol level compared with a 30 percent reduction for nicotinic acid in the same patients. There was some suggestion that 500 milligrams of MER/29 daily would cause a more substantial lowering during the second 3-month period of treatment in the 6 patients so studied on both doses.

*January 31, 1961.*—Letter to the drug company: Reporting a case of ichthyosis and one of loss of hair, and asking if there are references or other cases of dermatitis reported during the use of triparanol.

*February 7, 1961.*—Drug company report to the clinical investigators: They had received reports of skin reactions among patients taking MER/29, but the incidence was extremely low, perhaps less than 1 percent. The skin conditions were of two types: An occasional case of urticaria which may be of allergic origin which usually develops early during the period of therapy. Then there is a later reaction which occurs after the patient has been taking MER/29 for several months. This usually is a dry, scaly, itching condition. Both types of skin reactions cleared when the patient discontinued the use of MER/29. There had been no reports of ichthyosis and the company was interested in knowing more about the patient. A few cases of thinning of the hair had been reported, but the incidence was extremely low. In all cases in which the drug was discontinued, there had been regrowth after a few weeks.

*February 20, 1961.*—Report to the drug company: A change in the color of hair from dark to blond and with increased loss of hair was reported for one patient.

*February 20, 1961.*—Drug company letter to the clinical investigators at the Mayo Clinic: Anxious to obtain as much information as possible about the patients with skin and hair reactions. The company expressed the importance of evaluating the nature and incidence of the reaction so that the information could be provided the medical profession.

*February 25, 1961.*—Report to the drug company: Now have 5 cases with some effects on hair.

*February 29, 1961.*—Drug company letter to clinical investigations at the Mayo Clinic: The company is in the process of collecting all available data on any type of side effect which may have occurred while patients were taking MER/29. The company requested any new information available on side effects.

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*April 26, 1961.*—"Cutaneous Side Effects from Use of Triparanol (MER/29)." A Preliminary Report, Achor, R. W. P., Winkelmann, Richard K., Perry, H. O., Proceedings of the Staff Meetings of the Mayo Clinic, vol. 36, No. 9, Apr. 26, 1961.

A report of two patients with ichthyosis, loss of hair and change in color of hair as side effects of triparanol. Loss of hair with dry skin without ichthyosis of five other patients was discussed.

*August 14, 1961.*—Patient listed as case 1 in the above report was examined in the eye section because of blurred vision for a duration of several days. There were bilateral posterior and anterior subcapsular cataracts.

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<sup>1</sup> Editor's note: The above chronology covers only the experience with the drug and with patients of one group of investigators at the Mayo Clinic; in particular, those who encountered changes in skin and hair, followed by cataract formation. The subcommittee notes that another investigator at the Mayo Clinic, J. Earl Estes, M.D., used the drug as early as 1958. See p. 824 for the title of a paper he presented at the 1958 Princeton Conference.



*October 5, 1961.*—Patient listed as case 2 in the above report was examined because of blurred vision. He was found to have bilateral posterior and anterior subcapsular cataracts.

*October 7, 1961.*—The drug company was notified by phone that both patients reported earlier with moderately severe skin and hair changes had developed cataracts and that one other patient who might fit the same category had been heard of by correspondence.

During the summer and fall of 1961, the investigators had received several letters from patients and physicians inquiring about the skin and hair reactions to triparanol. One patient related the development of cataracts. This letter was answered on October 13, 1961, stating that we had no certain information that cataracts were secondary to MER/29 treatment; however, it was a likely possibility.

*October 11, 1961.*—A representative of the drug company met with the clinical investigators at the Mayo Clinic in Rochester. All available information concerning the skin, hair, and eye reactions to MER/29 was given to him.

*October 19, 1961.*—Two of the clinical investigators met with the drug company officials while attending the meeting of the American Heart Association in Miami. The experience with side effects of MER/29 was again reviewed. The Mayo Clinic investigators suggested that other clinical investigators be notified of the side effects so that more information could be obtained; also that all physicians be given a warning about the possible side effects of the drug.

*October 22, 1961.*—The same physicians met again with a representative of the drug company with Dr. John O. Nestor, of the FDA, in Miami. Again, the experience with MER/29 and the side effects was reviewed. They were informed that preliminary discussions between the drug company and the FDA were to be held on Thursday, October 26, 1961, in Washington, D.C. Doctor Nestor requested that any additional information obtained be sent to him.

*October 27, 1961.*—The drug company representative informed one of the Mayo Clinic physicians by phone from Cincinnati that the preliminary meeting with the FDA had been held and that further plans were awaiting the results of that discussion.

*October 27, 1961.*—One of the clinical investigators received a phone call from a Mr. John Nicholson, of the Drug Research Reports in Washington, D.C. He inquired of our experience with MER/29 and the side effects encountered. He was referred to a published abstract in the October 1961 issue of *Circulation*, and to the paper published in the Proceedings of the Staff Meetings of the Mayo Clinic on April 26, 1961. He asked if we had seen cataracts in patients treated with MER/29. He was told that we had seen two such cases and heard of a third. It was stated that we could not prove causal relationship at this stage of information.

*November 6, 1961.*—The drug company representative called, inquiring if we had further information as to side effects of MER/29. We had nothing new. The drug company representative mentioned that some dogs on MER/29 had been rechecked. Those animals on supplemental vitamins and minerals had developed no skin or eye changes, while some of those on no supplemental vitamins or minerals had developed these complications. He suggested supplemental vitamins and minerals for our two patients with cataracts.

*November 20, 1961.*—Report to the drug company: Follow-up examination of our third patient with severe skin and hair reaction shows no evidence of cataract, and the skin and hair had returned to normal. All of our other patients on triparanol have been examined and none shows evidence of cataract. This includes those with mild to moderate hair loss reaction. The first patient who developed cataracts continues to show some progression of the lesions. Attempts to photograph the cataracts have been unsuccessful. A copy of the report was sent to Dr. Nestor of the FDA.

*November 24, 1961.*—Phone call, drug company representative to Mayo Clinic physicians: As a consequence of the hearings with the FDA, the company was preparing a letter of warning to be sent to all physicians. The letter would recommend that periodic slit lamp examinations be made for all patients taking MER/29. In addition to our two cases of cataract, two others had been reported to them, one from Houston, Texas, and another from Los Angeles.

*November 29, 1961.*—Letter from drug company representative to the clinical investigators. Enclosed was the drug warning dated December 1, 1961.

*December 5, 1961.*—Following a phone call from the drug company representative, a Mayo Clinic ophthalmologist sent him pencil sketches of the cataracts observed in our two patients. Attempts were made to photograph the cataracts but were unsuccessful.



*December 5, 1961.*—Copy of the report to the drug company dated November 20, 1961, was acknowledged by Dr. Nestor of the FDA. He expressed thanks for keeping him informed, hoped we would continue to do so.

*December 12, 1961.*—Letter from the drug company representative: They would keep us informed of any new information concerning lenticular changes. The distribution of the warning letter may bring forth other cases which would need careful evaluation. They were surveying a large number of patients who, for one reason or another, had been followed by ophthalmologists during the period of time while they were taking MER/29.

*December 13, 1961.*—Three clinical investigators met with another drug company representative in Rochester and discussed with him the findings and current information concerning the use of MER/29. He was given copies of the results of our year's investigation, plus a summary statement regarding our experience. In addition, he discussed his company's plans to survey the ophthalmologists who had prescribed MER/29.

*December 14, 1961.*—Memo from drug company representative: Three of four dogs which had developed lens changes during high dose chronic study with triparanol were now showing clearing of the opacities. They had been off the drug for several weeks and had had the nutritional supplement added as outlined to us. This observation (by an ophthalmologist) was interesting and they would keep us informed.

*December 22, 1961.*—Medical World News, Vol. 2, No. 26: "Drug firm cautions MD's on antilipid agent."

*December 28, 1961.*—Letter to the drug company representative: Both of our patients with cataracts are on the vitamin supplement as suggested. The progression of the cataracts in one of the patients seems stabilized somewhat, but the other has been progressively worse. The decrease in vision is enough that the ophthalmologist feels that cataract surgery will be necessary before long.

*December 30, 1961.*—Letter to the editor of Medical World News from Dr. Achor: "In the interest of accurate reporting I would like to call attention to two errors in the article entitled 'Drug Firm Cautions MD's on Antilipid Agent' which appeared in Medical World News, volume 2, Number 26, page 34, December 22, 1961. In the article it was stated that the group at the Mayo Clinic encountered 4 cases of cataracts. This is not true as we have seen 2 cases only. Again it is stated that no cataracts have been reported by any investigators other than the Mayo Clinic group. This again is not true since at least 2 have been reported from other sections of the country.

"I hope that these corrections can be called to the attention of the readers of your magazine."

This letter of correction appeared in volume 3, No. 3, February 2, 1962.

*January 10, 1962.*—Letter from the drug company representative: There is no question of regression of the cataracts in the dogs. It is now possible to see the retina in the animals, whereas a few weeks ago this structure was completely obscured by the lenticular lesions. We have no idea why this is occurring but are very encouraged by it.

In February 1962 an editorial was submitted to the Archives of Ophthalmology at the request of the editor. The editorial was printed in the correspondence section of the Archives of Ophthalmology, vol. 67, pp. 543-544, April 1962. Enclosed is a copy of this editorial giving our experience with cataracts and triparanol. (See attached copy.) [Not reprinted herein.]

*March 22, 1962.*—Letter to the drug company representative: The cataract problem is much the same except that they are progressive. It seems impossible at this time to assess the prevalence of the reaction or to predict when it will occur. In our experience, cataracts have not appeared except in patients who have had skin reactions. Our ophthalmologist plans to report the two cases which we have followed. The report will be submitted to the AMA Archives of Ophthalmology. The decision to report them has been stimulated because of the widespread interest and requests for information received concerning the subject and the article which appeared in the December 1961 issue of Medical World News. It is unfortunate that more time is not available for deliberation. Our dermatologists have collected an increasing series of cutaneous reactions among patients of all ages and with varying periods of treatment. Usually the dose, age, and duration of therapy are unrelated to causation of reactions. Individual reactivity must play a very important role.

*March 21, 1962.*—Cataracts developed in a 6½-year-old child treated with triparanol for hypercholesterolemia and xanthomatosis. The drug company was notified.



*March 26, 1962.*—Letter to the drug company giving detail of the child's history and treatment. A carbon copy of the above letter was sent to Dr. John O. Nestor of the FDA in Washington, D.C.

*April 2, 1962.*—Two drug company representatives came to Rochester and the details of the case were given to them. They met with one of the ophthalmologists who had examined the child. The ophthalmologist expressed the opinion that the cataracts were drug induced.

*April 16, 1962.*—Phone call from the drug company. The decision had been made to take the drug off the market.

*July 28, 1962.*—Paper by Laughlin and Carey: Cataracts in Patients Treated with Triparanol, JAMA 181, Number 4: 339-340 (July 28) 1962. Two case histories are presented in which the patients developed cataracts rapidly with progressive loss of vision shortly after discontinuing triparanol. One patient had been taking the drug for 18 months and the other 15 months. It seemed probable to the authors that triparanol was responsible for the lens opacities in both cases.

*August 10, 1962.*—Request from JAMA for an answer to a question to be printed in their Question and Answer Section. Below are the question and answer as they appeared in the JAMA:

"Q. I have 2 patients who have developed cataracts following cessation of triparanol therapy. Is cessation of administration the triggering mechanism in these cases; in other words, would the cataracts have developed if therapy had been continued? Robert Friedenberg, M.D., Albuquerque, N. Mex.

"A. This question is similar to that proposed in the comment portion of a recent article entitled 'Cataracts in Patients Treated with Triparanol' by Laughlin and Carey (JAMA 181: 339, July 28, 1962). Although information concerning triparanol-induced cataracts is limited, a number of carefully observed patients have developed cataracts while treatment with the drug was being continued. In addition, other patients have maintained their usual vision for many months after stopping therapy with triparanol and before the formation of lens opacities. Cataracts have also been found to form during uninterrupted treatment with triparanol in experimental animals (dogs and rats). Consequently, the cessation of administration of triparanol should not be considered the cause of cataract development; rather, it is the drug which has furnished the toxic stimulus. What cannot be answered is whether stopping triparanol therapy may accelerate, at least for a time, the progression of lens opacities in some patients.

"Available information and experience concerning patients with triparanol-induced cataracts permit some tentative observations which may be useful as a frame of reference. The age of the patient, the dose of triparanol, and duration of treatment are not critical factors in the development of cataracts. The course of triparanol-induced cataracts has been relentlessly progressive with eventual severe disability requiring surgical correction. However, the progression is often erratic and there may be periods of quiescence followed by bouts of rapid worsening."

*October 1962.*—"Cataract Formation after Triparanol (MER/29) Therapy," Kirby, Achor, Perry and Winkelmann, Archives of Ophthalmology, 68: 486, Oct. 1962. A report of three patients who developed cataracts after treatment with triparanol.

*November 1962.*—"Side Effects of Triparanol Therapy," Perry, Winkelmann, Achor and Kirby, American Journal of the Medical Sciences, 244, No. 5, Nov. 1962. A report of the same 3 patients who developed cataracts plus a discussion of the skin and hair reactions of other patients who had not developed cataracts.

*January 16, 1963.*—"Treatment of Hypercholesteremia with Triparanol and Comparison with Nicotinic Acid," Achor, Christensen, Berge and Mason, Proceedings of the Staff Meetings of the Mayo Clinic, vol. 38, No. 2, Jan. 16, 1963.

*March 1963.*—"Cutaneous Syndromes Produced as Side Effects of Triparanol Therapy," Winkelmann, Perry, Achor and Kirby, Archives of Dermatology, vol. 87, pp. 372-377, March 1963.

Sincerely yours,

T. J. KIRBY, M.D.



## EXHIBIT 130

## COMMENT IN THE TRADE PRESS WITH RESPECT TO DECISION BY HEALTH, EDUCATION, AND WELFARE DEPARTMENT HEARING EXAMINER FOR SUSPENSION OF NEW DRUG APPLICATION ON ALTAFUR

Three principal developments in the hearing held with respect to Altafur were referred to as follows in the trade press. For additional background, see exhibit 131, p. 948.

November 6, 1961.

F-D-C REPORTS—"THE PINK SHEET."<sup>71</sup>

## ALTAFUR NDA ORDERED SUSPENDED BY HEW EXAMINER WHO FINDS FDA CAN CONSIDER COMPARATIVE EFFICACY; HE CRITICIZES FDA AND EATON

Suspension of the New Drug Application (NDA) for Eaton's Altafur was ordered by HEW Hearing Examiner Edward E. Turkel in a stiff decision that (1) swept aside testimony offered by Eaton at the secret hearings held in February and (2) criticized the Food and Drug Administration (FDA) for giving initial clearance to the drug.

"Most of the reports in the NDA," said Turkel, taking dead aim at FDA, "fail to show adequate clinical research data to evaluate the efficacy and safety of use of Altafur, particularly in the light of additional investigations to determine such matters after the NDA became effective."

Turkel, a Hearing Examiner for the Social Security Administration in New York City, presided at the first hearing on a contest over suspending an effective NDA for a brand-name, pharmaceutical specialty for human use. Eaton is reported to have contested the case, as a matter of principle, to test the validity of FDA's long-held legal view that efficacy is a consideration in determining the safety of new drugs.

*Comparative Efficacy Sealed Into Case, If Eaton Goes to Court*

Turkel not only went along with FDA on efficacy, but he extended the legal frontier—between the beginning and the conclusion of the secret hearing—to embrace "comparative efficacy," a nasty phrase in American Medical Association and pharmaceutical industry quarters. On the basis of written briefs, the examiner ruled at the start of the hearing that:

"Therapeutic efficacy is a material and relevant issue in determining whether Altafur tablets are safe for use under the directions set forth in the labeling."

By the time he had heard the evidence, Turkel went all the way. "Altafur is represented as efficacious in the treatment of serious conditions, not admitting of delay in treatment," he concluded. "Under such circumstances, therapeutic efficacy is a relevant, material, and highly important factor, as well as toxic potential, in determining whether it is safe for use under the conditions of use upon the basis of which the NDA became effective."

He backed this finding up with 10 citations from the secret hearing record, ranging all the way from page 224 to page 2,403.

His next finding sealed the "comparative efficacy" legal issue into the case, if Eaton takes it to court. Listing 13 citations from the record he declared: "Altafur is not therapeutically efficient, as are other available antibacterial drugs, although the latter may also produce side reactions. The efficacy of other antibacterial drugs, as compared to Altafur, is a factor in the issue of safety of use of Altafur inasmuch as Altafur is capable of significant toxic side reaction without exercising counterbalancing therapeutic efficacy."

Turkel's 30-page findings and order become final on November 24, if no exceptions are filed to it by Eaton. The order is subject to an initial review by FDA Commissioner Larrick, if Eaton continues the contest. Eventually, it can be brought into a courtroom.

With the exception of two experts, Turkel declared, Eaton's medical witnesses "did not engage in any clinical research or planned study of Altafur. Limited and inadequate research were conducted by the other two witnesses." He continued:

"Although medical witnesses testified that the administration or ingestion of Altafur had caused the cure or improvement of a number of patients, such

<sup>71</sup> Vol. 23, No. 45, pp. 18-20.



evidence is of less significance and is of less evidentiary weight than the results shown by clinical research conducted to determine the efficacy of Altafur [by Government witnesses].

"Moreover, the evidence relating to the cure of improvement as a result of treatment of patients with Altafur is insufficient to establish a reliable pattern of therapeutic efficacy and shows the superiority of clinical and laboratory research and study and over the reports of clinical cures and improvements without such research having been done."

*Even an MD Specialist Is Not Necessarily a Competent Evaluator*

Medical witnesses for Eaton included Doctors Province, Brundenell, Loftus, Scott, Glass, Lysaught, and Formon. The two whom the examiner said had done some research work were Glass and Lysaught.

Those who testified for FDA included Doctors Finland, Yow, Bryne, Gocke, Jackson, and FDA's Reedy. Finland carried the case for the Government and was on the stand for a long time, but the examiner, in preparing his decision, leaned heavily on Jackson's testimony and the paper by a group, headed by Jackson, that appeared in the New England Journal November 10, 1960.

In determining the efficacy of a drug, the examiner declared, "it is not enough" to show that it "has cured or helped some patients." To be efficacious, the examiner indicated, a "drug must be sufficiently reliable in curing or treating patients."

Turkel laid down a stiff standard for judging the competence of clinical evaluators. "A physician engaged in practice of a medical specialty is not necessarily competent to conduct clinical investigation in new drugs dealing with infections in their specialty, irrespective of reported clinical experience. Procedures followed in clinical research with drugs are different than procedures followed in the ordinary practice of medicine. In evaluating the toxicity and efficacy of a new drug, a whole variety of in vitro and in vivo work is done in clinical research which is not done in the private practice of medicine.

"Such procedures are taken for preciseness in the diagnosis of the condition and in evaluating the role which the drug plays in the patient's recovery and to eliminate as much as possible other causes for recovery."

Turkel slashed the testimony by Eaton's witnesses, but he also paid his respects, in various ways, to FDA for clearing the drug. Data in the NDA, he said, with respect to alleged 30 cures of staph pneumonia, "without a single failure," were termed "inadequate." At another point, he took aim at FDA with the following:

Altafur is capable of toxic manifestations or side reactions when ingested. The overall side effects as reported in the NDA are somewhat greater than 10 percent. Such reactions are generally not irreversible.

Here's how Turkel handled the testimony of Dr. Lysaught, one of Eaton's witnesses. The examiner said he diagnosed staph pneumonia in 20 patients—to be given Altafur—by "cultures of material taken from the nasopharynx." Accurate distinguishment couldn't be made between staph and viral pneumonia, Turkel ruled. "In the great majority of viral pneumonia cases the patients recover spontaneously without antibiotic drugs." \* \* \*

Turkel listed Altafur's side effects as including blood, neurological, and gastrointestinal disturbances, systemic sensitivity reactions, skin reactions, cross sensitivity and anaphylactic reactions—"particularly serious," the examiner noted. Testimony indicated Altafur's incidence of side effects was about 33 percent, Turkel reported, adding that they "have not always been reported, or recognized, giving rise to a reasonable inference that the evidence of toxicity is not complete. The absence of underlying data at the hearing \* \* \* gives further rise to such inference."

Turkel tackled the testimony of another Eaton witness, Dr. Scott, by saying: "Underlying data \* \* \* did not include clinical objective data required for an adequate evaluation of the role of Altafur."

December 27, 1961.

DRUG RESEARCH REPORTS—"THE BLUE SHEET."<sup>72</sup>

Eaton's Altafur appeal from an HEW Hearing Examiner's report suspending effectiveness ("D-R-R" Nov. 8) of the Altafur New Drug Application (NDA) is based fundamentally on the contention that the Food & Drug Administration

<sup>72</sup> Vol. 4, No. 24, pp. 15-16.



has no statutory authority to consider "efficacy" as well as "safety" in clearing a drug for the market or seeking to remove it. Adopting this basic legal posture, Eaton cited no factual data intended to rebut Hearing Examiner Turkel's findings—set down at great length—that the latest evidence shows the drug is not effective and that clinical proof offered by Eaton was inadequate. Mr. Turkel also stated that medical practitioners in general are not necessarily competent to perform clinical research and to evaluate the results with required precision.

Eaton's appeal, filed by Vincent Kleinfeld, specialist in food & drug law, argued that Altafur side effects, cited by FDA, are relatively unimportant, are all reversible and are covered by the labeling of the drug. "Even witnesses appearing for the Govt. would not have been seriously concerned with any of the potential side effects if they felt the drug was efficacious," Mr. Kleinfeld said. Examiner Turkel had found that Altafur is not safe because it is not effective in the serious illnesses for which it was used. "Therapeutic efficacy should not have been a consideration in determining the safety of Altafur tablets," the appeal declared. "The testimony of each of the Govt.'s medical witnesses and the findings of the examiner are inextricably interwoven with the concept of efficacy of Altafur," it said. "This is not only with reference to 'absolute efficacy,' a concept which the Govt. is now seeking to have included by amendment of the statute, as part of the requisite evaluation for new drugs, but also with respect to 'relative efficacy,' a concept which the Govt. has disavowed."

The appeal goes to the Food & Drugs Commissioner and probably will be handled by Deputy Commissioner John Harvey. There is no chance whatsoever that Mr. Harvey or any other top FDA official will side with Eaton and rule against the Hearing Examiner. Their current appeal is simply a necessary step along the road to the Fed. Court which has jurisdiction over NDA cases (unlike other appeals from FDA administrative proceedings that go to the U.S. Circuit Court). Thus far, no NDA suspension has been taken to court.

September 3, 1962.  
DRUG TRADE NEWS.<sup>73</sup>

#### FDA ORDERS SUSPENSION OF EATON LABORATORIES' NEW DRUG APPLICATION COVERING ALTAFUR TABLETS

WASHINGTON.—Suspension of Eaton Laboratories' new drug application covering "Altafur" tablets has been ordered by Deputy Food and Drugs Commissioner John L. Harvey, after lengthy legal proceedings.

In ordering the suspension, Mr. Harvey upheld and followed very closely a recommendation on November 1961 by Hearing Examiner Edward E. Turkel, who conducted protracted closed hearings on a Food and Drug Administration notice of suspension, issued Dec. 27, 1960. The case was the first formal contest of revocation of a new drug application.

Eaton appealed Mr. Turkel's proposed order to Commissioner George P. Larrick, who delegated the job of review to Deputy Commissioner Harvey.

In its appeal, Eaton raised a number of legal objections, all of which were rejected by Mr. Harvey. One of the objections went to Mr. Turkel's finding that "therapeutic efficacy is a material and relevant issue in determining whether 'Altafur' tablets are safe for use under the directions set forth in the labeling."

#### HARVEY REPLIES

To Eaton's contention that therapeutic efficacy is "immaterial and irrelevant" to the issue of revocation of a new drug application, Mr. Harvey replied:

"It is clear that the use of an ineffective drug for the treatment of a serious disease is not a safe practice. Many infectious diseases are progressive and life threatening.

"To hold off treatment by the use of an ineffective remedy is clearly unsafe. The usefulness and the effectiveness of a drug under such conditions is clearly relevant and material to the safety of its use."

The original NDA for "Altafur" became effective July 6, 1959. Later it was amended to include improved labeling. After conferences with representatives of FDA's New Drug Branch, Eaton was formally notified Dec. 27, 1960, that FDA intended to suspend the effectiveness of the NDA.

<sup>73</sup> Vol. 37, No. 18, p. 14.



FDA contended that clinical experience and tests and methods not deemed reasonably applicable when the NDA became effective showed that "Altafur" was unsafe when used according to labeling directions.

Mr. Harvey's order also denied a supplemental NDA filed by Eaton Oct. 18, 1960, which endeavored to correct FDA objections to the original one.

Eaton Laboratories withheld comment on the FDA order.

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EXHIBIT 131

EXCERPTS OF REPORT BY HEARING EXAMINER OF DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE FINDING THAT ALTAFUR WAS BOTH UNSAFE AND INEFFECTIVE

Part 2, exhibit 78, pages 504-508, contained a chronology prepared at the subcommittee's request by the Food and Drug Administration with regard to the New Drug Application for Altafur. On March 20, 1963, the drug was mentioned in the testimony by Dr. Nestor. There follow now excerpts from the extensive report by the Hearing Examiner appointed by the Department of Health, Education, and Welfare on the case of Altafur. As indicated in part 2, on page 508, the examiner, Edward B. Turkel, signed a tentative order on October 25, 1961, suspending the New Drug Application and all supplements thereto. The judgment of the Hearing Examiner was subsequently confirmed by Deputy Commissioner John L. Harvey.<sup>74</sup>

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UNITED STATES OF AMERICA  
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

IN THE MATTER OF "ALTAFUR TABLETS," EATON LABORATORIES, DIVISION OF  
NORWICH PHARMACAL CO., NORWICH, N.Y.

FDC-D-62<sup>75</sup>

1. On December 27, 1960, the Deputy Commissioner of Food and Drugs issued Notice of Hearing, FDC-D-62, notifying the respondent herein, Eaton Laboratories, Division of Norwich Pharmacal Company, Norwich, New York, of its intention to suspend the effectiveness of New Drug Application No. 11-965 and all amendments and supplements thereto, and to refuse to make effective the finding supplement thereto, filed on October 18, 1960. The grounds for the proposed actions are that clinical experience and tests by new methods not deemed reasonably applicable when such application became effective show that such drug is unsafe for use under the conditions of use upon the basis of which the application became effective; and that the supplement filed on October 18, 1960, does not show that Altafur is safe for use under the conditions of use prescribed, recommended, or suggested in the proposed labeling in that:

(A) Clinical experience, and in vitro tests not deemed reasonably applicable when such application and supplement thereto became effective show that the drug is of little or no value in the treatment of serious and life-threatening infections for which it is offered in its labeling or for which it is represented by means of the distribution of sensitivity discs purporting to determine its clinical usefulness, which infections when not checked by the drug would produce serious injury or fatal results.

(B) Clinical experience and in vitro tests show that Altafur is not sufficiently efficacious in the treatment of infections to justify the risk of the serious toxic effects of neurological disturbances, hemotological reactions, gastrointestinal side reactions, dermatological reactions, and adverse reactions to the concurrent administration of alcohol which are shown to result from its clinical use.

(C) The reports of investigations which were submitted with the supplemental application filed October 18, 1960, fail to demonstrate the safety of the drug for use in treating the infections specified, in that the reports fail to demonstrate that the drug would be effective to halt the progress of said infections and the resulting injury therefrom.

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<sup>74</sup> See exhibit 130, p. 947.

<sup>75</sup> The references, such as exhibits, tables, etc., mentioned within the text of this HEW Department finding are not printed herein.



The Hearing Examiner affirms his rulings at the hearing, after consideration of the arguments presented in the written arguments of the parties, as follows:

(1) Therapeutic efficacy is a material and relevant issue in determining whether Altafur tablets are safe for use under the directions set forth in the labeling (exh. 110, 111, and 112).

(2) The refusal of the Hearing Examiner to take the deposition of Dr. Deter or to remove the hearing temporarily from Washington, D.C., to El Paso, Tex., to take his testimony was not an abuse of discretion.

(3) The use of medical literature on direct examination was proper; and it was also proper to permit the questioning of witnesses on cross-examination as to the contents of treatises or medical texts not recognized as authoritative by the witness.

The respondent contends that evidence given at the hearing by Dr. Yew and Dr. Davis concerning the evaluation of data submitted relating to the original New Drug Application is irrelevant (R. 524ff, R. 808-852). The Hearing Examiner is of the opinion that such evidence is both relevant and material upon the issues presented in the notice of hearing, inasmuch as such evidence should be considered with all the other evidence concerning clinical experience and investigations.

Upon considering the entire record and written arguments of counsel for the respondent and for the New Drug Branch, the Hearing Examiner makes the following

#### TENTATIVE FINDINGS OF FACT <sup>76</sup>

(1) The New Drug Application for Alafur tablets originally became effective on July 6, 1959. On January 8, 1960, exhibit 110 was allowed to become effective as the authorized labeling for the produce (exh. 5).

(2) On July 6, 1960, representatives of the Food and Drug Administration and the respondent conferred upon the subject of a proposed revision of the package insert (labeling) for Altafur tablets and related matters, in lieu of withdrawing Altafur from the market as had been apparently proposed by the Food and Drug Administration. A memorandum of interview, dated July 20, 1960, recites agreement between the parties that a proposed revised package insert then submitted by the respondent (exh. 111) would be processed as a conditionally effective supplemental application for interim use with the understanding, among other things, that within the period of the next 3 months consideration will be given, on the basis of additional evidence which may be submitted, as therein specified, as to whether marketing of the drug should be discontinued completely or to determine a pattern of labeling under which the drug can be regarded as safe for continued sale. The respondent was advised of the conditional effectiveness of the supplement by letter of the New Drug Branch, dated July 25, 1960 (vol. V. of exhibit 5). The Hearing Examiner finds from the foregoing that the new packaging insert, exhibit 111, was authorized for an interim period of not more than 3 months from July 20, 1960 (vol. V. of exhibit 5), but that nevertheless the burden is upon the Food and Drug Branch to show that the new evidence submitted does not meet such conditions.

#### *(Confidential matter deleted)*

(4) The labeling for the drug (exh. 110, 111, 112) sets forth that "Altafur Sensi-Dises" may be used for bacterial sensitivity tests. Such tests are not reliable to discriminate between bacteria; therefore such labeling declarations misleadingly imply or suggest that Altafur is therapeutically effective for the infections indicated in the said labeling caused by strains of bacteria. Such misleading suggestions or implications of therapeutic efficacy are based upon 50 microgram impregnation of the disc with Altafur, whereas, Altafur is not capable of exerting or maintaining such blood level concentration in the body (table I, exh. 121, R. 1094, 1095, 1114, 1125-1126, exh. 121, exh. 103, page 928). As is hereinafter shown such misleading declarations are a material factor in the issue herein presented; namely, whether Altafur is unsafe for use under the conditions of use set forth in the labeling (see finding).

<sup>76</sup> Hearing Examiner's footnote: The proposed findings of fact submitted by the attorneys for the respective parties were also considered by the Hearing Examiner in arriving at these tentative findings. [Additional footnotes which follow were also those of the Hearing Examiner.]



(5) At the minimal inhibitory concentration of Altafur, 7.8, there is little bacterial killing in vitro and no bacterial growth (R.1097); when the concentration falls below the minimal inhibitory concentration there is little or no inhibitory effect on bacteria, in vitro (exh. 103, fig. 1, R.1097-1099). It is therefore necessary to maintain an inhibitory concentration of the drug or of greater concentration, in the human body, as long as possible for effective therapy (R. 1099-1100, 1113, 1125, 2997).

(a) In November 1958 through March 1960 a study of Altafur was conducted by Dr. Jackson, a qualified physician, whose qualifications include training and experience in medical investigation and research (R. 1088). This study shows Altafur failed in the treatment of 20 out of 28 patients and serious doubt whether Altafur was of any therapeutic value in the other 8 cases (exh. 103, published in the *New England Journal of Medicine*, Nov. 10, 1960).<sup>77</sup> Twenty patients were treated with the oral form and 8 with the intravenous form of Altafur. These patients suffered from moderate to severe infections of staphylococci or micrococci; i.e., coagulate positive and coagulate negative staphylococci (R. 1101, 1102). Thirteen patients received Altafur as the first treatment and 15 patients had received one or more antibiotics before Altafur (R. 1188). Types of infections for which these patients were treated are: septicemia, endocarditis, superficial or deep wound infections, pneumonia, empyema, osteomyelitis, pyarthrosis, and meningitis (exh. 103, table 2; exh. 103, p. 928; R. 1102, 1105, 1197-1198).

(6) Other indications of failure or lack of efficacy of Altafur are extension of infection during the period of treatment and presence of bacteria demonstrated in the bloodstream (i.e., bacteremia) at varying periods of time after patients had been treated for local infections (R. 1105-1107, 1219, 1224, 1225, 1270).

(7) With respect to the said 28 cases, in instances where positive blood cultures were obtained, in vitro determinations were made of the infecting types of bacteria and were found to be sensitive to Altafur (R. 1272). Some of the patients suffered side reactions as a result of Altafur (see Finding no. 15 (d), (g), (h), (i)). Specimens of blood taken from all 28 patients under treatment at definite time intervals, namely, 2, 4, and 6 hours after administration of the oral or intravenous Altafur, and the serum from these patients were tested for presence and amount of drug. At 2 hours 60-percent, at 4 hours 75- to 77-percent, and at 6 hours 88-percent of the specimens did not demonstrate the presence of Altafur. The mean or average values at each time interval, namely 2.1, 1.4, and 0.2 at 2, 4, and 6 hours respectively, are below the minimal inhibitory concentration for about 90-percent of the staphylococci strains (R. 1112-1113).

<sup>77</sup> The study of the drug was discontinued after completion of studies in 28 patients because Dr. Jackson who conducted the study had no confidence in the therapeutic efficacy of Altafur for the treatment of the infections, as well as completion of anticipated studies. The original plan of study called for treatment of 20 patients to receive the oral form of drug, and because of disappointing results with such oral form, additional studies were undertaken with the intravenous form in 8 cases (1122-1123). Although in his published article (exh. 103, p. 903) Dr. Jackson stated that 8 or 29 percent of the 28 patients responded favorably to treatment and lists 8 cases, he modified such declaration in the article and by his testimony at the hearing. He expressed doubt concerning 4 cases as "cures" in serious staphylococcal bacteremia (exh. 103, p. 933); and with regard to the other "cures" indicated the basis therefor as temporal relationship of the recovery of the patients and administration of Altafur and testified to details regarding the condition of these patients as follows: Included in the 8 patients are 4 septicemia or endocarditis cases listed as cured. The witness testified it is dubious that Altafur affected a cure in 3 of such cases; thus one patient had a coagulase negative type of bacterium induced from a blood transfusion and not an established infection; another patient in the final summary had infectious mononucleosis, a nonbacterial disease, with coagulase negative staphylococci thought to be a contaminant from the skin at the time of taking blood culture; the bloodstream of another patient was inactive for infection as determined by blood cultures just before administration of the drug; 4 other patients had wound infections, 2 of superficial character which do not extend rapidly and gradually clear themselves; and 2 patients had received antibiotics in addition to Altafur so that it was not possible to ascribe the cure to any particular drug therapy (R. 1107, 1108-1109, 1243, 1249, 1276, 1257, 1276-1278, 1201-1205, 1218, 1242, 1244, 1245, 1246, 1249, 1258-1259). Altafur is described as toxic and therapeutically ineffective (R. 1123-1125).

<sup>78</sup> This witness, Dr. Finland, is associate professor, Harvard Medical School, trained and experienced in the fields of clinical research, teaching of methodology of clinical research and, treatment of patients, with major interest in the area of infectious diseases (R. 116-122, exh. 108, exh. 109).



(8) In another study of the effects of Altafur performed by a highly qualified expert<sup>79</sup> Altafur was administered in intravenous form to 9 seriously ill patients, and 12 postoperative patients for the purpose of preventing infection in contaminated wounds. (The latter cases are part of the 50 cases investigated by Dr. Byrne also, as described below.) Two patients received the oral form of Altafur when they were able to ingest the drug (R. 174-175, exh. 107, p. 5). This study demonstrated that Altafur had no therapeutic effect in any of these patients (R. 429, 440). Extensive laboratory testing upon samples of blood, serum, urine, and bile taken from the 21 patients and selected highly sensitive bacteria failed to show any antibacterial activity resulting from the administration of either the intravenous or oral form of Altafur (R. 181-202). Although the respondent contends that lack of antibacterial activity was due to the storage of the serum containing Altafur at -20 degree temperature (exh. 107, p. 4) such contention is not warranted by considering all of the evidence on this question.<sup>79</sup>

(9) A study was conducted in February and March 1960 by another physician, Dr. Gocke, also trained and experienced in medical investigation and research (R. 1436-1439, 1441). The study consisted of two parts, namely in vitro (or laboratory) work to determine the activity of Altafur against bacteria, primarily against staphylococcus, and clinical studies concerning staphylococci skin and wound infections; and clinical investigation, i.e., treatment of 10 hospitalized patients with Altafur, suffering from mild infections, namely 6 staphylococcal skin infections, and 4 pneumonias (1449-1451, 1459-1461, 1463). Altafur has been held out by respondent as effective, when given systematically, against a variety of bacterial infections, particularly staphylococcal infections (R. 1440). The laboratory work included testing the sensitivity to Altafur of 99 strains of staphylococcus aureus, and showed that 93 strains were completely inhibited by 25 micrograms per milliliter of Altafur, or less; and 7 out of 8 strains were inhibited by either 12.5 or 25 micrograms per milliliter; and that Altafur was effective in killing a number of strains of staphylococcus aureus (R. 1448). In the six skin infection cases Altafur was given over a period ranging from 9 to 28 days. Cultures from these patients showed staphylococcus aureus bacteria (R. 1509, 1521-1523, 1525-1527, 1531, 1460, 1461). In three cases there was a fair clinical response (R. 1452, 1458, 1460). In no case was there bacteriological cure, i.e., the pathogenic organisms persisted at the site of infection (1452, 1455, 1456, 1458, 1460-1461, 1531). An effective antibacterial agent functions to eliminate the causative organism from the skin lesion in addition to effecting improvement of clinical symptoms (R. 1463, 1509, 1531, 1545). The results of the effect of Altafur in the treatment of the pneumonia cases are inconclusive; no specific known etiological agent was found in the blood or sputum in any of the pneumonia cases (1453-1454, 1456-1457, 1458-1459, 1460). Clinical investigation of Altafur was discontinued because of the failure of Altafur to eradicate staphylococci from the skin lesions of the patients, and inadequate or indeterminable clinical response (1471).

(9A) Altafur is not useful in the prevention of infection following potentially contaminated or definitely contaminated surgical cases as shown in a study conducted by Dr. Bryne, a qualified medical investigator, in the winter of 1960 (exh. 104, published in the New England Journal of Medicine, Nov. 10, 1960, 745-746, 748, 750). The development of an infection or infections while the patient is receiving prophylactically an antibacterial drug intended for the treatment of such infection or infections in similar dosage is significant evidence that the drug

<sup>79</sup> Dr. Gocke, a witness called by the New Drug Branch, testified that a test conducted by him on serum containing Altafur 7 days after the mixture had been stored in deep freeze (25 degrees C. (R. 1443)) showed that the drug in the serum had only one-eighth its antibacterial activity (R. 1443). His data does not show and there is no other evidence, whether the loss took place at the time Altafur was added to the serum or while the mixture was in cold storage (R. 1540-1542). His testimony is not inconsistent with the test made by Dr. Finland, showing that the minimal inhibitory concentration of the drug was not affected by storage at -20 degrees C. (R. 1541, exh. 107, p. 4). The testimony of Dr. Reedy, a bacteriologist employed by the Food and Drug Administration, is in accord with the testimony of Dr. Finland (3061-3063).



would not be therapeutically effective against the causative pathogenic organism (R. 193, 589-590, 759-782; see also Finding no. 19.)<sup>80</sup>

(10) In order to be effective in the systemic treatment of infections a drug must be present in the blood so that it may be transported to the site of infection and the drug must be active against the organism causing the infection (R. 175-180, 379, 2918, 2920, 2921-2922). Although the respondent contends that the failure of the body fluids to demonstrate the activity of Altafur does not indicate that the drug is inactive and that the drug has some different therapeutic mode of action there is no substantial evidence to support such contention. There is a reasonable inference from the evidence that if the respondent's contention is correct, demonstration accordingly would have been made by the respondent, as the manufacturer of the product, and hence in a better position to resolve such contention, despite its testimony that it engaged in research upon the problem and has not as yet determined whether there is a correlation between the therapeutic efficacy of Altafur and minimal inhibitory concentration. The nature of animal studies conducted upon the question were inconclusive due to deficiencies in the method (R. 2854-2855, 2862-2864, 2886, 2914, 2915). There is no real evidence that tissue levels rather than blood levels is the significant factor in resolving the question (cf. R. 591-593, 677-678, 680, 2910-2911).

(11) In addition to the laboratory investigations referred to in the previous finding of fact, testimony was given by a witness on behalf of the respondent intended to show that Altafur need not produce a blood level in the human body at least equal to the minimal inhibitory concentration in vitro in order to be effective against organisms (R. 2967-2969). Certain determinations made by the witness have no relationship to in vivo or body fluid levels necessary to cure infection (R. 2981-2983, 3030-3031). Although attempts at measurement of the level of Altafur were made, there is no evidence to show whether the antibacterial active portion or the nonactive portion of the molecule was being appraised by the method (R. 2989-2990). Although animal studies were performed in order to determine blood level concentrations the data is insufficient for a conclusion (R. 2971-2972, 3026, 3007-3008, 3033-3035).

(a) In vitro bacteriological work with Altafur was also reported upon by a witness for the respondent (R. 2977-2978). No laboratory data of any kind was produced to support conclusions and opinions of the witness; and the Hearing Examiner deems the testimony given by the witness as insufficient to support such conclusions and opinions at least in the absence of underlying data (R. 2971-2972, 3020-3021, 3026, 3033-3036). (It is to be noted in this connection that the Hearing Examiner's order of January 17, 1961, issued pursuant to the pretrial conference provided for the production and examination of underlying data.)

(12) During the period a drug is being evaluated, the patient should be observed daily; controlled laboratory studies be performed; and repeated blood counts be performed. Moreover, liver function studies, repeated urinalysis, and frequent cultures should be performed. These studies are necessary to determine toxicity and the effect on the causative organism (R. 525-526, 533, 543-544, 545, 572-573, 580-581, 609, 611, 1315-1316, 1554, 2099-2100). The drug must be sufficiently reliable in curing or treating patients; it is not enough in determining the efficacy of a drug from a medical standpoint that it has cured or helped some patients (R. 677). Most of the reports in the New Drug Application and supplemental application submitted by the respondent fail to show

<sup>80</sup> In this study, Altafur was administered for 5 days to 50 postoperative patients who underwent potentially or definitely contaminated surgery. For the first 1 or 2 days following surgery, 500 milligrams twice a day intravenously was administered; later, when 30 of these patients could tolerate oral medication 250 milligram tablet was given 4 times a day in accordance with label directions for average dose (R. 787, exh. 110, 111, 112), and 2 patients received oral form from beginning of study (R. 751, 787, 799-800). These patients include 12 individuals from whom Dr. Finland collected serum specimens to determine whether Altafur produced antibacterial activity in the body (R. 769, 200, exh. 107, p. 10).

Five patients developed staphylococcal infections, in the form of either wound infections, pneumonias, or urinary tract infections, while receiving Altafur. Other causative organisms infecting 5 other patients while they were receiving Altafur are shown as pneumococcus and A. Aerogenes. One other patient suffered infection with B. Pyocyanous and C1 Welchii organisms while receiving Altafur (R. 757-758, exh. 104, table 3, p. 962). The most severe of the staphylococcal wound infections developed in 1 of the 2 patients who had received only the oral form of the drug. The wound drained for several weeks. The hole had to be opened and pure staphylococcus was withdrawn, namely hemolytic staphylococcus. This patient was on treatment for 9 days with Altafur (R. 800, 805). Altafur is represented by respondent as effective against pneumococci, B. coli and especially effective against staphylococci (exh. 110, 111, 112).



adequate clinical research data to evaluate the efficacy and safety of use of Altafur, particularly in the light of additional investigations to determine such matters after the New Drug Application became effective (R. 525-526, 530, 532-535, 538, 629-630, 817-818, 835-836, 828, exh. 5, 6, R. 12-13).

(13) The medical witnesses of the respondent with the exception of two such witnesses did not engage in any clinical research or planned study of Altafur (R. 1073, 1558-1559, 1566, 1596, 1785, 2613, 2615, 3087). Limited and inadequate research were conducted by the other two witnesses (2103-2104, 2380-2381). A physician engaged in practice of a medical specialty is not necessarily competent to conduct clinical investigation in new drugs dealing with infections in their specialty, irrespective of reported clinical experience (587, 631-634, 638). Procedures followed in clinical research with drugs are different than the procedures followed in the ordinary practice of medicine. In evaluating the toxicity and efficacy of a new drug, a whole variety of *in vitro* and *in vivo* work is done in clinical research which is not done in the private practice of medicine. Such procedures are taken for preciseness in the diagnosis of the condition and in evaluating the role which the drug plays in the patient's recovery and to eliminate as much as possible other causes for recovery (3120-3124).

(14) Although medical witnesses testified that the administration or ingestion of Altafur had caused the cure or improvement of a number of patients (R. 1079, 1566-1572, 1788-1794, 2120, 2377, 2568, 3082, 3084), such evidence is of less significance and is of less evidentiary weight than the results shown by clinical research conducted to determine the efficacy of Altafur.

(15) Moreover, the evidence relating to the cure or improvement as a result of treatment of patients with Altafur (discussed in Finding 14) is insufficient to establish a reliable pattern of therapeutic efficacy and shows the superiority of clinical and laboratory research and study over the reports of clinical cures and improvements without such research having been done, as demonstrated in results reported in principal categories of cases as follows:

\* \* \* \* \*

(16) Altafur is capable of toxic manifestations or side reactions when ingested. The overall side effects as reported in the New Drug Application are somewhat greater than 10 percent (R. 534). Such reactions are generally not irreversible (R. 1162, 2124, 2132).

(a) Neurological disturbances causing paralysis of the nerves affecting vision, swallowing and speech (exh. 102, p. 659; exh. 105, exh. 106, p. 975; exh. 121, p. 784; exh. 125, p. 85/62; R. 215, 229-231, 1120-1121, 1466-1469). In two neurologic side reaction cases (R. 1157, exh. 125, p. 62; exh. 102, p. 659), the reactions occurred when Altafur was used in excess of the 14 day dosage limitation set forth in the labeling (exh. 111, 112), and cleared after discontinuance of Altafur (R. 1496, exh. 125).

(b) At the hearing one witness reported two instances of diplopia in two individual patients (R. 1576) and one case of transient blurring of vision (R. 1577). These cases are discussed under Finding-B, Pyogenic Infections, subparagraph (d), pages 17-18, *supra*, and in subparagraph (f), the second complete paragraph of page 18, *supra*.

(c) Serious blood disturbances resulting from the use of Altafur are thrombocytopenia, hemolytic anemia and neutropenia (R. 1362, 1427-1428, exh. 103, p. 934, exh. 112), and are of added significance in the presence of infection (R. 1363). Hematological reactions, viz., leukopenia and anemia, in several cases have also occurred (R. 2124, 2177, 2278).

Severe reaction takes place when alcohol is ingested by patients taking Altafur, whether alcohol is taken as a beverage or a component of a food or drug (R. 3075-3076, 1796, 1585, 818-819).

(d) Skin reactions; namely rash and eruptions in varying degrees of severity, one with possible life-threatening severity, are other side reactions of Altafur (R. 1465, 1119, 1795, 2124). In some of these cases Altafur therapy was discontinued because of severity (exh. 103, p. 932, 954, 1078, 1465, 1797, 2568).

(e) Cross-sensitivity with other nitrofurans may occur, that is to say if a patient has become sensitive to a nitrofurans class of any drug he may be sensitive and react unfavorably to Altafur therapy (R. 2009-2013).

(f) A particularly serious reaction arising out of the administration of Altafur is described as constitutional sensitivity or anaphylactic reactions attended with such symptoms as fever, nausea, vomiting, malaise and general muscular pain (R. 1117, 1119, 2533-2535; 3091-3093, exh. 103, p. 932). The number and severity of such reactions would increase with the repeated use of Altafur (R. 3091-3093).



Although certain toxic manifestations are set forth on the labeling of Altafur (exh. 110, 111, 112), the anaphylactic or cross-sensitivity reaction is not mentioned therein (R. 3091-3092).

(g) Systemic sensitivity reactions indicated by eosinophilia are temporally related to the administration of Altafur (exh. 103, p. 932, 3087).

(h) Most frequent side effects are gastro-intestinal disturbances such as nausea or vomiting and one instance of diarrhea severe enough to cause discontinuance of the drug (exh. 103, p. 932; 844-845, 1159-1161, 1464-1465, 1117, 2124, 2378-2379, 2533). Vomiting is controlled by taking the drug with meals (R. 1078, 1514, 1528, 1078).

(i) Rise in blood urea nitrogen with cellular and hyaline casts in the urine (exh. 163; p. 927).

(17) The evidence with reference to the incidence of side reactions given at the hearing is as follows: 3 side reactions of 41 cases (R. 1787, 1794), 3 of 22 cases (R. 1561), 9 of 51 cases (R. 2124), 5 of 5 cases (R. 1362), 6-percent of 59 cases (R. 2378), 14 of 28 cases; and 6 cases (exh. 103, 105, 102, 125); however, toxic manifestations attendant upon the administration of Altafur have not always been reported, or recognized, giving rise to a reasonable inference that the evidence of toxicity is not complete (R. 2009-2013, 3101-3102, 1584, 2278, 2177). The absence of underlying data at the hearing in some instances as above shown (e.g., supra p. 17, 18) gives further rise to such inference.

(18) Exhibit 110, the earliest labeling in use, relating to the present proceeding, advises of the occurrence of apparent sensitization action in the form of maculopapular cutaneous eruption, gastric bleeding and blood disorders. The respondent has indicated this labeling is obsolete (R. 936, 1125).

(a) The interim labeling (exh. 111) sets forth additional side reactions; namely, 25 instances of neurological disturbances, reported in the Journal of the American Medical Association of May 28, 1960, consisting of ocular manifestations—diplopia, paresis of an extraocular muscle, nystagmus and blurring of vision, upon 38 days average duration of therapy; and in all instances the manifestations cleared without sequelae following termination of Altafur, except in the case of a diabetic who still has intermittent periods of blurred vision; 10 of the 25 patients with ocular disturbances also exhibited other neurological manifestations including diminished auditory acuity, peripheral neuritis, dysphagia, slurred speech and difficulty in phonation. The following hematologic side reactions are shown: thrombocytopenia purpura, one case diagnosed as idiopathic purpura, and the second case a 69-year-old diabetic with a staphylococcal abscess of the buttock.

(b) The most recent proposed labeling (exh. 112) sets forth that 69 cases of neurological disturbances have been reported in patients undergoing Altafur therapy; 8 of the cases are still suffering with residual effects, and all show definite regression of symptoms except one patient who still suffers diminished auditory acuity and another patient who suffered loss of taste perception; thrombocytopenia purpura reported in 5 cases including 1 idiopathic case and 1 case of bone metastases; 5 cases of neutropenia, 2 occurring in infants under 11 weeks of age and at higher dosage levels than recommended; 4 cases of hematemesis during administration, however, therapy was continued without further difficulty; one case had a subtotal gastric resection. The label cautions against use in infants without further study.

(c) The labeling restricts the use of Altafur to a period of not longer than 14 days (exh. 111, 112). Antibacterial therapy, for the treatment of some of the disease conditions set forth in the labeling, would require longer dosage periods, even if Altafur was basically a therapeutic effective drug for such conditions. (R. 558-562, 630 ff, 642-643, 943-944, 2038, 1699, 1749-1751).

(d) The side reactions preclude the use of Altafur as a drug of first choice (R. 1598, 2130, 2150); and side reactions require careful observation of the patient (R. 2180). The indications in the labeling that "Altafur should be confined to infections that are not amenable to other drugs now available to the physician" are ambiguous, contradictory, and confusing, rendering the drug unsafe for use in the serious conditions for which it is intended as shown in its labeling (R. 402, 403, 405-409, 603-618).

(19) Altafur is represented as efficacious in the treatment of serious conditions not admitting of delay in treatment (exh. 110, 111, 112). Under such circumstances, therapeutic efficacy is a relevant, material, and highly important factor, as well as toxic potentiality, in determining whether it is safe for use under the conditions of use upon the basis of which the application became effective.



tive (R. 224-225, 499-500, 558, 570-571, 943, 1123-1125, 1359, 1439-1440, 1472-1474, 2040, 2403).

Altafur is not therapeutically efficient, as are other available antibacterial drugs, although the latter may also produce side reactions. The efficacy of other antibacterial drugs, as compared to Altafur, is a factor in the issue of safety of use of Altafur inasmuch as Altafur is capable of significant toxic side reaction without exercising counterbalancing therapeutic efficacy (R. 485-486, 499-501, 578-579, 602, 647-655, 659-662, 223-224, 558-561, 761, 1124-1128, 1144-1145, 1152-1153, 1471-1474).

Based on the entire record of the hearing, and arguments submitted by counsel for both parties, it is concluded:

(A) The New Drug Branch has met its burden of proof upon all issues herein, including the issue of effectiveness of the October 18, 1960, supplemental application. The Hearing Examiner agrees with the respondent's contention that the burden of proof in all these issues is upon the New Drug Branch.

(B) Clinical experience as shown by planned study, and tests by methods not deemed reasonably applicable when the New Drug Application for Altafur (11-965) became effective, show that Altafur, when used according to the directions for use upon the basis of which the application became effective (exh. 110), is unsafe within the meaning of section 505(e), Federal Food, Drug and Cosmetic Act (21 U.S.C. 355(a)).

(C) Altafur is not safe for use under the conditions prescribed, recommended or suggested in the labeling relating to the conditional effective supplemental application of July 20, 1960 (exh. 111), within the meaning of section 505, Federal Food, Drug and Cosmetic Act (21 U.S.C. 355).

(D) Respondent has not submitted, pursuant to section 505(d), Federal Food, Drug and Cosmetic Act (21 U.S.C. 355(d)), reports which include adequate tests by all methods reasonably applicable to show that Altafur is safe for use under the conditions prescribed, recommended or suggested in the proposed labeling thereof relating to the October 18, 1960, supplemental application (vol. XV of exhibit 5, exhibit 112).

#### TENTATIVE ORDER

Based upon the foregoing findings of fact and pursuant to 21 U.S.C. 355(d), (e), and the New Drug Regulations (21 C.F.R. 130.1 et. seq.) it is Ordered

(1) New Drug Application 11-965 covering the drug "Altafur" filed by Eaton Laboratories, Division of Norwich Pharmacal Company, be, and is hereby, suspended.

(2) The effectiveness of the packaging insert or labeling described as exhibit 111 be, and is hereby, suspended.

(3) The supplemental New Drug Application for Altafur filed by Eaton Laboratories, Division aforesaid, on October 18, 1960, be, and is hereby, denied as an effective supplemental application.

If no exceptions are taken to this order within 30 days of its date, such order shall become the final order of the Commissioner of Food and Drugs (21 C.F.R. 130.25).

Date: October 25, 1961.

EDWARD E. TURKEL,  
*Hearing Examiner.*

#### EXHIBIT 132

#### OFFICIAL CHRONOLOGY BY THE FOOD AND DRUG ADMINISTRATION WITH REGARD TO ACTIONS ON FOOD ADDITIVE PETITION FOR MENADIONE (VITAMIN K<sub>3</sub>)

On June 22, 1963, Commissioner George Larrick furnished, at the request of Senator Humphrey, the following official chronology of Food and Drug Administration actions on the Food Additive Petition for menadione (vitamin K<sub>3</sub>).

#### CHRONOLOGY ON SQUIBB'S FOOD ADDITIVE PETITION FOR MENADIONE (VITAMIN K<sub>3</sub>)

1. The Food Additives Amendment to the Food, Drug, and Cosmetic Act was passed on September 6, 1958.

2. On 8/4/60 in a notice in the Federal Register the effective date of the food additive statute was extended to March 6, 1961, for menadione at levels of 1.0 milligram per day in dietary supplements.



3. On 3/7/61 E. R. Squibb & Sons submitted a Food Additive Petition requesting approval of the use of 1 milligram per day of menadione (vitamin K<sub>2</sub>) in a vitamin supplement for use by pregnant women.

4. On 5/16/61 FDA's Division of Nutrition recommended approval of the petition and on 5/23/61 the Division of Pharmacology recommended approval of the petition.

5. On 8/15/61 in a notice in the Federal Register the effective date of the food additive statute was extended to January 1, 1962, for menadione at levels of 1.0 milligram per day in dietary supplements.

6. On 10/11/61 Dr. Nestor recommended denial of the petition since evidence of the safety of the additive was lacking.

7. On 1/16/62 Dr. Nestor approved an order extending the effective date of the Food Additives Amendment covering menadione in dietary supplements for a period of one year. The effect of this order was to permit the use of menadione in dietary supplements while further consideration was given to the Food Additive Petition. This approval to the order was given at a meeting on January 16, 1962, attended by two physicians from the Bureau of Medicine, one of whom was Dr. Nestor, a representative of the Division of Pharmacology, two representatives from the Division of Nutrition, and two representatives from the Food Additives Petition Control Branch. At this meeting it was agreed among all that the petitioner should be advised that before FDA could issue a regulation for the use of menadione, the firm would have to show by adequate experimental data that the use of menadione is safe and efficacious for the newborn. Dr. Nestor was one of those who signed the memorandum expressing this concurrence of view.

8. On 1/27/62 in a notice in the Federal Register the effective date of the food additive statute was extended to January 1, 1963, for menadione at levels of 1.0 milligram per day in dietary supplements.

9. On 3/1/62 Mr. Einer T. Wulfsburg of the Food Additives Petition Control Branch wrote to Dr. Kessenich of the Bureau of Medicine asking for suggestions from the Bureau of Medicine in view of the need for a regulatory program if the petition is denied.

10. On 5/24/62 Dr. Kessenich, in reply, stated that the Food Additive Petition should be denied but that there is a more difficult decision in terms of what could be or should be done concerning the supplies of food products containing vitamin K currently on the market OTC. Dr. Kessenich suggested further meetings if needed.

11. On 7/20/62 a meeting was held with Dr. Nestor and representatives of other Divisions, and on July 23, 1962, Assistant Commissioner Kirk recommended that the petition be denied and the extension lifted so that menadione could no longer be a component of any dietary preparation for prenatal use. All other preparations of menadione would have to bear a warning against use by pregnant women or anyone taking anticoagulant drugs.

12. In early August 1962 the necessary papers were prepared to put Mr. Kirk's recommendation into effect. However, it had not been definitely decided during the July 20 meeting whether the evidence of possible harm warranted the conclusion that the daily ingestion of 1 milligram of menadione by pregnant women constituted any undue risk to the public. This question had to be resolved before a decision could be reached on the type of regulatory program to institute after denial of the petition.

13. On 8/10/62 another meeting was held presided over by Assistant Commissioner Rankin in the extended absence of Mr. Kirk. Among others, Dr. Nestor and Dr. Kline were present. The conferees again agreed that the article had not been established to be safe insofar as the effect on the newborn infant was concerned, and it was agreed that the Food Additive Petition would be denied. The second question discussed was that raised by Mr. Wulfsburg, namely, what to do about the products on the market which would become automatically adulterated by denying the petition and lifting the extension, and what kind of a program of enforcement should be instituted. To resolve this question required a determination of the degree of risk involved to the public by the continued sale of such products. These products had been on the market for a period of over 10 years and there were hundreds of such products. Dr. Nestor stated that there was a definite risk to the public as established by circumstantial evidence and all such products should be promptly removed from the market. This question was resolved by the conferees agreeing that the American Academy of Pediatrics be requested to name a group of experts to study the problem and make a recommendation.



14. On 10/4/62 the matter was presented to the ad hoc committee of experts selected by the American Academy of Pediatrics. The ad hoc committee, on December 4, 1962, reported to the Food and Drug Administration that since there was a lack of evidence of safety for the fetus the Food Additive Petition should be denied. As for the risk to the public and its warranting immediate removal of products with menadione from the market, the ad hoc committee stated that there was insufficient evidence to warrant the conclusion that the daily ingestion of 1 milligram of menadione by the pregnant woman constitutes a major threat to the fetus.

In order to determine the full meaning of the phraseology used by the committee, Dr. Kline on December 18, talked to Dr. Fomon, chairman of the committee, by telephone.

Dr. Fomon assured Dr. Kline that the committee meant: "Similarly, existing evidence is insufficient to warrant the conclusion that daily ingestion of 1 milligram of menadione by pregnant women constitutes any undue risk to the public health."

15. On 12/19/62 a conference was held between Dr. Nestor, Dr. Merendino, and Mrs. Panalee T. Ikari of the Food Additives Petition Control Branch. During this conference Dr. Nestor expressed his unhappiness with the committee report stating that it seemed to him the committee should have concluded that there should be an immediate cessation of the sale of supplements with menadione available to pregnant women.

16. On 12/14/62 Dr. Nestor reported to Dr. Kline a study by Dr. Feitel of the National Institutes of Health which Dr. Nestor stated substantiated his contention that menadione in a prenatal supplement is dangerous.

17. On 12/21/62 Dr. Kline requested the chairman of the ad hoc committee to circulate Dr. Feitel's report to members of the committee asking "Is this manuscript sufficiently convincing to warrant alteration of the statement we have prepared?"

18. On 12/29/62 in a notice in the Federal Register the effective date of the food additive statute was extended to July 1, 1963.

19. On 12/31/62 the chairman reported to FDA that the members of the committee do not believe that a change need be made in the committee's report on the basis of Dr. Feitel's manuscript.

20. On 1/9/63 a letter was prepared in the office of the Food Additives Branch notifying the petitioner that the Food Additive Petition was incomplete in that the safety of the additive had not been demonstrated and that an extension of the Food Additives Amendment had been granted for the product to July 1, 1963, or until FDA's action under section 409 is completed, whichever occurs first. This letter was transmitted on January 11 to the Bureau of Medicine and was approved by Dr. Smith, Acting Director of the Bureau of Medicine, on January 14 and the letter was issued to the firm on January 21, 1963.

21. FDA set a deadline for itself of 60 days or to March 21 for the firm to reply but the firm did not reply, and on March 22 Assistant Commissioner Kirk called the petitioner and questioned whether they intended to let the matter drop. Dr. Marks of E. R. Squibb said that they deliberately did not reply and that they had removed menadione for all formulations for human use 6 months ago. Dr. Marks was informed that steps would be taken immediately to deny the Food Additive Petition and terminate the extension.

22. On 3/28/63.—Attached is a reprint of an order from the Federal Register denying the petition for menadione and revoking the extension of the food additive statute to July 1, 1963, for menadione. In connection with issuance of this order, the Food and Drug Administration concluded that in light of the statement of the advisory committee that no imminent hazard to the public health is presented by the 1.0 milligram per day dosage of menadione, it did not consider that any emergency regulatory campaign was required against products previously shipped to wholesale and retail outlets because of the presence of menadione within this limit.



## DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

## FOOD AND DRUG ADMINISTRATION

## (21 CFR PART 121)

## FOOD ADDITIVES

## MENADIONE: DENIAL OF PETITION

In the Federal Register of June 3, 1961 (26 F.R. 4950), notice was given of the filing of a petition (FAP 433) by E. R. Squibb & Sons, Division of Olin Mathieson Chemical Corporation, Georges Road, New Brunswick, New Jersey, proposing the issuance of a regulation providing for the safe use of menadione in prenatal vitamin supplements.

After extensive study of the petition, including consideration of all available data by a group of experts selected from a panel named by the American Academy of Pediatrics to advise the Commissioner of Food and Drugs, it is concluded that the petition did not establish the safety of menadione for this use.

Therefore, *It is ordered*, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 409(c) (1) (B), 72 Stat. 1786; 21 U.S.C. 348(c) (1) (B)) and under the authority delegated to the Commissioner by the Secretary of Health, Education, and Welfare (25 F.R. 8625):

1. That the petition be denied and that no food additive regulation authorizing the use of menadione in prenatal supplements or any other food product be issued.

2. That the extension of the effective date of the Food Additives Amendment for the use of menadione as a dietary supplement, with a limit of 1 milligram per day, as published in the Federal Register of December 29, 1962 (27 F.R. 12896), be hereby revoked.

Any person who will be adversely affected by the foregoing order may at any time within 30 days from the date of its publication in the Federal Register file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 5440, 330 Independence Avenue SW., Washington 25, D.C., written objections thereto. Objections shall show wherein the person filing will be adversely affected by the order and specify with particularity the provisions of the order deemed objectionable and the grounds for the objections. If a hearing is requested, the objections must state the issues for the hearing. A hearing will be granted if the objections are supported by grounds legally sufficient to justify the relief sought. Objections may be accompanied by a memorandum or brief in support thereof. All documents shall be filed in quintuplicate.

*Effective date.* This order shall be effective on the date of its publication in the Federal Register.

Dated: March 22, 1963.

GEO. F. LARRICK, *Commissioner of Food and Drugs.*

(Published in the Federal Register March 28, 1963)

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EXHIBIT 133

ADDITIONAL EXCERPTS OF COMMENTS BY OFFICIAL AND NONOFFICIAL SOURCES  
WITH RESPECT TO FOOD AND DRUG ADMINISTRATION ACTION ON MENADIONE  
(VITAMIN K<sub>2</sub>)

In order to make available additional background information, the previous exhibit outlining Food and Drug Administration action on menadione (vitamin K<sub>2</sub>), has been supplemented by the present exhibit. The pages which follow contain a series of quotations, designed to "fill in" at least a few of the many details not otherwise generally available. The quotations from various documents were obtained, on subcommittee request, from both official and private sources.

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A FEW HIGHLIGHTS

*August 18, 1958.*—Senator Lister Hill, Chairman, Senate Committee on Labor and Public Welfare, reports H.R. 13254, 85th Congress, to the Senate. The com-



mittee report notes<sup>81</sup> that the proposed Food Additive Law has been considered by the Congress for not less than 6 years. Senator Hill states that, in the future, approval of food additives will be conditioned on

proof of a reasonable certainty that no harm will result from the proposed use of an additive.

He adds:

The safety of a given additive involves informed judgments based on educated estimates by scientists and experts of the anticipated ingestion of an additive by man and animals under likely patterns of use.<sup>82</sup>

September 6, 1958.—President Eisenhower signs Public Law 85-929.

March 1959.—Jerold F. Lucey, M.D., and R. G. Dolan, M.D., write that

The assumption has been made that this is a harmless prenatal vitamin.

It is being widely and needlessly used. This certainly does not seem wise.<sup>83</sup>

Their warning is specifically applied to *parenteral* administration of *high* dosage (72 mg.) and relates primarily to *premature* infants.

March 1962.—John O. Nestor, M.D., New Drug Division, Bureau of Medicine, Food and Drug Administration, inquires of numerous distinguished pediatric authorities as to their expert view of use of menadione in prenatal capsules.

March 10, 1962.—William A. Silverman, M.D., Babies Hospital, New York, N.Y., and Chairman, Committee on Fetus and Newborn, American Academy of Pediatrics, writes to Dr. Nestor:

As you know, the Committee on Fetus and Newborn has been concerned with the matter of potentially harmful effects on the human fetus produced by drugs administered to the pregnant mother (Pediatrics 28:678, 1961). In this connection, I was disturbed to hear that it has now been proposed that pregnant women receive daily supplements of menadione to prevent hemorrhagic disease in their offspring.

I strongly urge that the Food and Drug Administration insist on the presentation of positive evidence that such supplementation is safe and efficacious for the newborn infant. Doxiadis (Lancet 2:1040, 1961) has recently suggested that even small doses of vitamin K analogues may intensify hemolysis and produce hyperbilirubinemia in susceptible newborn subjects. In the present state of our knowledge and concern about brain damage associated with neonatal hyperbilirubinemia, I think the burden of proof of safety rests on those who have proposed menadione supplementation in pregnancy.<sup>84</sup>

March 12, 1962.—Dr. Nestor writes to William Kessenich, M.D., Director, Bureau of Medicine, Food and Drug Administration, that:

Review of all the data available to me on this subject and consultation with several medical authorities both in the Bureau of Medicine of FDA and outside civilians confirms my previous opinion that neither the safety or efficacy of up to 1.0 milligram daily of menadione for use in a prenatal supplement has been proved. In fact, we have been unable to find that any such studies have been performed.

\* \* \* \* \*

Dr. Evans, Dr. McGrath, Dr. Raffel, and Dr. Kelsey of the Bureau of Medicine of FDA concur with my opinion as do [various listed outside authorities].<sup>85</sup>

May 24, 1962.—Dr. Kessenich writes to the Office of the Commissioner that the Bureau questions the safety of menadione to the fetus. Dr. Kessenich states:

We cannot sustain the burden of proof of injury, but, there is, we feel, sufficient basis to raise the point that safety is not established.<sup>86</sup>

<sup>81</sup> S. Report 2422, 85th Congress, 2d Session, p. 3.

<sup>82</sup> Ibid., p. 6.

<sup>83</sup> "Hyperbilirubinemia of Newborn Infants Associated with the Parenteral Administration of a Vitamin K Analogue to Mothers," Pediatrics, 23:553, 1959.

<sup>84</sup> Letter from Dr. Nestor's personal file, as obtained by the subcommittee on its request. Several other physicians' letters likewise questioned the safety of the drug in the use described.

<sup>85</sup> Excerpts obtained on subcommittee's request.

<sup>86</sup> Ibid.



October 1, 1962.—P. T. Ikari, Food and Drug Officer, Bureau of Medicine, writes to Samuel J. Fomon, M.D., Department of Pediatrics, University Hospital, Iowa City, Iowa:

We are pleased to learn from Dr. Kline that you have agreed to serve as the chairman of the ad hoc committee of consultants consisting of Fellows of the American Academy of Pediatrics to advise the Food and Drug Administration concerning the safety and usefulness of menadione in prenatal supplements.

A number of pharmaceutical companies include menadione in vitamins and mineral supplements for daily use over a period of months by pregnant women in doses that range from 0.5 to 3.0 milligrams.

We have before us two petitions proposing that a regulation issue prescribing (1) safe conditions of use for menadione in prenatal dietary supplements and (2) safe conditions of use for menadione in vitamin supplements for human use not necessarily restricted to pregnant women. The petitioners propose that a safe level of use is 1.0 milligram per day. The question arises as to the safety of this practice in view of known toxicity to the infant of relatively small amounts of the water-soluble analogues of menadione when administered to the mother just before delivery or to the infant shortly after birth.

\* \* \* \* \*

In view of the clinical and experimental information available on menadione and its water-soluble analogues, we would like the opinion of your committee on the following questions about menadione in both prenatal dietary supplements and dietary supplements other than prenatal. We need, specifically, your opinion relating to the levels of use described in the Food Additive Petitions which are before us.

1. Does the available evidence justify a conclusion that the use of menadione is safe?

2. Has menadione in these supplements offered for use during part or all of the term of pregnancy been shown to be of value in preventing hemorrhagic disease of the newborn, or is the administration of menadione routinely, both in prenatal and other supplements, unnecessary and irrational?

3. If the use of menadione under any of these conditions is considered to be unsafe, is it unsafe to a degree that there may be a risk to the public health?

We are enclosing some excerpts from the Food Additives Law and Regulations to give you an idea of the framework within which we must operate.<sup>87</sup> The "excerpts" referred to state, in part:

Sec. 201(s) of the Food, Drug, and Cosmetic Act provides the definition of "food additives." Menadione and vitamin K<sub>3</sub> are "food additives" within the meaning of the definition.

Sec. 409(a) provides that the use in food of a "food additive" shall be deemed to be unsafe unless there is in effect an extension of the effective date of the amendment or a regulation prescribing safe conditions of use; and the use or intended use is in conformity with the provisions of the regulation.

Sec. 409(b) provides that with respect to any intended use of a food additive, any person may file with the Secretary a petition proposing the issuance of a regulation prescribing the conditions under which a food additive may be safely used.<sup>88</sup>

December 1962.—After 2 months of study of the evidence, the ad hoc committee concludes that the Food Additive Petitions should be denied because of inadequate evidence of safety. The committee also concludes that the presence of menadione in prenatal capsules does not constitute an "imminent hazard." When questioned by the Food and Drug Administration, it advises that existing evidence is insufficient to warrant the conclusion that daily ingestion of 1 milligram of menadione by pregnant women constitutes undue risk to the public health.

<sup>87</sup> Ibid.

<sup>88</sup> "Information for the Ad Hoc Committee on Menadione," American Academy of Pediatrics, Sept. 27, 1962.



*December 1962.*—The National Institute of Neurological Diseases and Blindness, in a report to the House Committee on Appropriations, states:

In the last few years, it has become a practice to add menadione to prenatal supplements in dosages of 1-3 milligrams daily. This dosage exceeds severalfold that considered to be safe for the newborn, and since it is taken daily for many months by pregnant women, the question arises as to whether the menadione taken by the mother is a factor in the hyperbilirubinemia or jaundice of her offspring. The approach to the resolution of this question requires an adequately controlled clinical study.<sup>89</sup>

*January 21, 1963.*—P. T. Ikari, Food and Drug Officer, advises a petitioner:

This is in reference to your request for an extension of the effective date of the Food Additives Amendment for 1 milligram menadione in dietary supplements, as described in FAP 352.

An extension has been granted for the use of 1 milligram menadione in dietary supplements to July 1, 1963, or until our action under section 409 of the Federal Food, Drug, and Cosmetic Act is completed, whichever occurs first.

In our study of the proposed regulations for the use of menadione we have reviewed the information in Food Additive Petition 352, in petitions proposing prenatal use, and published literature in reference to the product. Also, we have requested an ad hoc committee of consultants, under Dr. Samuel J. Fomon as chairman, to review the proposed prenatal use and study any other data on this subject. Our evaluations are now complete.

We find that the petition is incomplete in that safety in prenatal dietary supplements has not been demonstrated. The report of the committee in which this conclusion was reached is enclosed. In view of these findings we have no alternative other than to deny the petitions unless the petitioners can, and wish to, amend the petition with data now lacking or elect to withdraw the petitions without prejudice to future filing. These conclusions will, of course, be pertinent to the duration of the present extension.<sup>90</sup>

*March 20, 1963.*—Dr. Nestor testifies before Senate Subcommittee on Reorganization and International Organizations, at its request.<sup>91</sup>

*March 22, 1963.*—Food and Drug Administration publishes order denying petition for issuance of a regulation which would have provided for use of menadione in prenatal vitamin supplements. The agency states:

After extensive study of the petition, including consideration of all available data by a group of experts selected from a panel named by the American Academy of Pediatrics to advise the Commissioner of Food and Drugs, it is concluded that the petition did not establish the safety of menadione for this use.

Therefore, it is ordered \* \* \*

1. That the petition be denied and that no food additive regulation authorizing the use of menadione in prenatal supplements or any other food product be issued.

2. That the extension of the effective date of the Food Additives Amendment for the use of menadione as a dietary supplement, with a limit of 1 milligram per day, as published in the Federal Register of December 29, 1962 (27 F.R. 12896), be hereby revoked.<sup>92</sup>

*March 28, 1963.*—The Food and Drug Administration points out in a public statement:

Menadione has been used in vitamin preparations for several years. It is a food additive under the Food Additives Amendment of 1958, and thus it has been considered under the provisions of that amendment.

The amendment provided that extensions of time for assembling scientific proof of safety should be granted on the basis of findings that such extensions involve no undue risk to the public health.

In accordance with this provision of the law, FDA permitted continued use of menadione in vitamin preparations pending receipt and evaluation of a Food Additive Petition.

A Food Additive Petition was submitted seeking permission to use 1 milligram per day of menadione in a vitamin supplement for pregnant women.

<sup>89</sup> "Report on a Collaborative Project for the Study of Cerebral Palsy, Mental Retardation and Other Neurological and Sensory Disorders of Childhood," p. 26.

<sup>90</sup> Letter to Pharmaceutical Manufacturers Association, one of the petitioners.

<sup>91</sup> See p. 787.

<sup>92</sup> Federal Register, p. 3051.



Review within the Food and Drug Administration led to the conclusion that the petition should be denied, but there was a difference of scientific opinion as to whether this conclusion required immediate removal from the market of all vitamin products containing menadione. The FDA scientists agreed that advice should be sought from a committee of outside medical experts.

On October 1, 1962, the matter was presented to a panel of experts selected from names submitted by the American Academy of Pediatrics, consisting of:

Dr. Samuel J. Fomon, Chairman of the Committee on Nutrition, American Academy of Pediatrics; University Hospitals, Department of Pediatrics, Iowa City, Iowa.

Dr. Charles U. Lowe, Committee on Nutrition, American Academy of Pediatrics, Buffalo, N.Y.

Dr. Irving Schulman, a former chairman of the Committee on Fetus and Newborn, American Academy of Pediatrics; Department of Pediatrics, University of Illinois Research and Education Hospitals, Chicago, Ill.

Dr. William A. Silverman, Chairman of the Committee on Fetus and Newborn, American Academy of Pediatrics, Babies Hospital, New York, N.Y.

Dr. Carl H. Smith, hematologist, New York, N.Y.

\* \* \* \* \*

In order that due consideration might be given to all scientific factors, the petitioner was advised in January 1963 of the findings of the panel of experts and given an opportunity to submit additional information or withdraw the petition. At the end of 60 days (the period FDA allowed administratively for response), in the absence of either additional information or withdrawal of the petition, an order was published in the Federal Register (on March 28, 1963) denying the request for approval for use of menadione in prenatal vitamin capsules. The order also terminated the extension of the effective date of the Food Additives Amendment under which menadione has been used in food supplements.

This action has no effect on the availability of menadione for use on prescription of a physician.<sup>63</sup>

*April 2, 1963.*—Senator Humphrey states in the Senate with respect to the FDA's action on menadione that the delay in the ultimate decision was a key point at issue. He notes that the Food Additives Law has been on the statute books for 4½ years. He then states:

\* \* \* here is the crucial fact: The burden of proof was not on FDA to prove vitamin K<sub>3</sub> was unsafe. The burden of proof rested exactly to the contrary, that is, on the manufacturers to prove it was safe.

How could they prove it was safe if article after article contended it was potentially or actually harmful?

And, how could so much resistance within FDA be justified when the only pediatrician in the agency stated emphatically—over a year ago—that the medical literature contained adequate warning of hazard?<sup>64</sup>

Senator Humphrey states explicitly with regard to various drugs which were discussed at the subcommittee's hearing:

I do not attempt to judge whether [any] drug is safe or unsafe. I have merely described the doubts in the minds of medical and pharmacological officers. The fact that proof of safety does not exist does not, of course, mean that proof of harm exists.<sup>65</sup>

*April 17, 1963.*

SAMUEL J. FOMON, M.D.,<sup>66</sup> Department of Pediatrics, University Hospitals, Iowa City, Iowa.

DEAR SENATOR HUMPHREY: \* \* \* In my review of the literature I have been able to find no evidence indicating that prolonged administration of menadione during pregnancy is of greater value to the fetus than short-term administration

<sup>63</sup> Statement by Hon. George P. Larrick, Commissioner of Food and Drugs.

<sup>64</sup> Congressional Record, p. 5115.

<sup>65</sup> Ibid., p. 5117.

<sup>66</sup> Letter to subcommittee.



during the week or two before delivery. I therefore accept your conclusion that foods, food supplements and drugs proposed for use throughout pregnancy should not contain menadione.

I have found no evidence that menadione given to the pregnant woman by the oral route in dosage of 1 milligram daily constitutes a hazard to the fetus and I cannot agree with your implied conclusion that during the past year or two such administration has constituted an important hazard. The medical literature on this point is likely to be somewhat confusing because many authors have failed to distinguish between (1) acceptable medical data and vague circumstantial "evidence," (2) effects of high dosage and relatively low dosage, (3) effects of administration of a specified dose to the pregnant woman as opposed to effects of administration of the same dose to the newborn infant, (4) effects of parenteral as opposed to effects of oral administration. Toxicity from the parenteral route, for example, is generally considered to be 3 to 15 times that from the oral route for a specified dose of a vitamin K preparation.

Your statement (Congressional Record, Apr. 2, 1963, p. 5115) that "within a year of the enactment of the food additive law, the literature of medical science began to contain warning after warning against use of vitamin K<sub>3</sub> by pregnant women, particularly in high dosages \* \* \*" requires modification. Warnings have not, in fact, been numerous, and those based on acceptable data have applied only to high dosage. The warning of Lucey and Dolan specifically applied to *parenteral* administration of high dosage (72 milligrams) and actually applied primarily to premature infants. Such a warning, made by responsible and reliable investigators and concerning specific dosage and route of administration, warrants careful medical attention. However, this warning is not applicable to daily administration of 1 milligram orally.

The Letter to the Editor by Dr. d'Adesky (p. 5116) calls attention to an observation that is of interest but should not be confused with scientific evidence. As you know, unexplained hyperbilirubinemia is not infrequent when neither mother nor infant has received a vitamin K preparation. To interpret the letter by Dr. d'Adesky as a valid warning with respect to prenatal use of vitamin K would be medically irresponsible.

The article by Dr. Wilson (pages 5116-5117), "The Effect of Maternal Medications Upon the Fetus and the Newborn" (actually published in 1962 rather than in 1963) is a review article and does not present new data. The statement by Dr. Wilson (page 5117), "the dangerous ill effects observed when synthetic vitamin K preparations are given to newborn infants probably depend on cumulative effects," is not supported by available evidence. As mentioned in the report of the Ad Hoc Committee on Menadione, little storage of vitamin K preparations by the fetus appears to occur. Cumulative effects are therefore somewhat unlikely. The supporting statement in Dr. Wilson's article concerns effects of vitamin K<sub>1</sub> rather than of synthetic vitamin K preparations and Dr. Wilson has not reviewed the data accurately. She states, "In one study, hyperbilirubinemia was not observed when as large an amount as 25 milligrams of vitamin K<sub>1</sub> was given intravenously the first day, but when the same total amount was given orally in five divided doses at 3-hour intervals, hyperbilirubinemia was found." The study to which Dr. Wilson refers is one performed by Asteriadiou-Samartzis and Leikin (Pediatrics 21:397, 1958). When vitamin K<sub>1</sub> was given orally at 3-hourly intervals, the mean bilirubin concentration of the infants was almost identical to that of control infants who did not receive a vitamin K preparation. The fact that infants who received 25 milligrams of vitamin K<sub>1</sub> intravenously on the first day of life had lower concentrations of bilirubin than did infants who had received no vitamin K preparation remains unexplained.

The statement (pages 5115-5116) that dosages of menadione in prenatal capsules exceed severalfold that considered to be safe for the newborn and the fact that prenatal capsules are taken daily for many months by pregnant women may imply to the reader that similar hazard exists when a particular dosage is administered to the pregnant woman and to the newborn, and that administration on a daily basis results in cumulative effect. Evidence to support either of these possibilities is lacking.

From the scientific point of view, the statement of Senator Hill (page 5115) that "Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive" offers exceptional difficulty. On the basis of a strict interpretation, few drugs or food additives can be given to the pregnant woman with "reasonable certainty that no harm will result" to the fetus. I therefore consider the problem faced by the Food and Drug Administration to be no less than overwhelming. The most we can hope for is that we shall eventu-



ally be able to make a reasonable estimate of the benefit to be derived from a particular substance and may then be able to weigh this benefit in relation to the known or yet unknown hazard.

It seems certain to me that the Food and Drug Administration has made errors in the past and I find it inconceivable that errors will not continue to occur. I am in no position to judge which of the errors might have been prevented. However, if an error has been made with respect to inclusion of menadione in prenatal capsules, the consequences of such error would appear to be minor, namely, allowing a drug without demonstrated efficacy to remain on the market for some time. In the dosage marketed and by the oral route for which it is intended, there is as yet no evidence of serious hazard.

It is disturbing to me that a presumably responsible medical officer in the Food and Drug Administration, Dr. John Nestor, appears to have reviewed the evidence on menadione in such a superficial and uncritical manner.

On page 5123 of the Congressional Record you are quoted as finding it incredible that the Food and Drug Administration has not made systematic use of consultants. I should like to comment specifically on the situation with respect to menadione. The ad hoc committee, selected from members of the American Academy of Pediatrics, consisted of five professors of pediatrics. Two of these individuals were hematologists, one was chairman of the Committee on Fetus and Newborn of the American Academy of Pediatrics, one was past chairman and one was current chairman of the Committee on Nutrition of the American Academy of Pediatrics. During the several months of our deliberations we corresponded with 16 investigators in the United States and 1 each in Canada, Denmark, England, Greece, Holland, Sweden and Switzerland. In this instance, at least, the opinion can hardly be considered a "curbstone judgment." The Committee on Nutrition of the American Academy of Pediatrics has consulted with the Food and Drug Administration on a number of other topics during the past few years. These topics have included commercial formula services, fish flour, toxicity of vitamin D for infants, essential fatty acids and tolerances for pesticides in milk.

Although I am writing to you as an individual, I shall send copies of this letter to members of the Committee on Nutrition of the American Academy of Pediatrics, to members of the Ad Hoc Committee on Menadione, and to all of the consultants from whom opinions were requested by the Ad Hoc Committee on Menadione. I shall request that these individuals correspond with you if they detect errors of fact or interpretation in what I have written in this letter. I enclose a list of names and addresses of these physicians in the hope that you will send each one a copy of your memorandum of April 4, 1963.

Sincerely yours

SAMUEL J. FOMON, M.D., *Professor.*

June 6, 1963.

Senator HUBERT H. HUMPHREY: <sup>97</sup>

UNITED STATES SENATE,  
*Committee of Government Operations,*  
*Subcommittee on Reorganization and International Organizations.*

DEAR DR. FOMON: It is a pleasure to comment on issues of vitamin K<sub>3</sub>.

As you recall, your detailed letter on the subject was received during my temporary absence in South America. After my assistant's acknowledgement, we exchanged notes on my general memorandum, quoting seven pediatric sources on overall problems of pediatric drug therapy.

In the interim, I have been awaiting receipt of the Food and Drug Administration's detailed chronology on menadione. Rather than wait further, I am glad to summarize facts, as compiled at my direction, by the subcommittee staff.

Your thoughtful, detailed letter deserves similar response; for this reason, this letter is somewhat longer than might otherwise have been the case.

First, let me state that the constructive spirit in which you wrote is and was genuinely appreciated.

This subcommittee has benefited immeasurably from receiving the expert judgment of distinguished physicians such as yourself. Similarly, I am grateful to each of your numerous colleagues for sharing their views with us, at your thoughtful suggestion.

Second, may I mention that it has been very gratifying to receive pediatricians' and others' messages of commendation on the subcommittee's overall efforts.

<sup>97</sup> Letter from Senator Humphrey.



You, personally, had graciously stated that our committee's "diligence" is "impressive." Dr. Clement Smith (who had, incidentally, testified before our subcommittee in 1959) expressed "satisfaction" over my "continued interest and activities in complicated matters of research and health." And other physicians, likewise, have been complimentary.

Third, let me state that the unanimity with which your colleagues concurred in your judgment on vitamin K<sub>3</sub> is most impressive. Their strong measure of agreement speaks eloquently for the skill, experience and understanding which you personally brought to this problem. This was, of course, to be expected from an expert who enjoys such well-deserved eminence in the eyes of those best qualified to judge your many contributions to science.

Fourth, no layman would presume in any way to dispute your analysis of each of the principal articles in the medical literature, as regards menadione in prenatal supplements, or, for that matter, on any other technical issue.

Fifth, we turn to the basic issue, as I see it. It is a legal-administrative issue, unique to the Federal Government. It is the issue of fulfillment of the law.

As you appreciate, this particular issue is not a matter of how individual M.D.'s should practice medicine with their patients. *That* is and must remain the prerogative of medical science, alone. Physicians who have prescribed (and continue to prescribe) vitamin K<sub>3</sub> in prenatal supplements have exercised and continue to exercise their professional judgment. Each carefully evaluates evidence of potential benefits; each weighs possible hazard and then comes to his own decision in a manner which he feels will best serve his patient. No one here questions a physician's and researcher's prerogatives.

But, the Congress and the Food and Drug Administration are required to deal with a separate and different issue—namely, the law—its prompt and effective fulfillment. Specifically, the Food Additive Law of 1958 does not (as I had pointed out) require that FDA *prove* harm by an ingredient like menadione; the law requires "reasonable certainty" on the part of the manufacturer as to safety. Dr. Nestor never contended that there was "*proof*" of harm; and I certainly never did. Indeed, I stated—very carefully—exactly to the contrary. As you recall, I stated in the Senate on April 2, 1963:

I do not attempt to judge whether this or any other drug is safe or unsafe. I have merely described the doubts in the minds of medical and pharmacological officers. The fact that proof of safety does not exist does not, of course, mean that proof of harm exists.

And, from a medical standpoint, Dr. Clement Smith, in his letter of April 25, 1963, very soundly stated:

Careful observation and skepticism (both as to proof of harm and proof of harmlessness) must still be the physician's guide.

As for a guide to the Congress, let us look at a brief chronology. It consists, for purposes of simplicity, of but four key dates (out of scores of dates which might be cited, including those involving consultation with your own expert committee):

On September 6, 1958, President Eisenhower signed Public Law 85-929, the Food Additives Law. The law required, as the Senate and House Committee reports stated: "reasonable certainty that no harm will result" from a proposed use of a food additive.

On March 12, 1962, after the issue was brought to his attention by other FDA physicians, John Nestor, a physician with a quarter-century of experience, wrote to William Kessenich, M.D., Director, Bureau of Medicine, Food and Drug Administration, that:

Review of all the data available to me on this subject and consultation with several medical authorities both in the Bureau of Medicine of FDA and outside civilians confirms my previous opinion that neither the safety or efficacy of up to 1 milligram daily of menadione for use in a prenatal supplement has been proved.

Dr. Evans, Dr. McGrath, Dr. Raffel, and Dr. Kelsey of the Bureau of Medicine of FDA concur with my opinion as do [various authorities whom he had consulted].

On May 24, 1962, Dr. Kessenich wrote to the Office of the Commissioner, FDA, that the Bureau questioned the safety of menadione to the fetus. Dr. Kessenich stated:

We cannot sustain the burden of proof of injury, but, there is, we feel, sufficient basis to raise the point that safety is not established.

On March 28, 1963, 4½ years after the law was enacted, 12 months after Dr. Nestor made his suggestion, and 10 months after his superior concurred in



his suggestion, a Food Additive Petition, proposing the issuance of a regulation for the use of menadione in prenatal supplements, was officially denied by FDA.

The principal point which I had made was that FDA really had no alternative all along but to do precisely what it ultimately did do.

As you stated, too,

I \* \* \* accept your conclusion that foods, food supplements and drugs proposed for use throughout pregnancy should not contain menadione.

Sixth, you and your able colleagues on the ad hoc committee had soundly decided that use of menadione did not represent an "imminent hazard to the public health." There is not and never had been reason to doubt the wisdom of your joint conclusion. What should be remembered, however, is that, contrary to some erroneous reports, Dr. Nestor had never asserted that menadione in prenatal supplements *was* an "imminent hazard." (These two words are used, as you know, by lawyers to denote a danger *so absolutely acute* as to justify the extreme action of *immediate* Federal seizure of all stocks.)

Indeed, the records show that, exactly to the contrary, Dr. Nestor soundly wrote into FDA's file that no proof appeared as to "imminent hazard." Dr. Nestor simply wanted *reasonably prompt* FDA action to deny the petition, and that is all I wanted, but that is not what we got, as 4½ years' delay attests.

Further, let it be noted that there was unanimity in FDA's Bureau of Medicine on the need for denial of the Food Additive Petition. This was not just Dr. Nestor's judgment; he merely concurred in other medical officers' views; thereafter, still other M.D.'s in FDA concurred in his views.

Non-M.D.'s, in effect, forced the delay. The non-M.D.'s have important credentials and evidence for their respective positions; but, I repeat, they are not medical doctors.

In any event, Dr. Nestor carefully refrained from expressing formal judgment *until* he had

(a) made a critical review of the literature (based on many abstracts compiled, at his request, by FDA's Division of Research Reference), and

(b) invited the written judgment of distinguished pediatricians, outside the U.S. Government.

Seventh, you are absolutely correct that the problem faced by FDA is "no less than overwhelming." Indeed, that is not only true with respect to the strict provisions of the Food Additives Law; it is characteristic of a vast number of other responsibilities facing FDA. The Agency inherently faces immense difficulties because of the complex technical issues in its everyday work. Further, it is and has been, unfortunately, under-financed, under-paid, under-manned and under-appreciated. Under these circumstances, no reasonable person would expect it to be infallible, or, indeed, to be always as prompt in its actions as one might ideally wish.

Thus, the question before this subcommittee is:

Notwithstanding occasional exceptions (which would be quite understandable), is there a fairly consistent pattern of FDA being reasonably right and reasonably prompt?

OR

Do the records show otherwise?

Obviously, this broad question cannot be answered by citing the facts in one case alone, e.g., Vitamin K<sub>3</sub>, or any other single file. Fairness requires review of dozens of cases—an effort which, of course, you and your colleagues would not be in a position to make. But, comprehensive review is precisely what the subcommittee has endeavored—within the limit of its resources—to do. At my direction, the staff has compiled for us masses of facts in many cases. In every instance, the facts consist primarily not of the staff's or any other layman's judgment—but of the views of physicians, inside and outside FDA.

Thus, eighth, when you cite FDA's consultation with academy members on issues of nutrition, I can assure you that I am delighted to note your commendation of such consultation. Fortunately, in several instances, FDA's employment of the consultative process has no doubt been exemplary; the record speaks to the credit both of the agency and the consultants.

But, consultation in the one area of nutrition does not and could not negate the disturbing nature of overwhelming evidence of lack of consultation or faulty consultation in other areas. Thus, evidence compiled by the staff from physicians confirms serious flaws such as:



(a) failure to set up a systematic framework for prompt consultation, so as to anticipate problems or prevent them from growing needlessly acute, or at least to meet the problems head-on, as soon as they occur, rather than partially, sporadically or haphazardly;

(b) failure to make available to a consultant the full evidence in FDA's file or the full evidence which might be obtainable;

(c) failure to follow up promptly on consultants' suggestions, etc.

What this all adds up to is the fact that you and your colleagues can be assured that comments here on vitamin K<sub>3</sub> were and are made not in isolation, but out of a fair-minded and reasonably broad study.

If you and they do not agree with all of our interpretations, please bear in mind this fact: in no instance are these interpretations ours alone—in every instance we are quoting what M.D.'s have told us and which we, in turn, have sifted through masses of evidence, provided by still other M.D.'s.

We of the subcommittee respect medical judgment; we hope FDA will do likewise.

Finally, it will be a pleasure to print the facts on the menadione case and on other issues. In this way, you of medical science can judge for yourselves, out of your years of experience, and we in Congress can do likewise—each with respect to our particular responsibilities.

Please do not hesitate to give me the benefit of your further helpful comment.

In turn, I am forwarding to each of your colleagues who was kind enough to write in—a copy of this letter.

Sincerely,

HUBERT H. HUMPHREY, *Subcommittee Chairman.*

June 7, 1963.

THE MEDICAL LETTER ON DRUGS AND THERAPEUTICS.<sup>97a</sup>

*Vitamin K Supplements in Pregnancy and Labor.*—Recurring reports since 1955 have pointed to the use of large doses of vitamin K preparations, especially Menadione USP (fat-soluble K<sub>3</sub>) and its water-soluble derivatives, as a cause of hyperbilirubinemia and brain damage in the newborn. Two recent events have added to the public concern over vitamin K. One was the testimony on the hazard of vitamin K, given by an FDA physician at a Senate hearing; the other, the refusal of the FDA in March 1963 to authorize the use of menadione in any amount in prenatal vitamin supplements.

Neonatal hemolytic disease is usually caused by Rh incompatibility; but in a number of cases where Rh incompatibility was ruled out, large doses (72 milligrams) of menadione bisulfite given parenterally prior to delivery were suspect (J. F. Lucey and R. G. Dolan, *Pediat.*, 23:553, 1959). It has not been proved that smaller doses taken orally during pregnancy, whether alone or in "multi-vitamin supplements," have been harmful, but neither has their safety been established (report of a special committee headed by Dr. S. J. Fomon, prepared at the request of the Food and Drug Administration).

While doses of vitamin K preparations given during the last few days of pregnancy appear to be effective in preventing hemorrhagic disease of the newborn, probably more so than a single dose given during labor, the best practice, in the opinion of the Committee on Nutrition of the American Academy of Pediatrics, is to avoid giving any vitamin K preparation to the mother, and to administer it instead to the infant; and to use vitamin K preparations other than fat-soluble menadione or its water-soluble derivatives.

The method of choice, according to the Committee on Nutrition, is to give vitamin K<sub>1</sub> (Phytonadione USP; Mephyton—Merck; Konakion—Roche; Mono-Kay—Abbott) to the infant at birth, in a dose of 0.5 milligram to 1 milligram parenterally or 1 to 2 milligrams by mouth (*Pediat.*, 28:501, 1961); if hemorrhagic disorder occurs, it may be necessary to repeat the dosage, and if the mother has been receiving anticoagulant therapy, larger doses are generally necessary.

<sup>97a</sup> Vol. 5, No. 12, issue No. 115, pp. 46-47.



## EXHIBIT 134

SUBSEQUENT LETTER FROM THE STUART COMPANY WITH RESPECT TO  
MYLICON

Following the hearing on March 20, 1963, the subcommittee received a letter from the company which makes Mylicon, commenting upon the views expressed at the hearing. The text and an attached "Dear Doctor" letter follow.

ATLAS CHEMICAL INDUSTRIES, INC.,  
Wilmington, Del., April 19, 1963.

Subject: Mylicon ®

DEAR SENATOR HUMPHREY: During the past few weeks there has been a series of news reports with respect to the Mylicon products of The Stuart Company Division of Atlas Chemical Industries, Inc., as the result of testimony and statements incident to the March 20-21 hearings of your Subcommittee on Reorganization and International Organizations of the Senate Committee on Government Operations.

Unfortunately, some of the testimony regarding Mylicon was inaccurate and misleading, and subsequent statements regarding this testimony have not fully clarified the situation. As a result of the news reports, considerable confusion still exists regarding the history and the present status of Mylicon.

We endeavored to arrange a meeting with you to explain our position and the action we are taking regarding this matter. Unfortunately, your busy schedule did not permit a meeting at this time. Because we wanted you to know the facts as soon as possible, we are setting them forth in this letter.

By way of background, The Stuart Company is an ethical drug house, which directs its promotion of Mylicon to the medical profession and not to the consumer.

Mylicon Tablets and Drops are over-the-counter products useful for the treatment of gaseous distention associated with a variety of conditions. The first to be marketed were the tablets. As early as 1958, FDA said the tablets were not considered to be a new drug. Subsequently, the liquid drop form was developed because it is very effective and many doctors prefer the liquid form over the tablets. A complete review of our promotion program makes it evident that the liquid form has been promoted for all of the indications recommended for the tablets.

However, before marketing, the liquid form was discussed with FDA<sup>68</sup> late in 1960 because it was proposed that the drops have the additional specific indication for infant colic use. This infant colic use for methylpolysiloxane, the active defoaming ingredient in the Mylicon products, had been referred to in an article by Rider in *American Practitioner and Digest of Treatment* for January 1960, at page 56, and favorably reported again by Rider et al. in the *Journal of the American Medical Association* for December 17, 1960, at page 2054.

In these discussions with FDA, the conclusion was reached that the infant colic indication could be promoted to doctors but should not be included on the label which might get into the hands of the consumer. The statement, "Children Under 12 Years: As Directed by a Physician" was included on the initial label for Mylicon Drops as a cautionary statement, it being our understanding that infants are generally treated as a separate group by the medical profession and FDA.

<sup>68</sup> On June 24, 1963, John L. Harvey, Deputy Commissioner, Food and Drug Administration, wrote to Senator Humphrey in response to an inquiry of May 22, 1963: "Mylicon was originally marketed as tablets and it was considered by Dr. Ralph Smith in 1958 and later by Dr. Irwin Siegel in 1960. Both, in separate memorandum, held the tablets not to be new drugs. Infant colic claims were not at that time made. In December of 1960 Mr. Galindo of the Stuart Company met with Dr. Smith of the Division of New Drugs and separately with Mr. Yakowitz, then of the Division of Administrative Review, to discuss the firm's intention to market Mylicon Drops for infant colic. Mr. Galindo evidently misunderstood what Dr. Smith told him during that visit as to the status of this product under the new drug provisions of the act, and the firm proceeded to market it without an effective New Drug Application. On January 19, 1962, after the firm had been notified that FDA regarded the product for infant colic as a new drug, Dr. Smith told Mr. Galindo that he had apparently misunderstood FDA's position since FDA had already taken the position that the product was a new drug for infant colic use at the time of Mr. Galindo's visit in December 1960." (Footnote provided subsequently by editor of volume, following receipt of this information from FDA.)



Over 12 months after these discussions (early in 1962) FDA advised Stuart for the first time of FDA's reconsideration that the promotion for infant colic even to doctors should be the subject matter of an effective New Drug Application. At that time FDA indicated to us that their ruling was primarily for the purpose of placing the infant colic use on prescription to avoid indiscriminate use for colic without a physician's prior diagnosis. The drops were not ordered to be withdrawn from the market as a pediatric drug, only the infant colic use was questioned.

As you are aware, there are complications under the Humphrey-Durham amendment in the labeling of a product that would be Rx for one purpose and o-t-c for all others. Furthermore, the preparation and processing of an NDA for infant colic use would have taken considerable time. It developed in discussions with FDA that an alternative with more immediate effect was the withdrawal of promotion to the doctors of the infant colic use.

As a result, Stuart commenced the prompt withdrawal of this promotion and submitted a detailed withdrawal program to FDA, which is a matter of record in our files. After reviewing the program, FDA advised us that it appeared to eliminate satisfactorily all the promotion of Mylicon Drops for infant colic.

At the time of the withdrawal of the infant colic promotion to doctors, there were no changes made in the label for Mylicon Drops because there was no mention of infant use on the label. The label statement "Children Under 12 Years: As Directed by a Physician" was continued as a cautionary statement regarding children.

On the basis of this record, it is clear that we have in no way "circumvented" FDA rulings or opinions regarding Mylicon Drops. We believe that our decisions in the marketing of the drug have been proper and responsible, particularly in view of the fact that we were not dealing with a physiologically active drug or a drug with even the slightest indication of harmful side effects.

The active defoaming ingredient in Mylicon Drops is physiologically inert and is not absorbed from the gastrointestinal tract. In the opinion of our medical and scientific advisors, no harmful side effects could have resulted even in the use for infant colic and no such effects have been reported to us.

The recent news reports have resulted in a serious misunderstanding regarding the status of Mylicon Drops as evidenced by numerous inquiries to our detail men and letters to Stuart. The news reports also create a new situation in that they have brought to the attention of the general public our promotional material to doctors.

Therefore, we are mailing the enclosed letter to all physicians setting forth the current status of Mylicon, and are voluntarily recalling Mylicon Drops for relabeling to clarify the cautionary statement.

It is our hope that the letter to physicians and the relabeling program will end the current confusion and eliminate any possibility of misunderstanding. If you have any further questions about this matter, we would appreciate an opportunity to discuss the matter with you when your schedule permits.

Sincerely yours,

EDWARD J. GOETT,  
*Executive Vice President.*

THE STUART COMPANY,  
3360 East Foothill Boulevard, Pasadena, Calif.

Dear Doctor ——— :

Considerable confusion has been created recently by a series of news reports regarding statements concerning Mylicon® made at the time of hearings of a subcommittee, headed by Senator Hubert Humphrey, of the Senate Committee on Government Operations. These statements concerned the withdrawal early in 1962 of the promotion to doctors of the use of Mylicon Drops in infant colic. The product, Mylicon, itself has never been questioned—but, specifically, only the treatment of infant colic with Mylicon Drops.

Stuart's promotion of Mylicon Drops has always been directed to the medical profession. We are convinced that no harm has ever resulted from any use of this product. The widespread and confusing news reports to the general public have created a new situation which should be clarified. We wish to avoid the possibility that an uninformed person might administer the product for the infant colic use not presently authorized by FDA. Therefore, Stuart is voluntarily recalling Mylicon Drops for relabeling to eliminate any possible confusion.



In addition to the previously established uses for Mylicon, late in 1960 the infant colic indication was brought to FDA's attention before Mylicon Drops were first marketed. However, early in 1962, we were notified by FDA of a new ruling that the promotion for the infant colic use required an effective New Drug Application (NDA). At that time FDA indicated to us that their ruling was primarily for the purpose of placing the infant colic use on prescription to avoid indiscriminate use for colic without a physician's prior diagnosis. Alternatively we were advised that in the absence of an effective NDA, promotion for this use would have to be withdrawn. The news accounts incorrectly tended to indicate that the withdrawal of all Mylicon products was ordered. This is definitely not the case.

Because the preparation and processing of NDA for infant colic use would have taken considerable time, Stuart commenced the immediate withdrawal of promotion for the infant colic indication after the FDA notification. FDA reviewed the promotion withdrawal program and advised us that it appeared to eliminate satisfactorily all the promotion of Mylicon Drops for infant colic.

The company has continued to market Mylicon Drops and Mylicon Tablets for use in treating gaseous distention associated with spastic colitis, aerophagia, postoperative gas, postgastrectomy syndrome, hiatus hernia, diverticulitis, and peptic ulcers.

As you may know, methylpolysiloxane (simethicone) is the active defoaming ingredient in Mylicon Drops and Tablets. According to available scientific literature, this ingredient is physiologically inert and is not absorbed from the gastrointestinal tract. In the opinion of our medical and scientific advisors, no harmful side effects could have resulted even in the earlier use for infant colic. In fact, the use of Mylicon has never been challenged, even for infant colic, on the basis of any reported harmful or undesirable side effects in its clinical use. A summary of pharmacological and clinical data on methylpolysiloxane is available. If you are interested in receiving a copy, please check the appropriate box on the enclosed card and mail it to us.

The liquid form of Mylicon Drops is very effective and for some patients many doctors prefer it over the tablets. In the event that the temporary recall of the drop form of this product for relabeling in any way inconveniences you or deprives your patients of the beneficial effects of the liquid dosage form, please advise us by checking the appropriate box on the enclosed card and returning it to us. A Stuart representative will place a supply at your disposal during this period for any of the users mentioned above, other than infant colic use.

Sincerely yours,

ATLAS CHEMICAL INDUSTRIES, INC.,  
ARTHUR HANISCH,  
*Vice President, the Stuart Company Division.*

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EXHIBIT 135

SUBSEQUENT LETTER ON BEHALF OF PURDUE-FREDERICK COMPANY ON THE DRUG  
PAREMYCIN

Subsequent to the hearing of March 20, 1963, a law firm, Chapman and Friedman, representing the Purdue-Frederick Company conveyed the following statement to Senator Humphrey with regard to the reference which had been made to the drug, Paremycin, by Dr. John O. Nestor.

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LAW OFFICES, CHAPMAN AND FRIEDMAN,  
*Washington, D.C., April 1, 1963.*

DEAR SENATOR HUMPHREY: This is in reference to the recent hearings of your subcommittee concerning certain operations of the Food and Drug Administration.

We have noted in the press and have subsequently obtained copies of the transcript relating to testimony about the drug Paremycin, which is distributed by The Purdue Frederick Company. The nature of this testimony is such that it may tend to be misleading to the committee. We have complete confidence in your desire for accuracy and fairness in conducting your hearings, and for that reason we are sure you will welcome information which will prevent any erroneous impressions.



We are sure you will understand that misleading and unfounded statements concerning a drug inhibits physicians in prescribing the drug, and thus may well deprive the public of the benefits of a valuable therapeutic agent. This is particularly true where the distributor of the drug is a small company which lacks the resources to counteract the widespread publicity which accompanies such misleading and unfounded statements made before a congressional committee.

In particular, we would like to call your attention to the following excerpts from the testimony and give you the facts pertaining thereto.

In the prepared statement of the witness, Dr. John O. Nestor, which is quoted at page 38 of the transcript of the hearing held on March 20, 1963, Dr. Nestor states:

"There have been new drugs on the market that never were subjected to the necessary preclearance procedures of a New Drug Application to demonstrate safety. Waivers should not have been given *verbally* and without circularizing the information to the *physicians* in the Bureau of Medicine. (Examples are Mylicon, Paremycin, Formulase, Coldaid.)" (Emphasis supplied.)

As regards Paremycin, this statement is erroneous in two significant respects:

1. The Purdue Frederick Company did not seek nor obtain a verbal waiver such as is referred to in the statement. On the contrary, a written ruling was obtained from the Food and Drug Administration.

2. The Bureau of Medicine was specifically informed as to this drug. After verbal discussion of the status of the drug with a medical officer of the New Drug Division of the Bureau of Medicine of the Food and Drug Administration, a written communication was addressed to the Bureau of Medicine relating to the drug. Exhibits A and B, attached, constitute documentary proof of these statements. Exhibit A, the letter of June 19, 1957, to the Bureau of Medicine, constituted an inquiry as to whether a New Drug Application was necessary. The reply, exhibit B, explicitly stated: "We do not regard the preparation as a 'new drug.'"

At page 39 of the transcript the same witness, Dr. Nestor, characterizes Paremycin, along with other products, as a new drug presently on the market without the benefit of a New Drug Application. This creates the erroneous impression that the marketing of the drug was improper. Reference to exhibit B clearly demonstrates that the drug was considered by the Food and Drug Administration and classified as *not* a "new drug" and was then placed on the market pursuant to this ruling.

The next portion of the testimony which tends to be seriously misleading appears at pages 42 and 43 of the transcript. Dr. Nestor was questioned with reference to an advertisement appearing under date of November 30, 1962, a copy of which is annexed as exhibit C, and which includes pediatric dosages.

At page 43, Dr. Nestor was questioned by the chairman concerning Paremycin and with particular reference to the advertisement:

"Senator HUMPHREY. \* \* \* Now, this drug is on the market. Was not this drug declared to be ineligible for pediatric use?"

"Dr. NESTOR. Yes, sir, it was declared to be a new drug, and it did not have an effective New Drug Application."

This statement is entirely misleading. The fact is that Paremycin was never declared to be ineligible for pediatric use nor was it ever declared to be a new drug insofar as its pediatric use was concerned. The question pertaining to the promotional material for Paremycin, which will be hereinafter discussed, had nothing whatsoever to do with its use as a pediatric drug.

At some time after its introduction, promotional material relating to the drug, which of course was addressed solely to physicians, the drug being a prescription drug, made reference to the amebicidal action of neomycin, one of the ingredients in the drug.

Following the visit of a Food and Drug Administration inspector who made inquiry respecting labeling including promotional material concerning the drug, a representative of the company was advised by the Food and Drug Administration that it considered that any reference to amebic dysentery, amebiasis or amebicidal activity would, in the opinion of that agency, place the product with respect to such reference into a "new drug" category. Rather than argue the merits of the company's position, for which there is substantial scientific authority, the company, in deference to the position taken by the Food and Drug Administration, promptly removed such reference from all of its promotional material. It is submitted that the matter was handled in such fashion both by the company and the Food and Drug Administration so as to resolve the question promptly and expeditiously.



It is respectfully requested that this letter be made a part of the record of the subcommittee and be included in the printed record of your proceedings.

Sincerely yours,

MARTIN L. FRIEDMAN,  
*Attorney for the Purdue Frederick Co.*

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*Exhibit A*

June 19, 1957.

WILLIAM KESSENICH, M.D.,  
*New Drug Branch, Bureau of Medicine,  
Food and Drug Administration,  
Department of Health, Education, and Welfare,  
Washington, D.C.*

DEAR DR. KESSENICH: Attached is proposed label for Elixir Paremycin, a preparation containing neomycin sulfate 150 milligrams and tincture of opium 0.2 milligrams per teaspoonful (5 milliliters).

In accordance with our telephone conversation, we would appreciate your advice:

- (1) Whether a New Drug Application is necessary;
- (2) Whether the attached proposed labeling is in order.

Many thanks for your cooperation and prompt reply.

Sincerely yours,

SIDNEY M. KARLTON, *Vice President.*

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*Exhibit B*

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,  
FOOD AND DRUG ADMINISTRATION,  
*Washington, D.C., August 6, 1957.*

MR. SIDNEY M. KARLTON,  
*Laboratories for Pharmaceutical Development,  
45 Sawmill River Rd.,  
Yonkers, N.Y.*

DEAR MR. KARLTON: We regret the extreme delay in replying to your letter of June 19 requesting comment on proposed labeling for "Elixir Paremycin."

We do not regard the preparation as a "new drug."

It is our opinion that the neomycin content of the product is insufficient to be effective. We believe that either the neomycin should be omitted from the formula or the amount should be increased to provide adequate dosage of this drug (not less than 1,200 milligrams in the recommended daily adult dose). The label would then need to have a warning essentially as follows:

Warning: High dosage levels and prolonged administration should be avoided in view of possible systemic effects. If signs of kidney damage appear, the drug should be discontinued.

We also question the propriety of the name "Paremycin," which would seem to suggest that the product contains paregoric, and we also question whether the label can properly refer to the tincture of opium as "Paregoric Equivalent."

Sincerely yours,

N. E. COOK,  
*Assistant to the Director, Bureau of Enforcement.*

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EXHIBIT 136

ARTICLES IN THE TRADE PRESS WITH RESPECT TO ISSUE OF EVALUATING  
PEDIATRIC DRUGS

A few illustrative articles in the trade press follow as regards evaluation of pediatric drugs by the Food and Drug Administration.



December 12, 1955.

F-D-C REPORTS—"THE PINK SHEET"<sup>99</sup>

Children's dosages and pediatric medication specialties are currently the subject of regulatory review. FDA Medical Director Holland told the Proprietary Association (P-A) Scientific Session in New York City last week (see two preceding stories). Under discussion in Food and Drug Administration (FDA) for a long time, the regulatory problem involves at least two tough questions:

(1) What should be the cutoff age for the statement of children's dosages in the labeling of over-the-counter (o-t-c) drug products? FDA is currently following a policy of no directions for children under the age of 6—FDA likes to have labeling contain the following statement: "For children under the age of 6, consult your physician." In two of its recent Rx to o-t-c switch proposals, FDA included this statement for children under 12 (Hoffmann-LaRoche's Asterol and Merrell's Kolantyl.)

(2) Should a special Rx legend category be established for pediatric specialties consisting of ingredients and formulas which are considered o-t-c in adult medication? Creation of such an Rx category conceivably could threaten the existence of some longstanding and widely sold proprietaries for children. This could probably be handled by (a) making certain exceptions—for example, children's aspirin; and (b) reducing the cutoff age—referred to above—to 3 years.

FDA staffers are understood to hold varying opinions on the answers to the two questions, and the policy issue has been tossed back and forth for some time. Discussing FDA's current policy of using 6 years as the cutoff age, Holland told P-A: "Rigidly adhered to, this means that the manufacture of a non-Rx item designed solely for the pediatric age group cannot adequately label his product so that it can be safely administered to the age group for which it is intended. It is equally untenable to conclude that manufacturers cannot or should not devote whatever degree of special attention they choose to products designed especially for pediatric use." Holland continued:

"If, as was considered, we adopted the policy that such pediatric preparations could be handled as a special Rx class, other obstacles present themselves. In the first place, a situation would arise where the same drug was available o-t-c for adult use but Rx for pediatric use. There is ample precedent for this type of exception under the D-H section of the law. For example, some drugs used in ophthalmic preparations and some antihistaminic preparations are on Rx whereas the same drug is o-t-c for general use or in lower dosage forms. In addition, there is the troublesome problem of a myriad of good drugs now available for children on a non-Rx basis, labeled for age groups under six, and which rightfully enjoy this privilege because experience has shown them to be safe.

"Another alternative solution exists which is currently under study. It is the possibility of lowering the age restriction for label dosage directions. Does age 6 represent any magic number involving physiological or pathological considerations which would preclude lowering it? If so, we have been unable to identify these considerations. In fact, many hold the view that safe dosage directions all the way down to 1 year old would be more in the public interest than, at best, an arbitrary cutoff point at 3 years or 5 years or 6 years.

\* \* \* \* \*

September 25, 1961.

F-D-C REPORTS—"THE PINK SHEET"<sup>1</sup>

#### FDA'S NEW PEDIATRIC LOOK AT DRUG USES AND DOSES MAY RESULT IN "NOT FOR PEDIATRIC USE" LABELING IN ABSENCE OF SPECIFIC WORK

The Food and Drug Administration (FDA) may soon require "not for pediatric use" labeling on all new drugs that do not have clinical evaluations supporting the safety of pediatric dosages. Also, FDA is requiring specific clinical work and proof before permitting dosages and claims for pediatric use. It is stressing age-group differentials.

<sup>99</sup> Vol. 17, No. 44, pp. 13-14.

<sup>1</sup> Pp. 21-22.



In the new pediatric emphasis, FDA's pharmacologists ask manufacturers if a new drug is intended for perinatal use. It so, tests on humans and animals of the intended age group must be submitted.

FDA's new pediatric look also includes close attention to drugs promoted for use by pregnant women, chiefly to determine effects on the unborn child.

Key man in FDA's intensified pediatric drug program is the newest member of its New Drug Division staff, Dr. John Nestor, a strong-willed, crusading pediatrician, who also engages in a part-time private practice, specializing in pediatric cardiology. He figured prominently in the conferences on White's Entoquel.

The American Academy of Pediatrics (AAP) is expected to issue a policy statement next month supporting FDA's closer scrutiny of pediatric drugs and its thinking on the pharmacology work needed to establish pediatric uses and dosages, particularly neonatal testing.

#### *All NDA'S With Pediatric Implications Routed To New Dr. Nestor*

An outline of FDA's current thinking on perinatal, and especially neonatal, drug uses can be found in a comprehensive article in the July Journal of Pediatrics by Dr. William Nyhan, Johns Hopkins pediatrician. "There is currently no program in FDA to require proof that a compound is nontoxic to the very young infant," he said. Obviously, this has changed since he wrote the article.

Dr. A. J. Lehman, FDA's Pharmacology Director, agrees with Nyhan's statement that "the need [is indicated] for a pediatric or neonatal pharmacology, since the responses of the young to pharmacologic agents cannot be predicted until they have been carefully studied." Lehman concedes that tests on neonatal animals and children—and clinical tests on worrisome mothers—may pose some methodology problems, but he does not believe they are insurmountable.

Nyhan's article reviews the lack of a microsomal enzyme system in newborns, emphasizing that many drugs may be dangerously toxic due to its absence, unless doses far below normal are administered. He also points to problems of absorption, excretion, and distribution of drugs introduced in newborns. Generally, he discounts various "formulas" designed to reduce adult dosages for children according to weight, body surface, age, etc.

FDA'ers question the formula methods, too, because they are finding that exceptions are becoming the rule. Side effects of certain drugs, easily handled by the adult system, may be far more serious in children, even with reduced dosages, FDA'ers say. And sometimes—in the case of digitalis for ages 1 month to 3 years, for instance—*increased* dosages may be necessary for effective use in children.

All NDA's that may have pediatric implications are now being routed to Nestor for special scrutiny. He is the FDA staffer with whom pharmaceutical MD's have to discuss pediatric drugs, uses, and dosages.

Two MD's in FDA's Medical Review Division that has jurisdiction over "old drugs" and cleared "new drugs" also have pediatric backgrounds. The division's drug supervisor is Dr. Denis McGrath, who had pediatric training, although he's primarily a general practitioner with 11 years private practice in Baltimore. McGrath's been with FDA for 2 years.

Dr. William Raffel, the other pediatrician in FDA's Medical Review Division, has been a District of Columbia practitioner for 23 years. Like Nestor, Raffel combines a limited private practice with his FDA work. He's Medical Review's "official" pediatrician.

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June 25, 1962.

DRUG TRADE NEWS.<sup>2</sup>

#### **LABEL ON PREGNANCY DRUG SHOULD AFFIRM ITS SAFE USE: FDA**

ELLENVILLE, N.Y.—Labeling of a new drug which may be used during pregnancy should include "a forthright statement" explaining whether its safety for use in this condition has been shown, the Food and Drug Administration believes.

Many drugs are incidentally administered during pregnancy, according to Dr. Ralph G. Smith, director of FDA's Division of New Drugs. Therefore, he observed, a statement to this effect may prove useful to a physician deciding whether or not to use a drug on a female patient during the childbearing age.

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<sup>2</sup> Vol. 37, No. 13, p. 6.



The recent European tragedy resulting from use of the hypnotic thalidomide "forcefully calls attention to possible serious effects of new drugs on the fetus as a result of use during pregnancy," he declared at the annual meeting and seminar of the Drug & Allied Products Guild here.

At the same time, he added, "it poses the problem of what constitutes adequate animal and clinical studies to detect this potentiality. Most certainly, steps must be taken to develop requirements in this connection."

The problem, he observed, is further underlined by the fact that continuous development of new drugs of new chemical structure invariably produces new problems of safety. "This increases the problem of testing for toxicity. Within the past year, two well-known antibiotics have unexpectedly been shown capable of producing impairment of liver function and jaundice—indicating that they should have been subjected to more thorough studies before marketing."

#### EXPERTS GIVE VIEWS

Experts in the field of pediatrics, he noted, have pointed out that infants and children may react to drugs differently than do adults. "Incompletely developed enzyme systems may result in impaired metabolism of drugs or, conversely, drugs may impair normal enzymatic processes to a greater degree in children than in adults."

Today, he noted, "it is no longer considered safe to derive childrens' doses from safe adult doses by an age or weight formula. Safety of new drugs for infants and children must be shown by actual use in the various age groups."

It is significant, Dr. Smith concluded, that none of the examples quoted "indicates that the required testing of new drugs will become simpler or less laborious—and this is an understatement."

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#### EXHIBIT 137

#### EXCERPTS FROM VARIOUS SOURCES ON THE ISSUE OF ALLEGED "RIGGING" OF RESEARCH IN SOME NEW DRUG APPLICATIONS

On p. 784 Dr. John Nestor testified as to what he believed to be "rigging" of research. The following materials bear upon the subject. All are from the open literature with the exception of an internal memorandum from the Food and Drug Administration. The items are arranged, as in the case of numerous other exhibits, in chronological order with date and source appearing first in a flush left position.

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September 8, 1961.

FOOD AND DRUG ADMINISTRATION.

(Internal Agency Memorandum)

To: Medical Officers, DND.

From: John D. Archer, M. D.

Subject: Clinical investigators contributing incredible data for NDA's.

The Office of the Medical Director has asked this Division to maintain a file for our own use containing the names and other identifying information of clinical investigators who have contributed incredible reports to New Drug Applications. The investigators should be so patently unbelievable that their very appearance in another application would create suspicion. The medical officers are invited to furnish nominations for this file. Dr. Smith or I will receive them. Once the file has been established, it will be kept for your reference in the New Drug secretarial office.

For this file to serve its intended purpose, it should not contain the names of investigators who simply are substandard, poor reporters, overly enthusiastic, etc. Instead, it should contain names of those for whom there is good reason to suspect untruthfulness, psychosis, or dangerous incompetence and irresponsibility.

Your help in this matter will be appreciated. This file, if carefully compiled, can be of great benefit to all of us in evaluating applications.



May 16, 1962.

K. L. MILSTEAD, DEPUTY DIRECTOR, BUREAU OF ENFORCEMENT, FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE.<sup>2a</sup>

#### RIGGED CLINICAL RESEARCH

There is one final area of quackery that I would like to refer to and that involves the scientific integrity of the medical profession. "Rigged" scientific experiments or investigations are repulsive and abhorrent to all scientists. In the medical field they are particularly so because they involve the lives and welfare of sick people and their families. We have two problems in this area that are causing us great concern:

(1) The professional research quack—yes, the M.D.—who specializes in arranging for "tailored studies" of products intended for sale directly to laymen. He makes a few uncontrolled observations on a few of his patients to which he gives the product and then permits the promoter to claim in the advertising and promotion that the product has been "clinically tested" and all the other phrases with which you are familiar.

(2) The physician who is engaged in the clinical testing of new drugs for a fee but who does not test or who rigs the tests to fit a predetermined result.

These practices are the ultimate in quackery because they represent not only the most unethical conduct of physicians but man's worst meanness to his fellow-man. Neither the medical profession nor the regulatory agencies can permit such practices to continue. We intend to use every enforcement facility available to the Government, including the statutes which prohibit the giving of false reports to the Government, to deal with physicians who we find engaged in these activities. We are sure the medical profession, the licensing boards and the local enforcement officials will use all their facilities against any member of the medical profession when it has been established that he is engaged in this type of reprehensible activity.

June 11, 1962.

DRUG TRADE NEWS.<sup>2b</sup>

#### FDA REVIEWING NDA CLAIMS OF CALLED-IN DRUGS

WASHINGTON—A thorough review of clinical and other evidence supporting the New Drug Applications of products recalled by manufacturers during the past two years is being made by the Food and Drug Administration, Drug Trade News has learned.

This review is a direct result of discovery by FDA that questionable information has been submitted by some manufacturers and that in some instances phony evidence of clinical research has been furnished, an FDA official said.

The matter first came to public attention in a recent speech by Deputy Director Kenneth L. Milstead, of FDA's Bureau of Enforcement, to the Yonkers (N.Y.) Academy of Medicine.

#### HINTS CRIMINAL ACTION

Later, in a brief statement to the House Antitrust and Monopoly Subcommittee headed by Rep. Emanuel Celler (D., N.Y.), Commissioner George P. Larrick indicated that FDA might initiate criminal action in some instances where material information was withheld when a new application was submitted or where false information was furnished.

Preliminary information gathered in FDA's checkup of the kind of information submitted with NDAs indicates that a few "big" manufacturers may get caught in the net, a spokesman told Drug Trade News. In his Yonkers speech, Dr. Milstead said FDA is going after physicians who participate in furnishing false information in support of NDAs.

FDA is greatly concerned about doctors who arrange "tailored" studies of proprietary products, Dr. Milstead told the Yonkers Academy. These "studies" sometimes turn out to be only uncontrolled observations on a few of the physician's patients, he said. Some manufacturers have used this kind of "study" to advertise that their products have been "clinically tested," Dr. Milstead said.

Another thing which worries FDA, he declared, is the physician who purports to do clinical testing of new drugs for a fee, but who doesn't actually make such tests or rigs his "research" to fit a predetermined result.

<sup>2a</sup> "The Food and Drug Administration's Program Against Quackery," delivered at the Yonkers Academy of Medicine, Yonkers, N.Y., pp. 11-12.

<sup>2b</sup> Vol. 37, No. 12, pp. 1-8.



The FDA spokesman acknowledged that, in its review of NDA's covering products subsequently involved in recall programs, the discovery may be made that the product should not have been cleared in the first place. This, of course, may result in blame being placed on FDA and will prove highly embarrassing to the agency.

In defense of FDA, it is pointed out that the Medical Bureau has been faced with an extremely difficult task in recent years because of a constant turnover of its medical personnel and the difficulty of recruiting competent people to review the often complex reports which accompany new drug applications. This situation is being overcome slowly, it is now believed. FDA is trying to recruit physicians who not only have practiced medicine actively, but who are experienced in evaluating clinical reports.

#### OFFICIALS STUNG

For some time FDA medical officers have been scrutinizing NDAs more carefully than in years past. At least part of this is the result of charges made before Senator Estes Kefauver's Antitrust and Monopoly Subcommittee of laxity in allowing NDAs to become effective.

FDA officials were somewhat stung by statements made by Dr. Helen B. Taussig, Johns Hopkins University professor of pediatrics, indicating a belief that the drug thalidomide ('Kevadon') could have slipped through FDA's new drug procedure. Dr. Taussig repeated her statement before the House Antitrust and Monopoly Subcommittee recently, saying that "most opinions were that the drug could have passed the Food and Drug Administration here."

Asked to comment on Dr. Taussig's statement, Assistant to the Commissioner Winton B. Rankin remarked that "any drug 'could' be passed, but the significant fact is the 'Kevadon' did not pass." He said "it was no fluke" that the new drug application did not become effective. On the contrary, it was not cleared because of excellent work done by Dr. Frances Kelsey and Dr. John Archer, of FDA's Medical Bureau, who handled the application, Mr. Rankin asserted. Dr. Kelsey was in immediate charge of the job.

"We all owe Dr. Kelsey and Dr. Archer a vote of thanks for doing their jobs well," Mr. Rankin said.

Speaking specifically of the new drug application for thalidomide, a spokesman for FDA said the agency's medical officers determined "some deficiencies" in the NDA and so notified the applicant shortly after it was filed. (Representative Emanuel Celler said during a hearing of his Antitrust and Monopoly Subcommittee that the applicant was the Wm. S. Merrell Co. FDA does not disclose names of new drug applicants.) The NDA was incomplete and inadequate to demonstrate safety of the drug, according to the FDA spokesman.

He noted also that, in May 1961, FDA notified the applicant that there was insufficient evidence available to support the safe use of the drug during pregnancy. This was at least six months before the applicant told FDA the drug had been withdrawn from the German market because of birth defects it had caused, the spokesman stated.

*October 6, 1962.*

GEORGE LARRICK, COMMISSIONER, FOOD AND DRUG ADMINISTRATION.<sup>20</sup>

It would seem that the promoters of cosmetic quackery have learned their tricks from the patent medicine boys. More and more we are running into what we are sure is "rigged research"—the study that was set up and written up to support a claim, rather than to seek for scientific truth.

We have with us today the professional research quack—the M.D. who specializes in arranging for "tailored studies" of products intended for the over-the-counter market. The pattern, which is becoming a familiar one, generally involves the finding of a new twist or gimmick for an old and well-known drug. This avoids the research needed to sustain a New Drug Application. Since it is not a prescription drug it will not be necessary to convince doctors that it has any value—except to get enough evidence so that the Government will find it difficult to prove the negative to its claimed value. Here is where the "tailored study" comes in. It does not have to be conclusive; in fact, it must usually be inconclusive. Only enough work is done to point in the proper direction and to get the report published in a medical journal; only enough to raise a doubt, or to put the Government to the task of proof by a preponderance of the evidence.

The labeling and advertising are likewise designed to get around the law. The

<sup>20</sup> Proceedings of National Congress on Medical Quackery, Oct. 6-7, 1961, Washington, D.C., sponsored by American Medical Association and Food and Drug Administration, 1962, pp. 17-18.



label may even be devoid of claims, or they are so stated that expensive studies in advertising psychology or mass communications must be made to determine what ideas and impressions the consumer actually receives from reading this copy. The skillful wordsmith has an easy mark in the consumer who is hopefully seeking some easy, inexpensive and painless treatment for his condition.

Getting clinical studies done to establish the facts for law enforcement often turns out to be quite difficult. And this is an area in which we need more help from the medical profession.

We sometimes get this reaction from research authorities:

"Why do you want this tested? It *obviously* is no good; and it wouldn't be ethical to try such a thing on patients. And why waste research manpower to prove something is worthless, when there are so many more important things to work on?"

This is a point of view that we can easily understand. Medical research people and public health workers naturally prefer to devote their efforts to finding new and effective therapeutic measures. Accentuate the positive, eliminate the negative, is a popular American philosophy. But if we are going to crack the growing problem of quackery in the United States we will need more research and more education that is devoted to getting the facts and exposing outmoded and ineffective treatments.

Progress is made by eliminating what is unworthy as well as finding what is better, and there are many situations where we cannot afford to wait for the cure that will finally solve a medical problem.

Quackery is big business. It is a serious public health problem. It takes a lot of manpower and money to fight it in the courts. It takes a lot of education to warn the public against it.

My message to you is an invitation. Join us, the AMA and the FDA, in this fight. We promise that you will find it a worthwhile and rewarding experience.

October 6, 1962.

WILLIAM W. GOODRICH, ASSISTANT GENERAL COUNSEL FOR FOOD AND DRUG<sup>24</sup>

We also are concerned with the physician investigator who doesn't investigate or who plans his investigation to yield a predetermined result. No one can justify reporting results for a fee, without taking account of the serious consequences that may attend the interstate distribution of an inadequately studied new drug. There surely will be closer attention to all such practices as we uncover them.

#### EXHIBIT 138

#### SUBSEQUENT MEMORANDUM BY SENATOR HUBERT H. HUMPHREY, LISTING EXCERPTS OF 8 YEARS OF COMMENTS BY VARIOUS AUTHORITIES ON FOOD AND DRUG ADMINISTRATION'S NEED FOR CONSULTATION

In May 1963 Senator Humphrey issued a memorandum on a subject which had been mentioned by Dr. Nestor in the latter's testimony. The memorandum cited excerpts from the open literature and from Food and Drug Administration files as regards recommendations submitted during the years 1955-62, toward the goal of utilization of consultants by the agency. The memorandum was sent to interested sources as a reference tool and as an invitation for comments. One such comment appears in exhibit 172, p. 1252.

<sup>24</sup> Ibid, p. 23.



UNITED STATES SENATE,  
COMMITTEE ON GOVERNMENT OPERATIONS,  
SUBCOMMITTEE ON REORGANIZATION AND INTERNATIONAL ORGANIZATIONS.

Background memorandum from: Senator Hubert H. Humphrey, Chairman, Subcommittee on Reorganization and International Organizations.  
Re: THE ISSUE OF PROFESSIONAL CONSULTANTS AND COUNCILS FOR THE FOOD AND DRUG ADMINISTRATION—EXCERPTS FROM 8 YEARS OF SUGGESTIONS AND REACTIONS.

PURPOSE: TO MAKE BACKGROUND INFORMATION MORE READILY AVAILABLE

This memorandum is submitted to individuals interested in the future of the Food and Drug Administration. It offers background information which might not otherwise have been available.

The Senate subcommittee has found, generally, that busy physicians and other experts often do not have time to locate and read vast numbers of documents which may bear upon a given phase of FDA's or any other agency's policy. (This limitation of time is particularly severe if documents are not easily accessible, e.g., are located only in an agency's files.)

For that reason, I asked the staff to assemble in one memorandum pertinent excerpts from the public and private record of the past 8 years on several key drug subjects. This is, I feel, one of the valuable services that a factfinding committee of the Congress can perform.

8 YEARS OF SUGGESTIONS ON CONSULTANTS FOR FDA

This particular chronology includes 8 years of comments on proposals for professional advisors to the Food and Drug Administration, particularly as to evaluation of new drugs.

I may point out that literally dozens of letters to the Senate subcommittee have urged that mechanisms for such counsel be set up in FDA. However, many of the correspondents indicate that they have been unaware that the same suggestion has been made over and over again for almost a decade. Actually, the suggestion has been made in various forms by various sources, both official and unofficial, publicly and privately.

OUR GOAL: TO LOOK AHEAD TO A STRONGER FDA

Now, my hope is that review of the past record will enable us to "pick up from where others have left off"—i.e., to avoid needless repetition. With such review, we can find out *why* action did or did not take place on this or any other subject and then proceed to assure sound and timely action in the future.

Our goal is, of course, to look ahead to a stronger Food and Drug Administration, i.e., to an agency of highest excellence.

CHRONOLOGY 1955-1963

The chronology below begins in 1955 with the Report of the First Citizens Advisory Committee on FDA. Actually, excerpts from *earlier* years might also have been included. But in the interest of brevity, only 8 years of selected quotations are reprinted.

The chronology starts with the record of the suggestion, in June 1955, that Advisory Committees or Councils be set up. It concludes with the indication—7 years and 11 months later, in May 1963, that in the fall of 1963, a National Advisory Council is expected to be set up, supplementing other advisory groups.

*June 30, 1955:* G. Cullen Thomas, Chairman, First Citizens Advisory Committee on the Food and Drug Administration: "Consideration should be given to the creation of a committee (possibly similar to National Research Council committees or the advisory councils of the Public Health Service) to advise the FDA on complex problems in the field of new drugs."<sup>3</sup>

*July 1 1959:* Paul L. Day, Ph. D. (then Scientific Director, Food and Drug Administration): Recommendation—"Arrange for the appointment of a Scientific Advisory Board of distinguished scientists from universities, foundations, industry, and other Government laboratories.

<sup>3</sup> Report to Secretary, Health, Education, and Welfare, reprinted as House Document 227, 84th Cong., 1st Sess., June 1955, p. 42.



"It is contemplated that this body would serve in an advisory capacity for research only, and would have no concern with regulative and control matters."<sup>4</sup>

*October 27, 1959:* (FDA review and decision on the proposal): "Suggestion—Arrange for the appointment of a scientific advisory board of distinguished scientists from universities, foundations, industry, and other Government laboratories.

"Comments of the technical divisions and Bureaus of Biological and Physical Sciences and Program Planning and Appraisal: Opinion of the commentators was divided on this recommendation.

"Decision as to further action: There is agreement that Dr. Day should have topflight scientific help available to him on a consultant basis. This can be arranged without establishing a formal board. Dr. Day will consult the Division of Administrative Management about the procedure for appointing consultants and will recommend to the Commissioner the people he would like to have appointed to help him. The appointments will be on a term basis."<sup>5</sup>

*September 27, 1960:* C. Phillips Miller, M.D., Chairman, Special Advisory Committee of the National Academy of Sciences—National Research Council, to the Secretary of Health, Education, and Welfare: "The committee urges the Commissioner to seek such authorization as may be necessary to establish an advisory organization of scientific and technical experts as a recognized resource for advice on criteria, procedures, and policies for the execution of the responsibilities of the FDA."<sup>6</sup>

Arthur S. Flemming, Secretary of Health, Education, and Welfare (in comment on the Miller report): "I concur in this recommendation that the Commissioner of Food and Drugs seek authority to establish an advisory organization of scientific and technical experts. The complexity of present day new drugs and the constant flow of progress and new developments in the drug field makes it essential that the Food and Drug Administration have for its guidance the most competent scientific resources available in the United States. I have asked Commissioner Larrick to make appropriate proposals to me for the implementation of this recommendation."<sup>7</sup>

*October 12, 1960:* Paul L. Day, Ph. D.: "This suggestion for an advisory group of outside specialists has been interpreted by some as an implication that our own scientists are not competent to manage our scientific affairs. That misses the point entirely. Our budget does not permit us, and never will permit us, to obtain the services of some outstanding scientists with special knowledge and skills. But many such men would be willing to spend a few days a year, as members of an organized advisory panel, in considering and helping us with the overall scientific program of the Food and Drug Administration. In this way, for a modest honorarium, we could obtain the services of some of the outstanding minds in America today. Several ad hoc advisory panels have been appointed within recent months to help FDA solve a specific problem, and they have been quite useful. But a continuing advisory group would provide a stability to our program which would be immeasurably more valuable."<sup>8</sup>

*October 3, 1962:* Senator Humphrey: "It is incredible but FDA has made little systematic use of outside consultants. It has made virtually no use of the NIH; it has made almost no use of the specialty boards, or of the National Academy of Sciences.

"FDA did send, at my request, a list of alleged outside consultations. The list is nominally long. The only trouble with it is that it gives a completely misleading impression. It pretends that an isolated telephone call or letter or short visit for a curbstone—I emphasize—curbstone judgment represented 'consultation.' That is not really consultation. What is real consultation? Any scientist will give you the answer—a full-day meeting, a 2-day symposium, an expert full-time or at least a part-time panel which meets over an extended period of time for a thorough exchange of professional views. That is what we mean by consultation. But that is not what has occurred in or for FDA.

<sup>4</sup> Report to Commissioner of Food and Drug Administration, reprinted by Senate Committee on Government Operations, Subcommittee on Reorganization and International Organizations, "Interagency Coordination in Drug Research and Regulation," pt. 2, p. 324.

<sup>5</sup> Memorandum of conference between Commissioner George Larrick, other FDA officials, and Dr. Day, reprinted, *ibid.*, p. 335.

<sup>6</sup> Report, reprinted, *ibid.*, pt. 2, p. 342.

<sup>7</sup> Comments, reprinted, *ibid.*, pt. 2, p. 345.

<sup>8</sup> Statement to Animal Nutrition Research Council, Washington, D.C., reprinted, *ibid.*, p. 353.



"I am surprised to see in a letter to the House Commerce Committee, that FDA states that consultation has 'routinely' occurred. That is definitely not the case. The men who know it best are the men inside the agency who have fought and begged for professional consultation, but whose efforts have been discouraged at worst, or ignored, at best, from above.

"Sometimes consultation has taken place after the fact—after a drug has been on the market and reports of a flood of serious side effects have started to pour in. But the damage at that stage has already occurred."<sup>9</sup>

October 25, 1962: George Y. Harvey, Chairman, Second Citizens Advisory Committee on Food and Drug Administration: "1. It is proposed that a Food and Drug Institute be created to strengthen and give greater stature to the scientific and medical work of FDA.

\* \* \* \* \*

"The Institute should create one or more scientific advisory councils to provide counsel on policies, methods, procedures, personnel development, research, and developments and problems to be anticipated in science and medicine. These scientific advisory councils might be composed of members from professional scientific organizations, universities, and the National Research Council, as well as other eminent scientists and physicians (including some representation of practicing physicians)."<sup>10</sup>

March 20, 1963: John O. Nestor, M.D.: "Despite requests from the physicians in the Bureau of Medicine, panels of consultants have not been made readily and easily available for advice and opinion necessary to avoid wrong decisions. To a great extent, we rely on ad hoc panels to solve problems that might never had arisen had consultation been easily available in the beginning."<sup>11</sup>

April 26, 1963: Commissioner LARRICK: "Increasingly FDA has been seeking assistance and advice from outside experts. In the recent past, for example, we have sought advice from internationally recognized scientists on food additive and drug problems involving two nutrients, folic acid and menadione, certain antibiotic drugs, and the oral contraceptive Enovid.

\* \* \* \* \*

"But we need to do more. We are in the process of forming an advisory committee on investigational drugs. This will be made up of outstanding experts representing general medicine, pharmacology, and clinical pharmacology, experimental therapeutics, biochemistry, and other medical disciplines.

"The committee will bring to the Food and Drug Administration the views of responsible scientists throughout the country on the very important problems of testing investigational drugs on man.

"It will give advice that will help us administer the investigational drug regulations in the best interest of patients and science.

"We expect to appoint other advisory committees to help us in our scientific activities and we anticipate the formation of a National Food and Drug Advisory Council to give the Commissioner advice on broad problems.

\* \* \* \* \*

"Congressman O'BRIEN. My next question is with reference to bottom of page 18 of your statement. You make reference to a National F&D Advisory Council. Now, I, and I think some members of the Committee, and more particularly the Chairman, have received some mail in support of such a formation. May I ask if that is the general attitude of the industry?

"Mr. LARRICK. I don't think I can state with assurance what the general attitude of the industry is.

"I think that there is a very great consensus of viewpoint among the responsible element of industry and the responsible element of the scientific community that have a reason to have an interest in our work, who believe that our responsibilities are getting greater all the time and the technological problems that we are confronted with are growing to the extent that we do need to constantly expand our access to the best brains in science in America to be able to discharge our obligations to the best possible advantage."<sup>12</sup>

<sup>9</sup> Statement in Senate, with Memorandum, October 3, 1962, p. 20884, reprinted, *ibid.*, p. 586.

<sup>10</sup> Report, reprinted, *ibid.*, pt. 2, pp. 440-441.

<sup>11</sup> See p. 782.

<sup>12</sup> House Committee on Interstate and Foreign Commerce, Subcommittee on Public Health and Safety, Hearings on H.R. 2410, 88th Cong., 1st sess., to Amend Public Health Service Act to Provide Greater Flexibility in the Organization of the Service, and for Other Services, Hearing of April 26, 1963, Verbatim Transcript, Vol. 4, pp. 283-284, 312-313.



May 14, 1963: Mr. Boisfeuillet Jones, Special Assistant to the Secretary of Health, Education and Welfare (Health and Medical Affairs), in discussion with Congressman Rogers:

"Mr. ROGERS of Florida. There has been some talk in the pharmaceutical industry too that they would be interested in the creation of an advisory council on food and drugs.

"Has anything been done to consider this proposal?

"Mr. JONES. Yes, sir. There was a specific recommendation in the Citizens Advisory Committee report for the appointment of a National Advisory Food and Drug Council.

"This council will be appointed. The Commissioner expects to do this and our anticipation is that the council will be in operation in time to review the implementation of the Citizens Advisory Committee report probably this fall.

"Mr. ROGERS of Florida. The Advisory Council will be in effect?

"Mr. JONES. This would be the expectation.

"Mr. ROGERS of Florida. What legislative authority does the Secretary use to provide this council?

"Mr. JONES. His general authority for the Administration of the Food and Drug Act which does provide for advice from nongovernmental consultants.

"Mr. ROGERS of Florida. So that he can do with his present authority in the Department?

"Mr. JONES. Yes, sir. That is correct. This council, we think, will be a very important adjunct to a continuing review of the Food and Drug program by representatives of the public, of the regulated industries, of the consumers, and of the scientific community.

"Mr. ROGERS of Florida. What was the time limit when you expect this to be functioning?

"Mr. JONES. We would expect it to be in operation probably by late fall, although we haven't set a timetable. It takes some time to select and to get clearances on these people.

"Furthermore, we wish time to put into effect as many of the recommendations of the Citizens Advisory Committee prior to the creation of this council so the first job would be to take a look at the implementation and then begin the function beyond that.

"The Citizens Advisory Committee is in and of itself a form of council for advice, but it was more specific. We think a continuing council would be a very useful asset to the Commissioner and he feels this way about it and it will be appointed.

"Mr. ROGERS of Florida. When you firm this up could you let the committee have the details of it for the record?

"Mr. JONES. Surely."<sup>13</sup>

EDITOR'S NOTE.—For additional comment on the issue of consultants to the agency, see exhibit 139 which follows.

#### EXHIBIT 139

##### COMMENTS BY NATIONAL ACADEMY OF SCIENCES ON PROFESSIONAL CONSULTATION FOR THE FOOD AND DRUG ADMINISTRATION

On June 21, 1963, Frederick Seitz, President of the National Academy of Sciences, responded to an invitation conveyed by Senator Hubert H. Humphrey for comment on the issue of professional consultation with the Food and Drug Administration. The exchange of correspondence follows.

MAY 9, 1963.

DR. FREDERICK SEITZ,  
President, the National Academy of Sciences,  
Washington, D.C.

DEAR DR. SEITZ: I should like to confirm an invitation which was discussed by phone last August with Dr. Cannan, and, this month, with Dr. Cornell by our staff. It is for a statement by the academy which the subcommittee would publish in its forthcoming hearing-exhibit volume, part 3, "Interagency Coordination in Drug Research and Regulation."

<sup>13</sup> Ibid., Hearing of May 14, 1963, Verbatim Transcript, Vol. 5, pp. 392-393.



The statement might be on some such theme as "Cooperation by the National Academy of Sciences with the Food and Drug Administration on Drug Issues."

The statement could contain whatever background information and opinion you and your distinguished associates believe would be helpful to our subcommittee study. Please feel free, therefore, to give us the benefit of your able judgment on any of a broad range of issues which you might regard as pertinent.

Essentially, the subcommittee is interested, as you know, in helping to assure the highest degree of scientific excellence within this important agency as the basis for the highest caliber of actions within the "Federal Drug Community," so to speak.

We had very early noted the important report which had been made by the expert committee appointed by Dr. Bronk in June 1960.

The recommendations in that report will be published in our part 2. (Included in those recommendations was, you recall, a suggestion for "an advisory organization of scientific and technical experts." That particular recommendation is yet, unfortunately, to be implemented.)

The subcommittee would appreciate receiving a brief listing and description of each of the instances in which the academy has been asked by FDA to be of assistance on drug issues (if only, as we understand it, by the somewhat limited device of requesting the academy merely to suggest names of individuals who might be asked by the agency to serve on an ad hoc panel under FDA's own guidance).

Most important of all, we would be interested in receiving whatever suggestions the academy might now feel it is in a position to offer (out of its general background) as to how the highest degree of continuing excellence on drug issues might be fostered within and on behalf of FDA.

This particular volume which would contain the academy's comments, will probably not go to press until late June 1963. It will not be essential that we receive it prior to that time, although it will be most welcome as soon as you are in a position to send it.

Looking forward to the pleasure of hearing from you, I am,

Sincerely,

HUBERT H. HUMPHREY,  
*Subcommittee Chairman.*

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NATIONAL ACADEMY OF SCIENCES,  
*Washington, D.C., June 21, 1963.*

DEAR SENATOR HUMPHREY: It is a pleasure to transmit to you herewith a statement concerning the cooperation of the National Academy of Sciences with the Food and Drug Administration on drug issues. This was prepared by Dr. R. Keith Cannan, Chairman of the Division of Medical Sciences of the National Academy of Sciences-National Research Council.

Sincerely yours,

FREDERICK SEITZ, *President.*

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STATEMENT ON COOPERATION OF THE NATIONAL ACADEMY OF SCIENCES WITH THE  
FOOD AND DRUG ADMINISTRATION ON DRUG ISSUES

The requests for assistance that the Academy-Research Council has received from the Food and Drug Administration in the period 1950-63 fall into two broad categories:

- (1) requests for advice on specific drug issues, and
- (2) requests for the nomination of individuals competent to advise FDA directly on designated drug issues.

A number of requests have also been received for advice on questions of food additives and food contamination and, under Public Law 518, for the nomination of consultants to review petitions relating to pesticides. Because these are not drug problems, they are not detailed here.

REQUESTS FOR ADVICE

In its response to requests for advice on the following issues, NAS-NRC assumed full responsibility for the selection of consultants and advisers, for the assembly and review of pertinent information, and for the preparation and submission of approved statements of opinion or advice.



Date of request	Date of response	Issue
1 June 1950.....	18 April 1951.....	A statement on the treatment of venereal disease for inclusion in brochures distributed by manufacturers of penicillin.
1 December 1950.....	4 April 1951.....	A proposed protocol for the investigation of the safety of a dentifrice containing penicillin.
11 July 1951.....	13 August 1951.....	Whether the dentifrice containing penicillin should be made available over the counter for use without supervision by a dentist.
23 July 1952.....	7 August 1952.....	The association of aplastic anemia with the administration of chloromycetin.
26 November 1952.....	16 December 1952, 1 December 1953, 2 April 1954.	The clinical safety and proper labeling of polyvinyl pyrrolidone.
29 January 1954.....	9 February 1954.....	The safety of a dentifrice containing fluoride.
24 April 1958.....	30 April 1958, 21 October 1960.	The safety and efficacy of Hydrosulphosol in the treatment of cataracts.
2 June 1960.....	30 September 1960.....	The policies, procedures, and decisions of the New Drug Branch of FDA. (Advice was requested by and submitted to the Secretary, HEW).
28 November 1960.....	11 January 1961.....	A reevaluation of the question of aplastic anemia and chloromycetin.

## REQUESTS FOR NOMINATIONS

In respect of the following issues, the responsibility of NAS-NRC was limited to the nomination of panels of individuals competent to examine the specific question. FDA selected, from these nominations, consultants who were then instructed by and reported directly to an officer of FDA.

Date of request	Date of response	Issue
1 June 1960.....	4 August 1960.....	The safety of Saffrole in root beer.
4 April 1961.....	8 June 1961.....	Tolerances for quinine in carbonated beverages.
20 December 1961.....	26 January 1962.....	A new drug for the treatment of trichomoniasis.
8 March 1962.....	13 April 1962.....	The labeling of antibiotics.
25 October 1962.....	18 December 1962.....	The association of thrombophlebitis and thromboembolism with the use of an oral contraceptive. (The request was declined by NAS.)
15 March 1963.....	4 April 1963.....	Tolerances for pesticide residues.

## CONSIDERATIONS BEARING ON THE DEVELOPMENT OF ADVISORY SUPPORT FOR THE WORK OF THE FOOD AND DRUG ADMINISTRATION

The following thoughts are offered in response to an invitation from Senator Humphrey to the President of the Academy to present "whatever suggestions the Academy might now feel it is in a position to offer (out of its general background) as to how the highest degree of continuing excellence on drug issues might be fostered within and on behalf of FDA."

The statement that follows is exploratory; it is not based on an organized, deliberate study by advisory groups representing the scientific and professional interests involved. The views offered are derived, in the main, from the experience of the Division of Medical Sciences, NRC, in its relations with FDA and from the opinions developed at two conferences at which members of the division reviewed current problems bearing on the evaluation of the safety and efficacy of drugs.

In the past, FDA has sought diligently to fulfill its responsibilities with woefully inadequate resources. Year by year, as the pace of medical progress accelerates, the demands that will be made upon the agency for wise and informed judgments will increase in breadth and in depth. If FDA is to meet these expanding demands it must be materially strengthened within its own organization; it must receive greater support from other medical resources within the Government, and it must develop ways and means of securing more effective help from the community of medical science as a whole.

## NEEDS WITHIN GOVERNMENT

In the final analysis, the excellence of performance of FDA will rest upon the scientific competence, the intellectual power, and the professional integrity of the staff of the agency. Because the competition for men of high caliber and dis-



tion in the medical world is severe, the strengthening of the staff will not easily be accomplished. Greater economic rewards are not enough. More important is the dissemination of a feeling of confidence that the agency is so administered as to encourage individual initiative in the development of policies and practices, active fellowship with the community of medical science, and a lively interest in investigative work. It is necessary to dispel the deadening impression that the agency is interested only in regulation. This aspect of the mission of FDA is, indeed, an impediment to intellectual excellence. It is, however, one that can be overcome, as the Division of Biological Standards of NIH has demonstrated. This is an organization that has prestige as an institution dedicated to scientific endeavor, as well as to the exercise of legal controls. Its authority is respected in the community of medical science and its task is, thereby, more effectively carried out.

The first need would, then, seem to be the strengthening of the professional staff and the liberalization of management policies. The second need is to develop mechanisms for mobilizing the support of the scientific talent of other agencies of the Federal Government. The Government commands the services of many individuals of high distinction in all areas of medical science. It is the responsibility of the Department of HEW to establish the means and the habit of bringing this body of expertise to the service of FDA in the resolution of problems of national importance.

#### NEEDS FOR ADVISORY SUPPORT FROM OUTSIDE OF GOVERNMENT

Much can be accomplished within the Government, but experience has shown that the power, the authority, and the confidence of an agency with scientific and medical responsibilities can be materially strengthened if it has access to advisory groups drawn from the private sector of science and medicine—groups sympathetic to the mission of the agency and expert in its particular scientific and professional problems.

In many scientific enterprises of Government such advisory service is effectively provided by voluntary organizations of scientists such as the Academy-Research Council. When such services are used, the control of the mechanisms by which advisory opinions are developed and rendered rests with the organization that advises. In other situations, Government agencies have preferred to appoint and instruct their own advisory groups. The latter arrangement will probably prove more effective for FDA, inasmuch as sound judgment on the problems that FDA must solve requires familiarity with

- (1) the laws that FDA is required to administer,
- (2) the existing policies, practices, and procedures of FDA,
- (3) the intelligence system on which FDA depends for the information on which decisions are based, and
- (4) the confidential nature of much of the information available to FDA.

Whatever may be the administrative structure of the advisory organization, it must have continuity if it is to function with full understanding of the responsibilities and procedures of the agency. Advisory support sought on an ad hoc basis will generally be disappointing and, of greater importance, will contribute nothing to the authority and prestige of FDA.

The organization should be so structured as to be able to advise both at the level of policy and at the technical level of the evaluation of particular drug situations. This suggests that the advisory organization might take the form of a senior committee broadly representative of medical science and medical practice, supported by a number of panels of individuals who are expert in specific aspects of the field of drugs. The senior committee would devote its attention primarily to the refinement of principles, policies, and practices and their adaptation to new situations. Its advice should also be sought on questions of recruitment, personnel management, and relations with nongovernment institutions. Beyond this, it should be responsible for coordinating the specialized advice of the panels. With respect to the latter, experience will be the best guide in determining whether the panel system should be set up according to types of pharmacodynamic response, categories of drugs, or therapeutic usages.

A question that inevitably arises in relation to advice on problems involving the reconciliation of the interests of Government and of private enterprise is that



of "conflict of interest."<sup>1</sup> Almost inevitably those individuals with the greatest experience in the study of the action of drugs will be found to have developed working relationships with the pharmaceutical industry. This problem should be faced forthrightly and with confidence and imagination, rather than defensively. The pursuit of excellence involves the acceptance of risk and the pursuit of the best advice should not be overly constrained by an armor of fearfulness. The best advice should be sought in the faith that the administration of FDA will have the wit to discount any element of "conflict" that might prejudice a particular advisory statement.

#### BROADER CONSIDERATIONS

The thoughts outlined above have been confined to the consideration of ways and means of strengthening FDA in the execution of its responsibilities to society. Society does, indeed, look to Government to protect it from the hazard of improper practices in the development and use of drugs. At the same time society expects the continuous advancement of therapeutic practice through the cooperation, in research and development, of medical science, the medical profession, and industry. The goal of the national effort must, therefore, be to maximize progress while minimizing the risks of misadventure. In brief, the public welfare will best be served if the surveillance of the "drug problem" is sustained in the context of these broad objectives. There is need for continuous collaborative study of resources, practices, responsibilities, and opportunities by all groups in society that are concerned.

A number of private organizations have shown commendable initiative in this direction since the tragedy of thalidomide brought the problem of the hazards of drugs to the forefront of the public mind. The Pharmaceutical Manufacturers Association promptly established a Commission on Drug Safety, whose members are distinguished representatives of medical science, medical practice, and the scientific arm of the pharmaceutical industry. This commission has provided a forum for informed opinion and has initiated a number of special studies designed to define and illuminate some of the fundamental issues. The Council on Drugs of the American Medical Association has also taken formative action, particularly in the development of an intelligence system for the speedy reporting and evaluation of undesirable effects of drugs, while the Association of American Medical Colleges has established a committee to examine the interests and responsibilities of academic medicine in the investigation of drugs.

The Academy-Research Council has also been alert to its responsibilities in this area. The members of its Division of Medical Sciences were called in conference on the subject in November 1962, and again in March 1963. There have been a number of discussions with officers of FDA and HEW on the question of the roles that NAS-NRC might appropriately play. The Division of Medical Sciences has also been in close touch with the work of the Commission on Drug Safety almost from its inception. Recently, the President and the Governing Board of the Academy-Research Council have, at the invitation of the commission, reviewed this situation and have decided that the time has arrived for the initiation of its own program of studies in collaboration with those of other private groups. The primary objective will be to contribute authoritatively to the delineation of the principles that should guide the development of the national purposes and practices with respect to research, development and control in the production and use of drugs. These plans will be activated as soon as suitable financial support of the undertaking can be secured. It is understood that the Commission on Drug Safety may terminate its own activities when its present studies are completed if the program of the Academy-Research Council is then underway.

In conclusion, it would seem that there exist, or are in process of development, a number of private consultative resources that will be available for authoritative counsel and evaluated information to supplement the advisory resources FDA should itself establish.

<sup>1</sup> Editor's note: For background to the problem of conflict of interest, see: "Preventing Conflict of Interest on the Part of Special Government Employees," the President's memorandum of May 2, 1963. Illustrative of the actions of one organization in interpreting the President's memorandum is a 14-page memorandum with attachments, issued by the Office of Science and Technology, and entitled, "New Conflicts of Interest Legislation: Consultants and Advisers."



## EXHIBIT 140

## EXCERPTS OF COMMENTS ON AND BY FOOD AND DRUG ADMINISTRATION AS TO WHAT CONSTITUTES A "NEW DRUG"

There follow a series of comments on and by the Food and Drug Administration with respect to the issue of what constitutes a "new drug," as well as on procedures related thereto.

October 13, 1954.

RALPH G. SMITH, M.D., Chief, New Drug Branch, Food and Drug Administration.

WHAT IS A NEW DRUG?<sup>14</sup>

(By Ralph G. Smith, M.D.)

The Federal Food, Drug, and Cosmetic Act of 1938 includes a section which, in effect, prohibits the introduction into interstate commerce of any new drug unless an application for it is effective. Such an application must include full reports of investigations which have been made to show whether or not the drug is safe for use, a complete description of the procedure and controls used in the manufacturing, processing, and packing of the drug, and the general manufacturing facilities of the firm or individual. These details of manufacturing procedure are required to ensure that a product may be produced which is satisfactory from the standpoint of identity, strength, quality, and purity. The application must also include a statement of the complete quantitative composition of the drug and copies of the proposed labeling. The primary purpose of the application is to show that the drug may be used with safety under the proposed labeling. In other words, the burden of proof for safety is on the distributor before the drug may be marketed. Before 1938 a new drug could be distributed without making any presentation whatsoever to the Food and Drug Administration, and that is also true at the present time for a product which is not a new drug.

In spite of the fact that a distributor would ordinarily satisfy himself that a drug was safe, the preparation of a New Drug Application usually entails extra work, expense, and often delay. Accordingly this procedure is followed only when necessary; that is, when the product is a new drug. In many instances there is no question as to whether a drug is new or old, but there are many borderline cases which give rise to differences of opinion in this connection. Consequently, it is necessary to have some standard or definition which will aid in a decision.

Such a definition is included in the act and I quote directly as follows:

"The term 'new drug' means (1) any drug, the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof \* \* \*."

I would like to direct your attention to certain specific words and phrases in this definition. In the first place, it is noted that it is lack of recognition of safety which constitutes newness. This is qualified in that the lack of recognition of safety is among experts with the training and experience to evaluate the safety of drugs, presumably those who are particularly qualified in their respective specialties or fields of medicine. The word "generally" is also significant—"generally recognized as safe." Recognition of safety by one or two experts, possibly as a result of their own investigations, is insufficient to remove a drug from "new drug" status. Very important also is the concept that safety is considered from the standpoint of the "conditions prescribed, recommended, or suggested in the labeling." We are often requested to offer an opinion on the new drug status of a product without being provided with the proposed labeling. We may be able to comply if it is a product which has not previously been used as a drug or if it is regarded as a new drug under almost any form of labeling. In the absence of labeling, however, we cannot express the opinion that a product is not a new drug without at least making a number of qualifications.

<sup>14</sup> "What Is a New Drug?," presented before Medical Society of the District of Columbia; reprinted in Medical Annals of the District of Columbia, vol. XXIV, No. 2, Feb. 19, 1955, pp. 63-66.



Incidentally, there is an exception included in the definition to the effect that if the drug were distributed under essentially the same labeling prior to the effective date of the 1938 act, it is not a new drug even though it is not generally recognized as safe.

There is also a second paragraph in the definition of a new drug which is frequently overlooked or its significance not recognized. It is as follows:

"The term 'new drug' means (2) any drug the composition of which is such that such drug as a result of investigations to determine its safety for use under such conditions has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions."

In other words, even though a drug is recognized as safe under certain labeling as a result of investigations, it is still a new drug until it has been used for a material extent and for a material time. Even though an application for a drug has become effective and it is being marketed by a certain firm, it is still necessary for other firms to obtain their own effective applications before distributing it.

There is undoubtedly considerable wisdom involved in the second paragraph of the definition. When a New Drug Application is allowed to become effective we are reasonably sure that the product may be safely distributed and used under the conditions provided for in the labeling. Recognition of safety, however, is relative. Use of the drug under actual marketing conditions is a further test of safety. It has been the experience in more than one instance that a drug has been found to be less safe than was anticipated on the basis of reports of investigators. Such an occurrence is not entirely unexpected. During the investigative stage the drug may be used with particular care, with patients under close supervision and by men with special training and experience. Widespread distribution directly to the layman, or even as a prescription item is definitely a more rigid test of safety. Accordingly the provision in the law for a somewhat prolonged control under the new drug procedure is not without merit.

How long does a new drug maintain its new drug status? This is a question which naturally follows and is one which cannot be answered precisely. Each one requires individual consideration, and the answer depends on a number of factors. Marketing experience is a most important one. A relatively high incidence of complaints with respect to side-effects or serious toxic manifestations, or the necessity of adding restrictions to the labeling relative to dosage or to indications for use, may prolong the period of new drug status. The degree of distribution may be a determining factor. Extensive use without the occurrence of adverse effects will tend to shorten the time of control as a new drug. If there are difficulties in manufacturing control procedures such as with assay, maintenance of stability, or in the actual preparation of a pure or uniform product, a longer period may elapse before it is considered as not a new drug. If in the investigative studies an extremely wide margin of safety is indicated for a product, or if it is one for which there is some doubt that it should originally have been regarded as a new drug, reassurance of definite safety may require only a short marketing experience. In view of such a wide variation of circumstances for different preparations it is probably fortunate that an attempt was not made to specifically define what is meant by the terms "material extent" and "material time."

The legal definition of a new drug which has been discussed is further amplified by regulation. In this regulation there are five paragraphs, each presenting a different reason for considering a drug as new.

The first paragraph points out that not only the active ingredients of a product but also the so-called inactive ingredients, such as the menstruum, excipient, carrier, coating, or other components, may cause it to be a new drug. Attention has been called many times to the fact that it was the disastrous consequences of a vehicle, diethylene glycol in an elixir of sulfanilamide, which was responsible in no small part for the passage of the new drug section of the act. In recent years many new agents have been introduced into pharmaceutical industry as dispersing agents, preservatives, solvents, stabilizers, etc., which are not even necessarily mentioned on the label. The physician and patient are usually unaware of the identity of these components, and their safety is taken for granted. It sometimes happens that we are more concerned with components of the vehicle than with the active ingredients, not only from the standpoint of systemic effects but also of local reactions at the site of an injection.



The second paragraph states that a combination of two or more old drugs may be a new drug. This is readily understandable. There may be a possibility of synergism necessitating the experimental determination of safe dosage. A question of chemical incompatibility may arise. The stability of an ingredient may be affected, or one of the components may be changed to yield an undesirable compound. In many instances, such combinations, on the basis of extraneous experience, are not regarded as new drugs, but in certain cases we consider specific demonstration of safety desirable.

In the third paragraph of the regulation it is stated in effect that a change in the proportions of the ingredients of an old combination of drugs may cause it to be a new drug. Although there are undoubtedly many instances in which change in proportions would not present a problem of safety, it is conceivable that such might occur. If one of the ingredients were a corrective added to antagonize an undesirable side-action of an active component, a lowering of the proportion of the corrective might result in adverse effects. If one ingredient of a tablet were definitely more potent than a second ingredient with a similar type of action, an increase in the tablet content of the potent ingredient even with a decrease of the same weight unit of the second ingredient would result in a product definitely more potent than the original tablet. It is necessary, of course, to give due consideration to all such proposed changes.

The fourth paragraph brings out the concept that a drug commonly recognized as safe for a certain medical use may become a new drug if offered for a new purpose, to produce a different action, or to affect another structure of the body. It may be argued that if a drug is safe in a certain dosage for one therapeutic purpose it should be safe in the same dosage if used for something else. I believe that this is often true. However, certain pathologic conditions may modify the metabolism of a drug and consequently its concentration in the body with parallel changes in degree and in duration of action. Many drugs are destroyed in the liver. Others are excreted by the kidneys. Impaired function of these organs would be expected to result in undue responses to otherwise safe doses. Pathology in an organ may increase its susceptibility to the toxic effects of a drug. Mercurial diuretics are used successfully in the treatment of edema of congestive heart failure but are contraindicated for edema of acute nephritis. When a hormone well recognized in certain fields of therapy is advocated for some other endocrinopathic condition on theoretical or preliminary investigative grounds, the question will arise: What effect will this condition have on the response to the hormone, not only of the condition itself, but of other functions of the body? Other examples could be cited where questions of safety may arise when a drug recognized as safe in one field is offered for a new use. Each proposal is an individual problem, and a sound opinion on whether or not the drug, for this new use, becomes a new drug can be reached only after thorough consideration.

Included in the final paragraph of the regulation is the statement that newness of a drug may arise by reason of newness of a dosage, or method or duration of administration or other condition of use prescribed, recommended or suggested in the labeling. These points, I believe, are self-evident and require little discussion. An appreciable increase in dosage beyond usual experience will naturally pose the problem of safety. A new method of administration likewise requires investigation before general recognition of safety is possible. A drug safe for oral use may not be safe for parenteral use in the same dosage or even in reduced dosage. In most instances the necessary degree of reduction of dosage below that of the oral form is one of the main problems. Usually more rapid absorption results from subcutaneous or intramuscular injection than from oral administration, causing steeper and higher blood concentration curves. The by-passing of the hepatic circulation may be a factor. Local reactions at the site of injection should be considered. The tolerated rate of intravenous injections must be explored. Stability in solution and problems of sterility demand attention.

Even the introduction of an oral dosage form after recognition of safety for parenteral administration may present problems. This has been exemplified recently in hexamethonium, which requires much larger oral than parenteral doses as a result of incomplete and erratic absorption with consequent lower predictability of response and increased side-effects referable to the intestine. A drug with established use for systemic action may be a new drug for topical application to the skin or mucous membranes, since questions of primary irritation, sensitization, and tolerated concentration must be answered.



An increase in the recommended duration of administration may place an old drug in new drug status. The possibilities of cumulation, the development of increased sensitivity, and toxic effects on the tissues from prolonged use are matters for consideration.

"The newness of other condition of use" is, of course, broad terminology and serves to cover conditions which cannot be included under subjects previously discussed but which may well arise in causing a product to be a new drug. It might relate to the severity of illness in a certain disease, or to the degree of an emergency. It is possible that a drug use might be recognized as justified as a last resort measure in certain instances but would not be so recognized under other circumstances. There may be other examples which might well fall under this heading.

This discussion has followed closely the law and the regulation with respect to the definition of a new drug, since we are guided by them when we are requested to express an opinion on the new drug status of a proposed product. It is realized that even with these guideposts there are many borderline cases. At times we do not know whether a proposal for some combination of old drugs is merely the product of a pencil and a sheet of paper or whether it has a background of considerable investigation. In such instances we are much less hesitant to offer the opinion that a product is not a new drug if we are presented with a report of its successful use. When we express such an opinion, however, we are sharing with the distributor responsibility for its safety. Accordingly it is natural that we adopt a conservative attitude.

A tentative decision as to whether a product is a new drug may be made by either the Food and Drug Administration or the manufacturer. The latter may request our opinion in this matter, or he may form his own opinion without consulting us and proceed accordingly. In actual practice we are commonly consulted and our advice is usually accepted. If a serious difference of opinion arises which cannot be resolved, the Food and Drug Administration does not have jurisdiction in deciding the matter. This power is held by the Federal courts.

I have attempted to answer the question: What is a new drug? and to give you in a general way the criteria which we employ in reaching an opinion.

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July 30, 1956.

F-D-C REPORTS—"THE PINK SHEET".<sup>15</sup>

"FDA ducked the question of 'When is a new drug no longer new' in the regs, partly because important segments of the industry opposed spelling out when a 'new drug' is no longer in NDA status."

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May 29, 1957.

GEORGE P. LARRICK, Commissioner, Food and Drug Administration.<sup>16</sup>

"\* \* \* I should like to say a few words you may have heard before. Since, however, we continue to encounter this particular problem from time to time it may deserve some further emphasis. We are concerned when we find a drug product on the market which we consider a new drug, but find that there is no effective New Drug Application on file. We, of course, have the obligation under the law to take the proper legal action if we believe we can substantiate our views in court. This is not a course we relish taking, however. In most instances it appears that the manufacturer could easily have avoided the embarrassment, the inconvenience, the financial losses, and on occasion, legal action.

"When we have run into this situation we have advised the firm of our views concerning the new drug status of their product, asked that it be recalled from the market and not further promoted until they have filed a New Drug Application, and it has been made effective. It is obvious to you, I'm sure, that this represents a major and serious interruption to the company's business on that particular product, usually to their dismay. Executives in the industry can easily help prevent this from occurring in their own firms. Our New Drug Branch is always willing to express an opinion concerning the new drug status of

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<sup>15</sup> This comment appeared in an article (vol. 18, No. 25, p. 11), on new drug regulations which had been promulgated on July 25, 1956.

<sup>16</sup> Delivered at Annual Meeting of the American Pharmaceutical Manufacturers Association, White Sulphur Springs, W. Va., May 29, 1957, pp. 1-2.



a proposed product providing they are furnished sufficient information on which to base a judgment. This in effect is free insurance which is good business. It can save the necessity of undertaking costly and sometimes unpleasant actions. \* \* \*

September 23, 1957.

F-D-C REPORTS<sup>17</sup>

Prednisone has moved from "new drug" status in the view of the Food and Drug Administration (FDA), and both prednisone and prednisolone can now be marketed in oral tablets up to 5 milligrams without benefit of a New Drug Application (NDA), if they bear the "usual" labeling. However, under FDA's current regulatory view, NDA's are required when the two drugs are marketed in other dosage forms, higher strengths, or in combination with other drugs.

FDA's removal of the two drugs from the NDA requirement may accelerate a flood of "competitive" products to the market. With patent picture currently cloudy as a result of litigation pending in both the Patent Office and the Federal courts ("F-D-C" Aug. 26), elimination of FDA's NDA requirement removes at least one delaying step in the path of additional manufacturers who want to market products—providing they can get the material and care to run the risk that a patent will eventually issue which might put them out of the business.

Schering, which pioneered the two drugs, has cross-licensing agreements with Merck, Pfizer, Upjohn, and Parke-Davis, but recently at least several other companies also have marketed the two drugs, including U.S. Vitamin and Massengill. The latter is reported to be doing so under a patent held by Syntex which is claimed to cover the entire field. Schering and Syntex have filed suits against each other in the New Jersey and District of Columbia Federal courts. Schering, Syntex, Ciba, Merck, Pfizer, and Upjohn are parties to a Patent Office interference proceeding.

If the market becomes flooded with products offered on a price competition basis—pending clarification of the patent situation—a trend by manufacturers toward combination specialties may be anticipated. In fact, a number of combination products already are being marketed.

If the resolution of the patent controversy is delayed too long, the market for the two drugs themselves could go to pot—in the absence of FDA's NDA requirement. FDA, however, determined the need for the NDA procedure solely on the basis of the demonstrated "safety" of the drug under existing labeling.

Removal of a drug from NDA status is subject to no formal procedure, and simply reflects FDA's current regulatory view. In fact, there is no way for a manufacturer to know whether a drug is still on NDA status unless he specifically asks FDA. Usually, most drugs remain on NDA status much longer than prednisone and prednisolone which were first cleared through FDA and marketed by Schering in early 1955. As far as can be ascertained, some drugs remain in NDA status almost forever.

FDA control over promotion claims for prednisone and prednisolone will be retained despite removal of the drugs from NDA status. Under its NDA regs, FDA approves a brochure containing claims, indications, contraindications, directions, and warnings for "new drugs," and can threaten action to suspend NDA's if the brochure is changed. This tight control will continue because of FDA's proviso that prednisone and prednisolone do not require NDA's *if* they are marketed under the *usual* labeling. This means that FDA can require manufacturers to use the same claims, directions, contraindications, and warnings that were included in "official" brochures cleared for companies who did get NDA's. If these are exceeded, FDA can regard the product as a "new drug" again, and require an NDA from the manufacturer. This also means that manufacturers who have NDA's on the drugs are still limited to the claims in their "approved" brochures.

<sup>17</sup> Vol. 19, No. 38, pp. 13-14.



## EXHIBIT 141

## EXCERPTS OF COMMENTS ON THE ISSUE OF OFFICIAL REVIEW OF DRUG EFFICACY PRIOR TO ENACTMENT OF DRUG AMENDMENTS OF 1962

On page 786, Dr. Nestor referred in his testimony to the issue of whether or not the Food and Drug Administration had the authority to consider the efficacy of drugs, prior to enactment of Public Law 87-781. Numerous comments on this subject have appeared over the years.<sup>18</sup> A few such comments follow.

February 8, 1960.

WILLIAM H. KESSENICH, M.D.<sup>19</sup>

"While we cannot deny a New Drug Application on the basis of unsubstantiated claims unless such can be directly related to safety, this does not mean that effectiveness is ignored by any means, for how else can we establish the balance between benefit and hazard? Further, however, drugs, when marketed, are subject to the other provisions of the Federal Food, Drug, and Cosmetic Act. This includes the section which deems a drug misbranded if its labeling claims are false or misleading in any particular. In regulating drugs under this section, however, unlike the new drug section, the burden of proof in a Federal court is upon the Government."

May 9, 1960.

F-D-C REPORTS—"THE PINK SHEET".<sup>20</sup>

FDA DOES REQUIRE EVIDENCE OF EFFICACY TO CLEAR NEW DRUGS: SPEECH BY FDAER REPLIES TO MD CRITICS AT KEFAUVER HEARINGS

The Food and Drug Administration (FDA) does inquire into the efficacy of a new drug when clearing it for the market, Julius Hauser, assistant to FDA's Medical Director, declared in a May 5 speech that was frankly designed to answer criticism voiced during recent sessions of the Kefauver drug hearings.

Discussing FDA's administration of the New Drug Application (NDA) procedure at the St. Johns College of Pharmacy Seminar on Aerosol Technology, Hauser pointed out the basis on which FDA can reject NDA's and said:

This authority to refuse an application also gives FDA the responsibility to refuse any application until it has been adequately demonstrated that the drug is safe for its intended use.

Hauser observed that the new drug provisions of the Federal law make no mention of the need for submitting efficacy reports. Further, he said, there is no provision for refusing an NDA on the grounds that it fails to establish the efficacy of the drug. He added:

These facts may explain in part why some well-intentioned physicians have publicly criticized the drug manufacturing industry and the Government for permitting the marketing of new drugs inadequately tested, particularly with respect to their efficacy in the treatment of life-threatening conditions.

Although the misconception underlying this criticism may do no great injury to those critics, the misconception may be very costly to a drug manufacturer who submits an NDA. For this reason, it is important to develop a clear and correct understanding of the way FDA interprets and works with these provisions of the act.

*Good Evidence of Efficacy Needed for "Virtually All New Drugs"*

It is the deliberate policy of FDA, Hauser explained, to give the terms "safe" and "unsafe" as employed in the processing of New Drug Applications as broad a meaning as is reasonably possible to insure a maximum of protection to the public health.

<sup>18</sup> For additional comments by the Food and Drug Administration on this issue, see official replies by Commissioner George P. Larrick, as reprinted in exhibits 144 and 147, pp. 1018 and 1023 and decision by the HEW Department Hearing Examiner in the case of Altafur, exhibit 131, p. 948.

<sup>19</sup> "New Drug Review by the Food and Drug Administration," presented at the Pharmaceutical Manufacturers Association Central Regional Meeting, Chicago, Ill., p. 5.

<sup>20</sup> Vol. 22, No. 19, pp. 16-17.



This policy, he added, "makes it necessary for applications for virtually all new drugs to include good evidence that the drug is efficacious for the purposes claimed in its labeling, and generally the significant, potent new drugs cleared through the new drug procedure have been shown to be efficacious as well as safe."

It is only in cases involving essentially innocuous drugs employed in minor, self-limiting, or otherwise untreatable conditions, Hauser said, that the new drug provisions cannot be employed successfully to refuse an NDA for a drug that has not been shown to be efficacious. In cases of this type, he explained, FDA seeks to discourage unsupported claims by "persuasion." When this fails, he added, the NDA may be made effective, but regulatory action may be initiated on misbranding charges with FDA assuming the burden of proof that the claims made for the drug are false and misleading.

FDA's right to inquire into the efficacy of a new drug—despite the absence of specific authority to do so in the law—rests on the following "two basic concepts," Hauser said:

First, in the case of a drug offered as a treatment of a serious, life-threatening condition, FDA will not conclude that its safety has been shown until its efficacy has been demonstrated; this is particularly true when other reliable treatments are known.

Secondly, there are very few drugs which are not capable of producing some harmful effects. In such cases, FDA will not conclude that the drug is safe until there is adequate evidence to show that its usefulness outweighs its hazards. When the evidence establishes that the potential hazards of the drug are extremely small in comparison to the number of lives saved or prolonged in serious diseases, the drug is regarded as safe. Penicillin is an example of such a drug.

October 6, 1962.<sup>20a</sup>

WILLIAM W. GOODRICH, *Assistant General Council for Food and Drugs, Department of Health, Education, and Welfare.*

Misrepresentation does not reside wholly in the unorthodox treatment or in modern-day patent medicine. Indeed, it touches even the drugs promoted ethically to the medical profession; drugs that are used only on a physician's prescription. Secretary Ribicoff has recently cited a number of examples of such drugs. It is disturbing to learn that 22 percent of the drugs introduced since 1955 and evaluated since that time by the Council on Drugs of the American Medical Association are being promoted by some claims which the council considers unproved.

"Clarín" is one example.

The January 14, 1961, issue of the American Medical Association Journal contained an advertisement for the product, which is heparin potassium in a tablet to be taken under the tongue. The advertisement states that the drug has "demonstrated value" in "post coronary management," and that in a significant number of cases it has prevented recurrent heart attacks. Yet in the 1961 edition of *New and Nonofficial Drugs*, a publication of the AMA's own Council on Drugs, the same drug is given the following appraisal: "However, there is as yet no convincing objective evidence that heparin, given sublingually, either prevents or ameliorates any manifestation of cardiovascular disease. Hence, the use of heparin potassium in the hope of ameliorating the progress of atherosclerosis must be considered experimental."

The drug is being prescribed for these unproved conditions. While we cannot estimate its total sales, they exceed \$300,000 annually. Local prices are about \$8.50 for a bottle of 50 tablets. If 3 each day were the dose, the patient would be out over \$15 a month for what is probably an ineffective drug. The burden of this cost falls heavily on a post-heart-attack victim. Physicians prescribing the drug in reliance on claims such as are made in the advertisement are unwittingly experimenting with their heart patients at the patients' expense.

Promotional practices of that kind cannot be squared with the public interest. And the FDA will do all in its power to correct the situation.

<sup>20a</sup> Proceedings of the National Congress on Medical Quackery, op. cit., pp. 22-23.



## EXHIBIT 142

## REPORT PREPARED BY NATIONAL BUREAU OF STANDARDS TEAM ON FOOD AND DRUG ADMINISTRATION PROGRAM OF SCIENTIFIC AND TECHNICAL INFORMATION

In May 1962 the Data Processing Systems Division of the National Bureau of Standards reported to the Food and Drug Administration the results of a survey by a Bureau team as regards an overall technical information processing system for the agency. The report is printed in its entirety with the exception of a few forms which appeared in appendix A for illustrative purposes as regards maintenance of pesticide information.<sup>21</sup>

For a subsequent analysis by FDA's own Committee on Scientific and Technical Information, see exhibit 171, p. 1230.

FINDINGS, CONCLUSIONS AND RECOMMENDATIONS OF A COOPERATIVE STUDY OF THE WORK PROCESSES, PROCEDURES AND SYSTEMS INVOLVED IN THE COLLECTION, CREATION, EVALUATION AND APPLICATION OF CHEMICAL AND BIOLOGICAL INFORMATION AND DATA IN THE BUREAU OF MEDICINE, BUREAU OF BIOLOGICAL AND PHYSICAL SCIENCES AND FDA DISTRICT OFFICES

REPORT TO THE FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE BY THE DATA PROCESSING SYSTEMS DIVISION, NATIONAL BUREAU OF STANDARDS, DEPARTMENT OF COMMERCE

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## 1. INTRODUCTION

In September 1961 the National Bureau of Standards agreed to undertake a cooperative study of the information processing needs in connection with the technical activities of the Food and Drug Administration, including the "work processes, procedures, and systems having to do with the collection, creation, evaluation, application, storage and retrieval of chemical and biological information and data."<sup>22</sup> During the intervening period, the study has encompassed

<sup>21</sup> The subject of pesticide information was discussed at a hearing conducted by the subcommittee on May 23, 1963 (see "Interagency Coordination on Environmental Hazards—Control of Pesticides and Other Chemical Poisons," pt. 1, discussion with Commissioner George Larrick).

<sup>22</sup> (EDITOR'S NOTE.—This and succeeding footnotes appeared in the original N.B.S. report.) Memorandum of understanding between the National Bureau of Standards, Department of Commerce, and the Food and Drug Administration, Department of Health, Education, and Welfare, dated September 13, 1961.



the technical operations of the Bureau of Biological and Physical Sciences and the Bureau of Medicine of the FDA, and has maintained awareness of the operations of the several FDA district offices in this area of endeavor. A prime objective of the study has been an appraisal of the efficiency of the procedures and systems presently in use by FDA relative to fulfilling its technical responsibilities and an evaluation of the degree to which application of mechanized techniques might effect improvements in terms of speed, efficiency, and/or economy.

The NBS study team has investigated the information processing activities of the two designated organizational divisions. Problems associated with the Bureau of Biological and Physical Sciences have included those in the Food Division with respect to the harmful effects occasioned by chemical residues remaining on (1) raw agricultural commodities as the result of the use of pesticides, fungicides, herbicides, rodenticides, growth control substances, etc.; and (2) processed foods as the result of the use of coloring and flavoring materials, stabilizing and emulsifying agents, packaging, etc. In addition, consideration has been given to the means of checking on applicants' compliance with regulations concerning tolerances. The team has also studied information processing problems in the Division of Pharmacology with respect to the safety or toxicity of drugs, dealing with acute, subacute, and chronic toxicity, and with metabolic, potentiation, reproduction, and pharmacodynamics studies. Similar needs of the Division of Antibiotics have been investigated in connection with the study of the safety and efficacy of five major antibiotics and their derivatives. Likewise, the information processing needs of the Bureau of Medicine have been studied in connection with the processing of New Drug Applications and in connection with veterinary medicine.

This report presents the findings, conclusions, and recommendations of the NBS study team. A summary of the findings is presented in section 2 of the report. The primary conclusion reached by the study team is that there are indeed definite possibilities for improvements in speed, efficiency, and thoroughness of coverage in the processing of chemical and biological information used in the technical activities of FDA. These possibilities extend to both the requirements for maintaining current awareness of pertinent data and pertinent literature and the requirements for collection, storage, retrospective search, and retrieval of both data and information.

The possibilities for improvements definitely include the feasibility of ultimate mechanization of a large part of FDA's processing activities. Furthermore, failure to convert to modern methods of information processing may well result in progressively decreasing efficiency in FDA's operations and may actually prevent FDA from carrying out its legislative responsibilities.

It should be recognized, however, that major systems planning efforts must be directed to the interaction among the requirements for collection, evaluation, and application of information throughout the technical operations of the agency if mechanization is to be effective. In practice, direct translation from manual methods to machine methods does not allow for the design of an operational system that takes into consideration all of the advantages afforded by mechanization. It is recommended that the collaborative effort by NBS and FDA be continued over an extended period of time to plan and implement mechanization of selected portions of FDA's information processing. However, such a long-range plan of activity does not preclude concurrent initiation of experimental mechanization.

Therefore, it is recommended that the FDA take the following steps in the direction of conversion to improved information processing procedures:

1. The development, design and trial use of appropriate forms for the documentation of specific information usage and for the accumulation of pertinent chemical and biological data. The purposes of these forms for systematic recording include both the easy immediate use of the information by the researchers and the development of methods of input to a potentially mechanized data store. This recommendation is discussed in more detail in section 3 of this report.

2. The initiation of an educational and orientation program to acquaint technical personnel of the FDA with mechanized procedures for information processing and to provide the basis for a planned build-up of a systems approach to the meeting of present and future needs, as suggested in section 4.

3. The planning of an overall technical information processing system designed to meet the interdependent requirements of the various technical operations and to take maximum advantage of mechanized techniques. This might include, for example, the establishment of a centralized technical information service



to meet the information storage, selection, and retrieval requirements of FDA's scientists. It should be noted that while these requirements with respect to current awareness can be separated from those of search and retrieval in terms of possible short-range improvements, these two types of requirements should flow together in the planning and design of an integrated, mechanized system. Further details with respect to this recommendation are provided in section 5.

4. In addition, a special situation in the Division of Antibiotic Drugs suggests the possibility of relatively immediate mechanization of information retrieval procedures which can be isolated from the main flow and which can be separately managed with probable direct benefit. This special possibility is discussed in section 6.

Finally, sections 7 and 8 contain corollary suggestions, recommendations, and comments that have developed as a result of our experience in conducting this study, in accordance with section II.2 of the Memorandum of Agreement under which we have carried out this work.

## 2. FINDINGS

Scientific and technical information is increasing faster than even the most experienced and capable FDA researcher can absorb or evaluate it. Because of the accelerated rate of increase of such information, this situation can only grow more critical daily. The difficulty for FDA is compounded by the additional responsibilities with which it has been charged by Congress. It now seems essential that FDA promptly consider the acquisition of some means to provide its staff with timely, easily available, and pertinent reference material, with the corollary potential for searching for and correlating information and data. FDA is in a crucial period of change during which immediate availability of data and information is mandatory to the maintenance of orderly routine operations.

The nature of this principal problem with respect to technical information processing in FDA is by no means unique to FDA. Rather, it is becoming increasingly well recognized as crucial to continuing effectiveness of utilization of both scientific and decisionmaking resources. For this reason the deficiencies in present systems and procedures for collecting, evaluating, and applying information are less a reflection on any specific situation in FDA than they are an indication of the outcropping of a much more general phenomenon, as well as a warning that radically new techniques must be explored to meet the steadily growing workloads.

The situation as investigated at FDA does reveal some particular factors which make the requirement to seek new solutions especially urgent. The burden of heavy workloads, especially where new and expanded technical responsibilities are being assumed, leads almost inevitably to breakdowns in communication, as between person and person, from case to case, with relationship to prior decisions, and with relationship to the pertinent reference material. With the rapid accumulation of scientific and technical information in all fields, retrospective material as well as current awareness information must be made available to the researcher who needs it.

There is at present no official central repository of information that might serve as a guide to FDA analysts who seek a suitable method for examining a new combination of drugs or chemicals. If a member of the staff has developed a new method of analysis, he has no established means to make it available to others. In addition, there are many kinds of information now being generated at FDA which are not routinely recorded or maintained in a systematic manner in a central location. This information is thus not always available to others who may need it.

It is particularly important and urgent that some means of establishing a centrally available file or files, as a repository of all FDA decisions and the technical data upon which the decisions are based, be considered before FDA loses, through retirement or attrition, the experience of its capable trained technical staff. Their fund of experience, accumulated over the years, forms the basis upon which rests the present applications and petitions review, and, indirectly, the entire FDA decisionmaking structure.

In order to become acquainted with the scope and magnitude of the operational and data handling requirements of the FDA, the NBS study group has interviewed technical personnel of FDA, librarians, and other personnel who are concerned with FDA's informational needs. Much of the data and information handled are encyclopedic and almanac-like in character; FDA's complex operations are concerned with data which range from the very general to the



very specific. Often, it is impossible to obtain the exact information and data that are required to render positive and clear-cut decisions. This situation exists because in some cases the information is inaccessible or nonexistent; in others, techniques have not yet been developed for handling and retrieving it.

One of the handicaps under which both NBS and FDA personnel have operated since the inception of this project has been the lack of understanding of machine methods on the part of FDA technical personnel. Furthermore, there is evidence of lack of familiarity with the types of assistance that might be made available to hardworking staff through the use of reference services and other information aids. Of even more significance, there is considerable variation of opinion from individual to individual in the interpretation of the nature and relative importance of supposedly similar information.

For these reasons, it is believed desirable that a series of indoctrination and orientation lectures be given to those persons in FDA responsible for planning and using a mechanized information processing system. The seriousness of this problem is believed to present difficulties of so grave a nature that it is strongly recommended that FDA give consideration to providing for such a course before proceeding further with mechanization planning.

Under these circumstances, the major findings of the NBS study team may be summarized as follows:

1. A number of deficiencies in information processing procedures do exist in the technical operations of the FDA, but these are of a general rather than a specific nature, reflecting a generally critical problem in the adequate utilization of scientific and technical information. The nature of the problem at FDA is complicated by the fact that the information processing needs cover a wide subject matter spectrum and that, under present workload conditions, there is little or no opportunity to ascertain and coordinate the overall requirements.

2. It is certainly feasible to begin now the systematic planning for ultimate mechanization of information collection, storage, search, and retrieval operations, including possibilities for selective dissemination to potential users of specific new material. In view of present and anticipated workloads, the problem is urgent. The importance of making a start in the determination of needs for new or improved techniques for information collection, storage, search, retrieval, and application cannot be overemphasized.

3. Specific suggestions for total mechanization in an overall system for FDA are premature until such time as a major systems study has been made, until present widely divergent opinions as to the relative importance of different kinds of information have been reconciled, and until the interactions between information processing operations throughout the technical organization have been re-explored in the light of modern machine techniques.

4. Concurrently with the initiation of systems studies, the possibilities for applying one or more of a variety of new or improved information aids to small, manageable problem areas can be explored, including the possibilities for experimental mechanization of selected, isolatable information processing operations.

### 3. RECOMMENDATION 1: INFORMATION RECORDING FORMS

The NBS study team recommends that one or more sets of forms for documentation of information be developed and subjected to trial use. The set of forms will be purposely designed to obtain the maximum of information suitable for FDA's recordkeeping operations at the present time, and will be an excellent source of accumulated information to make up the initial store for a mechanized file in the future. Consideration of FDA's information processing needs must take into account the means for fulfilling these needs. Automation of data retrieval cannot be considered apart from the collection aspects of the problem. Any plan for eventual machine manipulation of data dictates the need for the systematic recording of all pertinent information as it is received or generated. These data can be comprised of administrative and operational data, as well as the technical and scientific information. When such data are recorded on well-designed forms according to a regular prescribed pattern, their transfer to a mechanized storage medium is a relatively simple operation which can be accomplished by clerical personnel.

In order to accumulate information which might be used as source material for a mechanized file, a set of trial forms has been designed for recording the



scientific information required by technical personnel of the Pesticides Branch of the Food Division. These forms might also be used as a means of retrieving or exchanging information in an organized format until such time as mechanization is installed. (Such a set of forms could have the added advantage of reminding petitioners of essential information to be furnished to FDA.) A set of sample forms is attached as appendix A. The set is intended to be the basis for the design of an improved version, revised in accordance with the experience and suggestions of FDA's technical staff in the Pesticides Branch. In addition, we anticipate that they will provide the stimulus for the development of similar sets of forms for food additives, new drugs, and antibiotics, mindful of the obvious need for including additional specialized information and data in each such set of forms. Empirical use of such forms would by no means prevent their replacement with other sets reflecting later improvements, as increased experience indicates need for further revision.

The systematic recording of information on the forms by administrative, clerical, and technical staff of FDA should impose only a small additional workload, since the information to be recorded will usually be at hand or immediately available to those with responsibility for listing it at the time an application or petition is under consideration. When information considered necessary to make up a complete file entry is not at hand, a research assistant might be engaged to acquire the missing entries so that the technical staff would not be burdened with such ancillary problems. Assuming that the systematic arrangement of data in the forms has been properly engineered, the subsequent effort required to translate such data from the forms to another medium or other media, as operating practice requires, should be slight, involving only the efforts of clerical personnel.

There is a distinct advantage to the immediate employment of forms for the purpose of accumulating a mass of (1) recordkeeping data and (2) scientific and technical information in such a way that when the need arises for their manipulation by machine, these data can be transferred directly to another medium to form the basis for a mechanized file or store for FDA's information retrieval operations. An orderly arrangement of data and information on the forms will tend to make it easier to develop a well-structured file organization for the eventual mechanized store, which in turn will facilitate information retrieval from the automatic data handling viewpoint.

#### 4. RECOMMENDATION 2: EDUCATIONAL AND ORIENTATION PROGRAM

The NBS study team recommends that a progressive educational and orientation program be initiated promptly under the leadership of the present Systems Development Branch or its equivalent. This recommendation is made because it is necessary to develop within FDA the basis for extending their staff competence to include the knowledge of new techniques so that effective information processing activities can flourish. Such a program will constitute the initial step toward achieving the kind of environment in which the information processing activities can best develop to meet present and future requirements.

The recommended educational and orientation program should be directed to three important aspects of the overall system design problem. These are (1) familiarization with mechanized techniques and the new potentialities offered by automatic information processing methods and equipment; (2) familiarization with a variety of possible information aids, whether or not mechanized; and (3) familiarization with the kinds of requirements imposed by systems planning in order to determine realistic user requirements for a mechanized system.

It is particularly important to recognize that the introduction of new and mechanized techniques is only a means to an end. The active participation of subject matter specialists in specific feasibility studies is required just as much as is their leadership in establishing overall goals and in considering the interdependence of the information processing requirements in the various technical operations.

Someone or some appropriate grouping of the scientific staff within FDA will have to participate in the responsibility for deciding what categories of information will be put into the mechanized store at the outset, what kind of storage information and retrieval system will be instituted initially, and what type of equipment will be purchased or rented, if equipment other than that now available or soon to be available to FDA is required. These three decisions obviously require different combinations of scientific and planning staff participation but a common-thread collaboration will be required.



In order to promote a more rapid development of a favorable environment for the growth of FDA's information processing programs, it is believed desirable to provide for the series of indoctrination and orientation sessions for all management and technical personnel in FDA who will be responsible for planning and using a mechanized information processing system. The purpose of the lectures and seminars is to acquaint FDA with the potentialities inherent in mechanized information processing, to discuss difficulties to be overcome in conversion to mechanized handling of information, and to assist in orientation toward machine philosophies in the planning of workloads.

Subsequent educational efforts with respect to appreciation of the potentialities of machine techniques may take the form of "learning by doing," especially as soon as it proves practicable to proceed with experimental mechanization on a small scale.

The second aspect of the orientation and indoctrination program is that of familiarizing FDA staff with available information aids, some of which could be put to use quite rapidly; use of others would depend upon the results of the overall systems design efforts. There is a variety of such aids, ranging from conventional library tools to new techniques and services which might be implemented in either a manual or mechanized form. More general and more consistent use by FDA staff of conventional reference services would, for example, provide some immediate improvements in operations involving access to pertinent previously reported data.

This aspect of the orientation and educational effort would also be directed to exploration, as appropriate, of various new techniques for information storage, selection, and retrieval, ranging from manual methods to inverted file or peek-a-boo techniques, to microfilm storage and retrieval devices, and to devices that combine microfilm storage and retrieval with a mechanized copy search-selection system. Appendix B illustrates some of the subject matter that might be covered in a series of presentations on these techniques. In particular, information selection and retrieval devices might be investigated with respect to relatively isolated information processing operations which can be kept reasonably separate from the main stream of information flow in FDA. Such a situation appears to exist in the Division of Veterinary Medicine, as discussed in a later section of this report.

The third and final aspect of the recommended educational and orientation program relates to the need to develop and apply efficient factfinding techniques in order to define realistic user requirements for the overall systems design effort. Here, the design and use of sets of forms for the documentation of information now required, as discussed under recommendation 1, should serve to assist in familiarizing the staff with the kind and degree of detail that is necessary for the planning and use of mechanized procedures. Use of the forms should help to pinpoint and focus attention on specific problems with respect to the availability, reliability, and completeness of technical data that are needed. Finally, the information derived from recording the pertinent data in a systematic way on well-designed forms could serve as the basis for a compilation of an experimental handbook or "directory" of facts, tables, indexes, and decisions useful to each researcher at his desk.<sup>23</sup> In turn, trial use of such a handbook would elicit user reactions and more precise definitions of requirements for implementing subsequent mechanized versions of a periodically updated personal reference tool for planning the structure of a mechanized data file.

##### 5. RECOMMENDATION 3: PLANNING AN OVERALL TECHNICAL INFORMATION PROCESSING SYSTEM FOR FDA

The findings and conclusions of the NBS study team come to a single focus on the need to initiate as rapidly as possible the planning of an integrated comprehensive technical information processing system. Mechanization of specific operations today, although technically feasible, cannot promise any continuing benefits with respect to speed, economy, or efficiency in present procedures unless serious long-range consideration is given first to overall objectives, interdependence of present and desired operations, and the determination in detail of actual usage requirements. Without a major systems planning effort, mechanization offers no solution to the problems of improved utilization of scientific and technical information, which become more critical daily.

<sup>23</sup> This possibility is discussed in more detail in sec. 7 of this report.



In practice, it has usually been found to be unwise to transfer the traditional handling of manual procedures to mechanized operations without a new system design which approaches the problem from the standpoint of specific machine characteristics, including particularly both machine shortcomings as well as machine capabilities. A direct translation of manual methods to machine methods normally produces an inefficient program which does not take advantage of the features afforded by automation. There are many other factors which affect an orderly transition from manual to mechanized procedures.

In recognition of the long-range needs of FDA, NBS believes sufficient planning time must be allowed. Consideration must be given to the quality, number, indoctrination, and organizational location of the FDA staff members necessary to carry out the comprehensive systems planning required. Development of mechanized information processing systems cannot be effectively pursued through occasional part-time participation on the part of an already overworked FDA staff. It needs to be the full-time occupation of knowledgeable and meticulous investigators who give it their full and first attention.

Since FDA's data processing needs cover such a wide spectrum, with diverse categories of subject matter, a simultaneous attack on all of them may not be feasible in the light of FDA's manpower resources. Before one can hope to handle intelligently the task of making plans for organizing and manipulating such a large heterogeneous mechanized file as that ultimately required by FDA, it may be advisable to study first a representative sample of the file to determine typical usage requirements. It may be well, therefore, to consider the mechanization of one complete area, such as pesticides or food additives, and undertake experimental operation of that area while systems design is still evolving in the mechanization of other areas, influenced by feedback factors from the empirical results of the ongoing data processing operation. The adequacy of the proposed approach can be economically explored by mechanization of one category of information, rather than by attacking at one time all of FDA's information processing requirements.

There are some categories of information in FDA which lend themselves to immediate processing by automatic means. There are other areas in which to date no well-defined procedures have been developed which are satisfactory for general application. One example of the latter is that of chemical structure searching. For limited areas or for small stores of chemical structure information, systems have been developed which have proved to meet limited requirements. When potentially very large magnetic files of stored information are to be searched, the search time becomes such an important factor that it is no longer economically feasible to consider use of the systems developed for small collections and limited, special purposes. There is a great deal of research going on at this time in chemical structure searching techniques; most of it has the purpose of meeting specialized needs for the sponsoring organization. FDA cannot be sure that research now being carried on by other organizations will fully satisfy its requirements. Here, again, the need for a competent planning staff, thoroughly familiar with FDA objectives and requirements and knowledgeable with respect to machine capabilities, is obvious.

NBS considers the planning, organization, and installation of a well-designed information file, capable of serving the needs of all of the technical activities of FDA, to be of primary importance in the systems planning effort. Such a file, especially in mechanized form, should represent a repository of all of FDA's technical information, whether generated in-house or acquired from outside sources, and the nature of the file organization should permit integration of related items in a large variety of ways. Provision should also be made in the file organization for the employment of sophisticated retrieval techniques, and correlation of fragments of structure with biological effects, physical or chemical properties, and the like.

A central mechanized file for FDA must be as complete as possible. The file organization and arrangement should be such as to enable the user to obtain answers to his inquiries with a minimum of inconvenience and in a reasonable time period. In many instances, it may be desirable to compel the system to try to predict the optimum amount of data required in fulfilling a request so that subsequent requests may be reduced. Conversely, an arrangement is desirable which does not overwhelm the questioner with too large a body of data.

A central facility which has in store, in the form of machine-usable records, the accumulated experience of the present technical staff would have the additional advantage of expediting the training for effective use of inexperienced reviewers. Another value of a central repository of information is that it ex-



tends to cover information related to those functions which cross Bureau lines; pharmacology is a case in point.

As an illustration of the difficulties of system design for a complete mechanized file, and of the importance of an early start in systems planning, a sample file entry which might include most of the information required for a pesticide inquiry is outlined in appendix C. There are also listed possible cross-reference access points for obtaining some parts of this file entry information from different viewpoints. Interrelationships among items are of significance in the light of some of FDA's requirements; provision must be made for linking or connecting such items, regardless of the structure of the file organization of informational material.

Provision must also be made for examination of data in many forms: graphic, tabular, English language text, condensed symbolic representations for large bodies of information, etc. A textual datum may in some cases consist of several paragraphs of text, as well as diagrams. It is not always easy to develop means of representing all of this information in machine form. The usefulness of any datum may depend upon its age, and the additional factor of reliability of information with respect to age, means of deriving it in the first place, etc., must be taken into account when designing the system. Another concern of FDA is that some of the information is proprietary in nature and may be divulged only on a limited basis. In such cases, some sort of flag must be attached to indicate this restriction.

Further detailed consideration of FDA's future needs for mechanized information processing may quite probably point to the necessity for the establishment of an information center or centralized information processing service. This would have the effect of placing responsibility for meeting all of FDA's information processing requirements within a single organizational unit. This would concentrate in one place the various related units whose functions affect FDA's total information processing system. Any machine system to be adopted would comprise a vital part of such an information center.

Therefore a major part of the NBS recommendation for a systems planning effort is that early consideration be given to the establishment of a central information center as a separate organizational unit of FDA. This information center, in addition to providing data as a basis for FDA decisions,<sup>24</sup> should be the repository of all its decisions, some of which are precedent making, others of historical interest.

Such an information center would undoubtedly require some mechanized equipment, but it is premature to discuss its equipment needs at this time because the functions it is to serve have been neither fully identified nor carefully delineated. However, it is not premature to mention one of the activities which should form a basic part of the information center: a reference service for all of FDA.<sup>25</sup> Indeed the first step toward achieving a coordinated information center for FDA would seem to be the establishment of a central reference service.

Long-range planning for FDA's needs for scientific and technical information must take into account the need for and consider the establishment of a centralized reference service. It is an essential if FDA is to maintain current awareness of the results of research and development in areas which concern it and which must be taken into account in its daily operations. It is also a necessity in order to have available the multitudinous kinds of information and data which FDA requires for orderly and effective functioning. Mechanized equipment can be acquired to supplement manual efforts as the need for it is shown and as techniques for employing mechanization are developed.

If a portion of FDA's information requirements is mechanized, a comprehensive list of questions which technical personnel of FDA would put to a machine file will be necessary in order to check the ability of the system to provide the

<sup>24</sup> The importance of systematizing FDA's technical procedures, where possible, will increase with the number and complexity of decisions that are deposited in the central information processing center. There exists a great potential in making a careful study therefore of FDA's present decisionmaking practice with a view toward systematizing the procedures as a pattern for future practices. This model system should be planned to provide guidance to trainees and inexperienced personnel and to supplement experience of other personnel.

<sup>25</sup> A prototype for such an organization now exists in the Bureau of Medicine. More detailed suggestions for the expansion of reference library services are provided in section 7.



proper response. The areas covered by such queries should range from the very general to the very specific, and the systems design should provide a feasible means for handling either extreme. It is hoped that an experiment with a small portion of the information processing needs can provide a general outline of the basic philosophy for the organization of the overall information system. This fragmentation of the problem should have the advantage of dealing with a small manageable piece of the problem before combining the various information handling pieces into a complete entity.

Some of the problems inherent in setting up a small machine experiment in information processing are (1) design of a suitable system, (2) data preparation for the machine file, (3) means of data addressing, (4) means of entry for querying and updating, (5) determination of the numbers and types of personnel necessary for maintaining and operating the system, and (6) introduction of its rationale to the personnel of FDA. Solutions of these problems will help to advance the overall approach to mechanized data and information handling in FDA, and assist in pinpointing the areas where mechanization will prove to be most advantageous.

FDA now has many information processing requirements which would lend themselves to mechanization. There exist complicated relationships among some of the data categories. It is desirable to incorporate into a planned mechanized system the means for connecting such related items, when the particular kinds of connections cannot always be anticipated. There exist several machine techniques for accomplishing this type of operation, and it may be to the advantage of FDA to employ more than one to determine which procedures have greatest utility for FDA in each such situation. An example of this type of FDA application is that of relating a main file entry, which contains a complete description of all data associated with a petition (or application) including physical properties and biological effects, etc. (see appendix D), to a listing in another portion of the mechanized file of a particular kind of biological effect.

The desirability of proceeding concurrently with initiation of general planning, limited experimental mechanization, and acquisition of familiarity with advanced machine techniques will undoubtedly be justified in the findings from such experiments. For example, it may prove to be of considerable advantage in file organization to employ string language or list processing techniques<sup>28</sup> to chain together information links in certain instances: one FDA application of this type of example is that of linking various uses (on different commodities) for the same pesticide. This type of procedure is particularly useful for adding new entries or parts of entries to the file without making major file structure changes. In this sense, it can be used for making "up-dating" additions. Because of the need for completeness of information, it is necessary to insure that the structure of the file organization is such that new information may be added promptly with a minimum of effort. This should therefore be a major concern in the recommended systems planning effort.

#### 6. RECOMMENDATION 4: EXPERIMENT IN SIMPLE MECHANIZATION

Since there appears to be little interaction between the searching requirements of the medical staff in the Division of Antibiotic Drugs who are concerned with veterinary medicine and those of most of the remainder of FDA's technical staff, NBS believes that this part of the information needs of the Division of Antibiotic Drugs represents a self-contained portion of FDA's total information processing requirements. Because of the nature of their information requirements, this particular segment has been identified as a recommended area for experimental mechanization. At this juncture, it appears that a relatively straightforward system could be installed at once to handle the imminent information processing needs of veterinary medicine in the Division of Antibiotic Medicine. Experience with such equipment in this limited area could give indication as to its suitability for additional FDA use.

The veterinary medicine antibiotic drugs researchers are concerned with certifiable antibiotics and their combinations with other drugs, food additives, pesticides, or other materials. There are now approximately 60 different formulations, but each of these formulations could have 10, 20, or more different quantitative variations. Once a particular formulation has appeared in the

<sup>28</sup> See bibliography, references 2 and 3.



Federal Register, other manufacturers may submit the same formulation without any background data. Because these manufacturers are likely to vary the formulation quantitatively, the Division of Antibiotic Drugs must know the maximum and minimum amounts they have granted previously. Thus, there is a requirement to locate the original data as quickly as possible, as well as to make sure that the new applications specify exactly the same formulation, the same species, dosages, and route of administration for the same disease or diseases.

There are several approaches which might be taken to mechanize the file in this fairly well defined area. One of the simplest and least expensive mechanical searching and retrieving devices involves the use of the McBee Keysort cards, where searching is accomplished by use of a needle. The needle is placed in the proper notch and the desired cards fall out. As many parameters as needed can be used for searching and the search is successfully refined from one index term to another. Attached as appendix D is an example of a card and an indication of how it might be designed to aid Antibiotic Drugs.

Other possible approaches could involve the use of several different conceptual systems for indexing, search, and retrieval which have worked quite effectively for small special-purpose data or document collections, and several different devices for mechanical selection and retrieval.

#### 7. RELATED SUGGESTIONS

As indicated in previous sections of this report, certain practical steps could be taken by FDA in the near future to provide for the extension of present reference services and to provide trial familiarization with new possibilities leading to eventual mechanization. The NBS study team therefore suggests two specific areas for consideration.

The first area is the extension of reference library services looking toward a central reference service for all of FDA.<sup>27</sup> As has been noted, a prototype for such a general reference service now exists in the Bureau of Medicine. The Medical Reference Section was designed primarily to serve the Bureau of Medicine staff and to a lesser degree other bureaus of FDA. It also assists other Government offices and libraries on questions regarding identity, composition, and source of brand name preparations and on questions regarding literature references on drug toxicity. It is responsible for the collection and organization of the Bureau of Medicine's literature collection, in which there are presently some 3,000 books and 200 journals, the titles of which are circulated monthly.

In addition, material received in the branch such as pamphlets, field reports, correspondence, etc., is reviewed and 3 by 5 abstract cards are made on items having to do with toxicity, therapy, etc. The monthly average number of cards, including cross-references, is 650. FDA precedent material, which includes statements of policy, news releases, speeches, etc., makes up part of the collection, as well as 500 special subject files that are maintained to supplement the abstracts. These include such things as accidental poisoning, drug reactions, vitamin supplements, etc.

The Reference Section performs the following services: automatic routing of certain journals according to circulation lists, arranging for interlibrary loans, and filling requests for information. There are also two special programs: adverse reaction reporting program and the hazardous substances program. In addition, it issues a weekly accession list of additions to the book and journal collection of the Bureau of Medicine.

There is reluctance on the part of some researchers and technical workers in any organization to make use of library and reference facilities available to them. In some cases, this failure is occasioned by inadequate formal training on how to exploit such facilities. Again, there is sometimes incomplete knowledge of the kind and extent of assistance available through use of the reference services. In yet other instances, the use of such facilities in some organizations is surrounded by such hampering difficulties or awkward operational procedures that researchers tend to become discouraged in their attempts to use such resources.

It is important that information and reference facilities be made easily available, and that their use be encouraged by ready and assisted access to them in the form of lists of new accessions and the generation by FDA of pertinent new material. In addition, it is desirable to acquaint the technical staff with announcement bulletins and other reference services available from other agencies.

<sup>27</sup> It is our understanding that a study is now being made looking toward the establishment of a central reference library to serve all of FDA.



The NBS study team has several specific suggestions for extending the reference services, as follows:

1. FDA should institute the periodic circulation of announcement bulletins or accession lists which contain author, title, and abstract, and other useful descriptive cataloguing material. Such information is now extracted from the journals and entered into the card files in the Bureau of Medicine. It can be made generally available at a slight increase in cost over that of the present entry into the card files. It is believed that any increased effort would amount to little more than that of inserting extra carbons in typing operations.

It would seem desirable to arrange the announcement lists in sections, by category, according to user needs; these could then be circulated in sections, with each recipient (assumed to be the FDA reviewer or other technical employee) obtaining only the announcement of material in the category of interest to him. (However, some categories of a general nature will undoubtedly be of interest to all recipients.) The effect of this procedure is to establish user profiles of interest. It may be of interest to note one example of what other companies are doing in this area.<sup>28</sup> The adoption of this procedure would insure a minimum of nonusable data normally going to each researcher; the receipt of large amounts of nonusable data normally has the effect of decreasing the use made of useful information. Some examples of such listings reflect an arrangement which has been deliberately designed to promote the clipping of individual items for personal files. It is sometimes desirable to provide for such duplicate information in a form which lends itself to easy use by the individual user.

2. FDA should consider the production of special bibliographies, as required. So long as the reference material collected from journals, FDA decisions, and other sources is maintained in a systematic manner, it is possible to produce without considerable effort, from time to time, special collections on particular subject matter, either in the form of special bibliographies or segmented files on desired topics. The periodic or occasional production of such reference material could well become an additional function performed by the reference service making up a part of the information processing activity. When mechanized information processing becomes available, the production of such accumulations can become largely a by-product of normal routine operations. Special-interest profiles can be initiated so that regular dissemination of new material on a particular topic will go as a routine procedure to the selected individuals. These activities will facilitate the collection and merging of information on particular topics so that requests for such compendia may be anticipated and filled immediately when required.

3. FDA should explore further the use of reference material from other repositories of scientific and technical information, for example, those of ASTIA, OTS, and NLM. It is recognized that FDA is now making use of the library facilities of the Department of Agriculture. When situations warrant making such a request, special searches of the collections of other agencies in the vicinity should be considered. As mechanization increases in the technical libraries of other Government agencies, FDA should look toward the possibility of exchanging information in machineable form.

FDA will undoubtedly want to consider the question of where best to fit an information center into its organization structure. However, decisions as to the final form of such a center should not delay FDA from taking immediate steps to initiate a central reference service with some of the functions as described above.

NBS believes that FDA's technical staff would benefit substantially from the provision of pertinent reference material in a form both convenient to use and available at the desk of each technical worker, e.g., in handbook form. Such a handbook might conceivably be a selective compendium, in hard cover, paperback, or looseleaf by section, of the information most frequently required by FDA reviewers and other professional and technical personnel.

A second area recommended by NBS for investigation and trial application is therefore the preparation and use of a reference handbook or directory. The book should be organized from the point of view or "access point" of the researcher who initiates requests for information. Entries in the book should consist of the information most frequently desired by the researcher, arranged in the form most convenient for his use. In some cases the entries might consist

<sup>28</sup> See bibliography, references 4 through 7.



of tables, in others of dictionary-like references, synonyms, or cross-references to more complete entries of the information contained in other sections of the book. Indexes to other sources of vital information would also be provided. In yet other instances, the information might appear in a condensed form of the original version.

Planning and preparation of the handbook should meet the criteria that the information be readily accessible, well-organized, easy to use, legible, and, hopefully, attractive in format. Considerations with respect to legibility and format include such factors as good resolution and appropriate type font. A "last carbon" appearance, a badly reproduced copy, or type font too small to read produces a psychological discouragement to determining the contents of the document.

Plans for accumulating and arranging the information content of the handbook must take into account the necessity for periodic reissue to update the information by the incorporation of new material that is constantly accruing in the files—at least once yearly. FDA now provides its reviewers with information generated in-house, e.g., lists of tolerances for commodities in the use of pesticides. The contents of the handbook should include all such information developed or generated at FDA, or solicited by FDA, as well as data furnished by the petitioners and information to be obtained from the open literature. The specific contents will be determined largely by the successful establishment of the information file organized with eventual mechanized storage and handling in mind. The information included in the handbook must necessarily contain a certain amount of redundancy to reflect multiple entry under headings which have been chosen from several different access points. This is recommended in order to promote ease of finding desired information in much the same way as in the classified telephone directory.

An FDA directory of facts, tables, decisions, reference material, and the like could be produced routinely, including the updating operation to add new material, after accumulation of the initial document content. Indeed, the directory might be issued in several sections which could be bound separately to reduce to a manageable size the amount of data which any one researcher might want to scan. Improvements, additions and updatings could take place at the time of the periodic reissues, in much the same way that a telephone directory is re-issued or as the yearly accumulations of *Index Medicus* are brought together in an annual publication. When mechanized information processing is undertaken by FDA, the material for such a directory should, of course, become part of the mechanized files. The issue of the reference material in the directory could well form one of the periodic routine outputs of mechanized processing and should be a useful by-product of mechanization, if not its primary concern. When such material has been made available in hard-copy form, many of the information requirements of the technical staff will have been anticipated, so that the consequent requirements for retrieving on-request technical information from a mechanized installation will be considerably reduced.

After an initial use period of such a directory indicates both its utility and its shortcomings, revisions can then be undertaken to improve its efficiency. Cross referencing to redundant or related items can form part of a more sophisticated organization of the file material<sup>20</sup> as experience dictates such changes. Development of machine methods for automatic handling of information in the magnetic store will encourage the evolution of more ambitious file structures. It is anticipated that the development of such extended file structures will go far toward meeting FDA's information retrieval requirements. As machine techniques are developed which make possible mechanized preparation of reference material, FDA can still retain the facility of manual use of hard-copy information, made available through the mechanized installation.

Expansion of the reference services and the creation of the handbook or directory together provide an early approach to a central reference service and to the mechanized information center. It is important that information and reference facilities be made easily available to the FDA researchers, that the use of such facilities be encouraged by ready and assisted access to useful data and information, and that FDA staff have effective reminders of material available to them in the form of lists of new accessions and the generation by FDA of pertinent new material.

<sup>20</sup> Here "file" refers to information and data in the mechanized store.



Needless to say, the growing information collection should be as complete and timely as it is possible to attain, with proper regard for appropriate organization of this central store of information. The new approaches to current awareness and to retrospective search together will increase significantly the chances of finding complete answers to most requests. This in turn has the result of greater encouragement to the technical staff to make use of such facilities. Legible and attractive output will enhance use of the facilities of the information center.

#### 8. IMPLEMENTATION

The findings, recommendations, and related suggestions of the NBS study team raise certain important policy questions for FDA consideration. In particular, the question is raised of appropriate organizational structure. If FDA is indeed to embark on a systematic plan for the mechanization of its information processing operations, it is well to consider who in FDA will be responsible for the successful accomplishment of the project. If such authority is vested in a single organizational unit, FDA can retain control over its actions by holding the unit responsible for meeting FDA's needs with respect to information processing. This is true regardless of whether the unit is one person or a group of persons.

During the period of the study, the NBS team has worked with various members of FDA's technical staff, all of whom are already overburdened with work. Time spent with NBS staff has necessarily shortened the time which FDA's technical staff has had available to carry out its normal workload. It is apparent to the NBS study team that FDA's professional personnel take great pride in their work, and that they must consciously or unconsciously resent any activity which prevents or delays the normal discharge of their responsibilities. Completely aside from the lack of time which they have available for exploring with NBS the means for developing mechanized aids to assist them, there is considerable difference of opinion among individuals as to the relative importance of different kinds of information. Development of mechanized information processing systems should, as previously noted, be the full-time occupation of assigned personnel. A group to which such responsibilities would be assigned would normally be called the "Research and Development" unit, or the "Operations Research Group." NBS respectfully calls to FDA's attention the existence of such groups in other organizations where situations similar to FDA's needs have been encountered, e.g., the U.S. Patent Office.

An R and D group could assume responsibility for determining operational areas amenable to mechanized processing and for establishing priorities. Such a group could and should anticipate FDA's research requirements and relieve the working staff from the dual burden of future planning and the execution of present workloads. Since an R and D group would have no responsibility for ongoing operations, its staff could be devoted completely to the development of techniques for FDA's information processing and to research in areas where no satisfactory means have as yet been found for handling certain kinds of information.



In the absence of an R and D group of its own, it is believed that the mechanization of FDA's information processing can best be accomplished by the reassignment of some of its technical personnel to work with NBS personnel as a permanent working arrangement. The effect of this action would be to accelerate the systems planning stage. Without the active participation of FDA personnel, the NBS study team must spend a great deal of time in eliciting information; such information is of necessity incomplete because no one is able to give complete information on every facet of the subject being studied. The information he reveals is (again of necessity) subjective. The nature and character of supposed similar information varies from individual to individual, as well as the relative importance placed on different kinds of information. NBS therefore takes the position that if FDA is unable to add a suitable organizational unit as discussed above it is necessary to NBS's further participation in the project to insist that qualified FDA technical personnel be assigned to work on a full-time basis.

A second major organizational question relates to the location of the proposed centralized information center. There is attached as appendix E a very simple flow diagram to indicate a proposed flow of information to and from such a center, and the possible structure of such a center. NBS believes that the installation of a well designed processing center is essential to meeting FDA's long-range information needs.

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## APPENDIXES

## APPENDIX A

## SAMPLE SET OF PROPOSED PESTICIDE FORMS

## I. GENERAL TECHNICAL INFORMATION

1. IDENTITY #	9. STRUCTURAL FORMULA
2. COMMON NAME	
3. TRADE NAME	
4. CHEMICAL NAME	
5. GENERIC NAME	
6. MANUFACTURER AND ADDRESS	
7. LEGAL CLASS	10. CIPHER
8. U.S. PATENT OFFICE NUMBER(S)	
11. PURPOSE FOR USE	
12. COMPOSITION OF CHEMICAL AS OBTAINED COMMERCIALY	
ACTIVE SUBSTANCE	% TO %
IMPURITIES	% TO %
13. RELATED STRUCTURES	
14. OTHER IDENTIFICATION	











IDENTITY # NAME			
IV. GENERAL TECHNICAL INFORMATION--CHEMICAL PROPERTIES			
1. VARIATION OF STABILITY WITH TEMPERATURE			
1.1 °C	1.2 HALF-LIFE	1.3 DECOMPOSITION PRODUCT	1.4 TOXICITY OF PRODUCT
2. VARIATION OF STABILITY WITH pH			
2.1 pH		2.2 DECOMPOSITION PRODUCT	2.3 TOXICITY OF PRODUCT
3. VARIATION OF STABILITY WITH U. V.			
3.1 WAVE-LENGTH	3.2 HALF-LIFE	3.3 DECOMPOSITION PRODUCT	3.4 TOXICITY OF PRODUCT
4. OTHER METABOLITES			
5. CHEMICAL GROUPS OR FRAGMENTS OF PARENT COMPOUND AND METABOLITES			



## APPENDIX B

## SAMPLE OUTLINE OF SUBJECT MATTER TO BE COVERED IN PRESENTATIONS ON MODERN TECHNIQUES FOR INFORMATION SELECTION AND RETRIEVAL

## Session I. Introductory:

- a. Needs for new techniques in information selection and retrieval systems.
- b. Role of selection and retrieval systems in utilization of scientific and technical information.
- c. Exponential growth of the scientific literature.
- d. Problems of unpublished literature, including data generated inhouse.
- e. Problems of maintaining current awareness.
- f. Problems of storage. Problems of search, selection, and retrieval.
- g. Problems of anticipating and meeting user needs.

## Session II. Subject content analysis, indexing, retrieval books:

- a. Classification schemes:
  1. Library of Congress.
  2. Dewey Decimal.
  3. Universal Decimal Code.
  4. Patent Office.
  5. Other hierarchical and semihierarchical schemes.
- b. Indexing schemes:
  1. Indexing terms are assigned: concept indexing, subject headings, descriptors, zatocoding, other.
  2. Indexing terms are derived from the document itself: word indexing, uniterms, permuted titles, KWIC, other machine indexing experiments.
- c. Special-purpose schemes—Chemical notation, chemical structure coding.
- d. Preservation of concept of relationships—generic, specific encoding, roles, links, other modifiers, syntax preserving codes, cues to positional location of element in chemical structure with respect to the nucleus, etc.
- e. Representation of classification or indexing terms in coded form—superimposed coding as special case.
- f. Aids available to the subject content analyst or indexer—authority lists, scope notes, dictionaries, thesaurus, machine aids, etc.

## Session III. Organization for subsequent search.

- a. Indexing terms and retrieval hooks are stored separately from the items themselves.
  1. "Terms-on-item" or "unit record" systems—catalog cards, edge notched or punched card with item identification, all pertinent indexing items coded or punched onto same card.
  2. "Items-on-term" or "inverted file" systems—book index, manually posted uniterm coordinate indexing records with record for each uniterm to which document accession number is posted if term applies to that document. Peek-a-boo system with term cards having holes punched out at the coordinate positions representing the document numbers to which the term applies, computer-implemented coordinate indexing systems for items-on-term records.
  3. Hybrid systems—terms-on-item systems with multiple cross-reference copies, e.g. Tabledex.
- b. Integral indexing—Indexing terms and retrieval hooks are stored on or near the items to be retrieved, e.g., library classification codes on back of books, aperture cards, Minicard, Microfilm Rapid Selector, etc.



## Session IV. Storage considerations:

- a. Storage media—paper, photographic material, microfilm, magnetic tape, etc. Serial versus discrete; i.e., long rolls and reels with many items or cards and film chips. Comparative characteristics.
- b. Organization of physical storage—random, ordered, compartmentalized. Comparative advantages and disadvantages.

## Session V. Search and selection techniques:

- a. Basis of search—
  1. Address, or name, or label of item must be known, only one item responds.
  2. All items which meet the requirements of a search prescription are located during the search process, the addresses or locations of these items are not known in advance, one or more items or no items may respond.
- b. Methods of search—manual, needle-sorted, punched card sorting, Peek-a-Boo or Termatrex superposition, computer search, other special search devices.
- c. Problems of preparing search prescriptions—logic or search strategy allowed in the system.
- d. Special problems—false drops, etc.

## Session VI. Output considerations:

- a. Output is name or number of item that must be separately retrieved.
- b. Output is data.
- c. Output is summary or abstract of document.
- d. Output is document itself or a replica copy.

## Session VII. Selection and retrieval equipment:

- a. Address-type selection only—manual: book is taken from shelf by its call number, microfilm aperture card is removed from file by its identifying number. Machine: Recordak Lodestar displays and copies document page by number, microimage file, Verac, etc.
- b. Search-type selection—manual; machine. Edge-notched cards, edge-notched aperture cards, EAM equipment, ILAS, Termatrex and Peek-a-Boo, WRO Searching-Selector System, Special Index Analyzer, Magnacard, Mini-card, Rapid Selector, Filmorex, File Search, many computer systems.
- c. Hybrid systems—e.g., Peek-a-Boo with Microcite.

## Session VIII. System design considerations:

- a. Collection—integrity, security, rate of growth, size, diversity, multiple-purpose usage, need for updating, criteria for inclusion, rejection, etc.
- b. Analysis and categorization—depth of indexing, specificity of indexing, skills required of analysts or indexers, quality control on consistency of indexing.
- c. Customer engineering—ease of use (must he learn special language?), efficiency of search (can many users use system in parallel?), convenience, adequacy of search product to user needs, attractiveness of output product.
- d. Comparative evaluation—examples of same problem handled by different systems—Steriod search by computer, EAM equipment, and Termatrex; spectrographic data on edge-notched cards, on Termatrex, on Microcite.



## APPENDIX C

SAMPLE FILE

IDENTITY NUMBER (the main file entry would be headed by the identity number)

Common name

Trade name

Chemical name

manufacturer

Legal class

Use

Cipher

Related Structures

.

.

.

Commodity

Tolerance

PP#

Date published

Physical Properties

.

.

.

.

Chemical Properties

.

.

.

.

Method of Analysis (code number)

Modification number

Recovery

Background level

.

.

.



OTHER ACCESS POINTS (from which to enter file)

Commodity

Identity number  $n_1$

•  
•  
•  
•  
•  
 $n_x$

Use

Identity number  $n_1$

•  
•  
•  
•  
 $n_x$

Legal Class\*

Identity number  $n_1$

•  
•  
•  
•  
•  
 $n_x$

There will no doubt be many more access point. These are just a few examples.

A specific example might be the following:

\*Cholinesterase Inhibitors

Sevin

•  
•  
•

$n$  (where  $n$  is the number in the file, and there is available a push-down technique for adding to the file every time a new cholinesterase inhibitor is received.



## APPENDIX D

## EXAMPLE OF A M'BEE KEYSORT CARD WITH TYPICAL ENTRIES

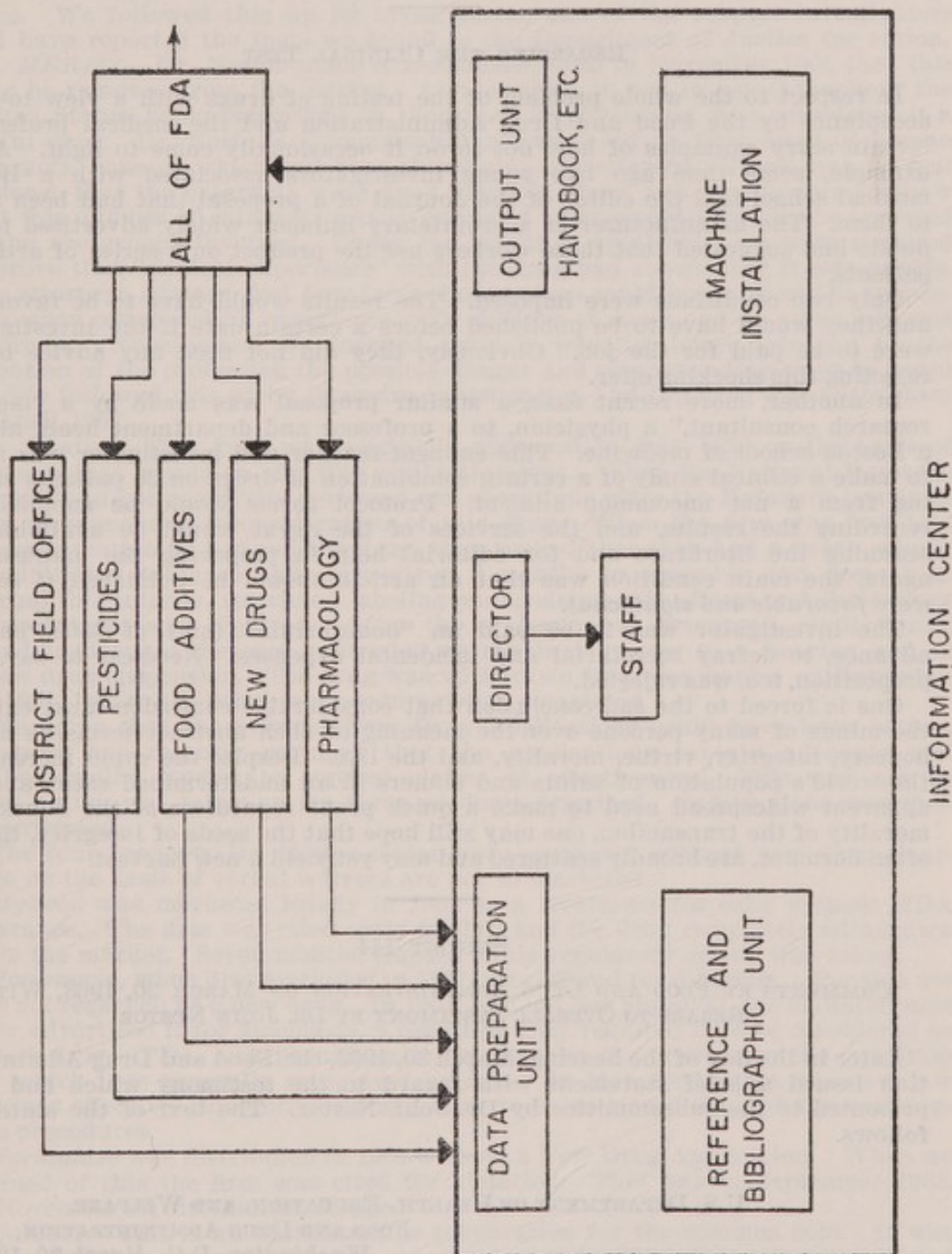
PENICILLIN		STREPTOMYCIN		CHLOTETRACYCLINE	
<p>MANUFACTURER</p> <p>QUANTITATIVE ANALYSIS</p> <p>DOSAGES</p> <p>SPECIES</p> <p>RT. OF ADMINISTRATION</p> <p>DISEASES TREATED</p>					
BACILLARIN		CHLORAMPHENICOL			

The entries shown on this card might be some of the items printed on the face of the card. Each of the holes under a particular antibiotic could be the base of the drug combination, e.g., ointment, oil, tablet, etc. All other holes could be used for the other ingredients present in the drug combination.



APPENDIX E

PROPOSED ORGANIZATION OF AN INFORMATION CENTER





## EXHIBIT 143

## EDITORIAL FROM NEW ENGLAND JOURNAL OF MEDICINE CRITICAL OF CONDITIONS OF SPONSORSHIP OF SOME CLINICAL EVALUATION OF DRUGS

The following editorial appeared in the March 21, 1963, issue of the New England Journal of Medicine (p. 680). This general subject was referred to by Senator Ernest Gruening during Dr. Nestor's testimony (p. 808).

## REGARDING THE CLINICAL TEST

In respect to the whole problem of the testing of drugs with a view to their acceptance by the Food and Drug Administration and the medical profession, certain sorry examples of how not to do it occasionally come to light. As an example, some time ago two young investigators associated with a Boston medical school told the editor of the Journal of a proposal that had been made to them. The manufacturer of a proprietary liniment widely advertised to the public had suggested that these workers use the product on a series of arthritic patients.

Only two conditions were imposed. The results would have to be favorable, and they would have to be published before a certain date if the investigators were to be paid for the job. Obviously, they did not need any advice before rejecting this shocking offer.

In another, more recent case, a similar proposal was made by a "medical research consultant," a physician, to a professor and department head, also in a Boston school of medicine. This eminent teacher and investigator was asked to make a clinical study of a certain combination of drugs on 20 patients suffering from a not uncommon ailment. Protocol forms would be supplied for recording the results, and the services of the agent would be available for scanning the literature and for editorial help in preparing the manuscript; again, the main condition was that an article should be published *if results were favorable and significant*.

The investigator was to be paid an "honorarium" (sic) of \$500, half in advance, to defray secretarial and incidental expenses. Needless to say, this proposition, too, was rejected.

One is forced to the sad conclusion that considerable confusion must exist in the minds of many persons over the meaning of such abstract terms as honor, honesty, integrity, virtue, morality, and the like. Despite the rapid increase in the world's population of saints and sinners in an undetermined ratio, and the apparent widespread need to make a quick profit regardless of the honesty or morality of the transaction, one may still hope that the seeds of integrity, though often dormant, are broadly scattered and may yet yield a new harvest.

## EXHIBIT 144

## COMMENTS BY FOOD AND DRUG ADMINISTRATION ON MARCH 20, 1963, WITH REGARD TO OVERALL TESTIMONY BY DR. JOHN NESTOR

Later in the day of the hearing, March 20, 1963, the Food and Drug Administration issued a brief statement with regard to the testimony which had been presented to the subcommittee by Dr. John Nestor. The text of the statement follows.

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,  
FOOD AND DRUG ADMINISTRATION,  
Washington, D.C., March 20, 1963.

## STATEMENT BY THE COMMISSIONER OF FOOD AND DRUGS REGARDING CHARGES MADE BY JOHN O. NESTOR, M.D.

Dr. Nestor, who has been employed in our New Drug Branch for less than 2 years, made his statement without any prior discussion of his points with the Office of the Commissioner. The statement was not shown to us in advance. We did know the general content of his assertions in advance.



First, we categorically deny that laymen have been making medical decisions. We operate under the terms of a law. Medical facts and judgments must be given effect in accordance with the law. Administrators and attorneys are properly entitled to evaluate the medical facts before embarking on a regulatory program that must be sustained ultimately in the courts.

1. *Entoquel*.—As soon as the first adverse report on this drug came to the attention of the Commissioner's Office—involving two children—we took immediate and vigorous action. A multiple-seizure campaign was initiated within 1 week's time to remove the drug from the market. It has not been marketed since. We followed this up by investigating one of the suspect investigators and have reported the facts we found to the Department of Justice for action.

2. *MER/29*.—Dr. Nestor made a recommendation in November 1961 that this drug be removed from the market. At that time, it was in use throughout the United States, being prescribed by thousands of physicians, who considered it a useful drug. Dr. Nestor's recommendation was based on four cases of human cataracts, none of which had been thoroughly investigated. There was no real evidence that the cataracts were drug induced; there was no evidence to show that this number of cataracts was in excess of what would normally be expected in the age groups involved. Under the law then applicable, we were required to prove that "clinical experience" with the drug had shown that it was unsafe. Our attorneys advised that four inconclusive cases could not support the suspension when countered by experience with millions of doses and no other reported cataracts. Nonetheless, we insisted upon a warning letter bringing to the attention of the profession the possible danger and recommending steps to avoid it. We followed this up by intensive investigation and the drug was withdrawn in April 1962.

3. *Altafur*.—This drug was originally approved in July 1959 on the basis of evidence that it was an effective antibiotic agent. When the National Research Council's ad hoc committee reviewed our operations after the Kefauver hearings, they recommended reconsideration of this drug. When the firm was first told of our intention to suspend the drug, they replied that they had a great volume of additional evidence and were given 3 months to assemble and present it. During this interim, restricted labeling emphasizing side effects and limitations on usefulness was required. After the evidence was presented, studied, and found inadequate the case proceeded as required by law to a hearing and to a new drug suspension. The drug was withdrawn from the market on November 16, 1961, before the hearing procedures were completed.

We agree that the original New Drug Applications could have been better; Congress has recently required that the applications contain adequate and well-controlled studies to support claims of effectiveness. This was not so when action was taken on the three products described. Safety alone was then the criterion.

The four products Dr. Nestor states were marketed without new drug clearance on the basis of verbal waivers are not so marketed.

*Mylicon* was marketed briefly in 1961 as a treatment for colic without NDA clearance. The firm was cited early in 1962 and the drug completely withdrawn from the market. Seven months elapsed while regulatory action was taken.

*Paremycin*, when first marketed in 1957, was offered for diarrhea. For this use it is not regarded as a new drug. In 1961, without our approval, the manufacturer later advertised it for amebiasis, a condition that required it to be considered as a new drug. FDA took prompt action to restrict the product to the condition for which it is generally recognized as safe. In May 1963, when the new law becomes effective, this antibiotic will have to be recleared through the certification procedures.

*Formulase* was distributed in 1961 without a New Drug Application. When we learned of this the firm was cited for violation. This was in September 1962. In November all distribution stopped.

*Coldaid*.—This is an antihistamine preparation for the common cold. It was not regarded as a new drug in the reduced dosage in which it is being distributed until quite recently. The firm has been advised that it may not be distributed without a New Drug Application for the symptoms of the common cold.

Dr. Nestor asserts that one drug, PRN, was allowed on the market without the necessary chronic toxicity studies. Animal studies with the drug on dogs were regarded as adequate by our Division of Pharmacology and Bureau of Medicine. As an extra precaution, long-term rat studies were requested. This drug has not been distributed since 1961. It was discontinued because it was not profit-



able. No evidence that we have seen calls into question the original judgment on the drug.

It is false to say that inadequate attention is being given to the special problem of drug therapy in children and pregnant women. These important factors were singled out for special attention in our investigational use regulations and in the new regulations we are promulgating to carry forward the purposes of the Kefauver-Harris Drug Amendments of 1962. Moreover, as long ago as March 1957 we issued a statement of policy on this very problem, acting on the best medical judgment then available.

Dr. Nestor criticizes the FDA's action on the Food Additive Petition for *menadione* (vitamin K). This nutrient was proposed for multi-vitamin mineral capsules. Dr. Nestor thought the product should be completely excluded from all such preparations even though the possible danger involved only prenatal use. We submitted the problem to an outside group of experts who reported:

"Thus, there is a lack of evidence of safety for the fetus from the proposed administration. Similarly, existing evidence is insufficient to warrant a conclusion that daily ingestion of 1 milligram of menadione by the pregnant woman constitutes a major threat to the fetus."

While Dr. Nestor was unhappy with this recommendation, because it did not confirm his belief that there was an established danger, and presented Dr. Feitel's paper (about which he testified) to the group to persuade them of the danger, the consultants adhered to their view. The status of the petition is that the petitioner has been advised that it is inadequate to establish safety. The firm has until March 21 to reply; the nutrient has not been approved; and the question of cost to the petitioner has had no part whatever in our decision.

Arousing fears and challenging actions on the basis of a partial statement of all of the facts and considerations involved will not improve the lot of the American consumer. We are satisfied that a balanced statement will establish that all of our actions have been taken in accordance with the directions given us by the Congress, and that we have done well, even in the troublesome instances highlighted by Dr. Nestor's statement, to discharge our responsibilities to the public.

Two major problems cited by Dr. Nestor—that we couldn't deal adequately with questions of effectiveness in the new drug procedures and that there were problems in suspending New Drug Applications once they became effective—can be dealt with more effectively when the Kefauver-Harris drug amendments become fully operative.

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#### EXHIBIT 145

INITIAL COMMENTS BY SENATOR HUBERT H. HUMPHREY RESPONDING TO STATEMENT OF MARCH 20, 1963, BY FOOD AND DRUG ADMINISTRATION ON TESTIMONY BY DR. NESTOR

On March 21, 1963, Senator Humphrey commented on a Food and Drug Administration statement of the previous day with respect to Dr. Nestor's testimony. Senator Humphrey's oral statement will be found in the opening pages of part 4. In order, however, that there be available in this particular volume, which contains Dr. Nestor's testimony, as many of the pertinent comments as possible, the text of Senator Humphrey's prepared statement is published at this point also.

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#### INITIAL REBUTTAL TO THE REBUTTAL

With regard to FDA's so-called "rebuttal," as summarized in this morning's Washington Post, let me just state a few points, initially:

The fundamental fact is that the record would appear to conflict seriously with FDA's contentions.

Thus:

1. *Menadione*.—The ad hoc panel of medical experts *did* support the stand of Dr. Nestor and the Bureau of Medicine, as a whole. It did recommend that the petition be denied because the data available did not substantiate either safety or efficacy for the use proposed.

I would like FDA to furnish to me written proof of medical judgment to the contrary.



2. *Mylicon*.—As revealed in the ad in the March 1963 trade publication, the firm is still advertising the liquid preparation for use in children under 12 years of age. Therefore, it does not seem to have been "withdrawn from the market," as FDA states.

3. *Paremycin*.—One of the reasons Paremycin was considered by the Bureau of Medicine—(I repeat, the Bureau of Medicine—not merely Dr. Nestor)—to be a "new drug" was because it was being promoted for amebiasis. FDA states it is being restricted to use *against* amebiasis. Therefore, so far as I can see, what Dr. Nestor stated yesterday was exactly correct. It is a "new drug" on the market *without* the slightest preclearance review of a New Drug Application.

4. On MER/29, documents in the subcommittee's possession would appear to confirm that the clinical evidence in the New Drug Application was definitely insufficient to establish the safety (or efficacy) of the drug before it was cleared in the first place.

I cite an FDA document of October 24, 1961, which indicated a mere 160 clinical cases—with very limited results obtained even in these cases.

Further, after reactions to the drug started to pile up, I cite Dr. Nestor's memorandum of October 27, 1961, to Dr. Kessenich. It pointed to "overwhelming evidence" that MER/29 (triparanol) produces severe adverse reactions and toxicity in both animals and humans. Most of this evidence was available in the NDA when it was made effective. Much of it has accumulated since.

5. With regard to drugs on which *waivers* to the New Drug Application procedure were granted, the subcommittee will want to see the waivers—in writing. It will want to see the medical reasons cited in the waivers, the names of the medical officers consulted before the waivers were granted, the names of the FDA medical officers notified after the waivers were granted.

Let the record speak for itself.

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#### EXHIBIT 146

#### CORRECTION BY FOOD AND DRUG ADMINISTRATION OF ONE PORTION OF ITS STATEMENT OF MARCH 20, 1963, WITH REGARD TO TESTIMONY BY DR. NESTOR

On March 23, 1963, Commissioner Larrick conveyed a statement of correction with regard to the March 20 statement by the Food and Drug Administration with reference to Mylicon. The letter and statement of correction follow.

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,  
FOOD AND DRUG ADMINISTRATION,  
Washington, D.C., March 22, 1963.

DEAR SENATOR HUMPHREY: We find that our statement of March 20, 1963, with respect to Dr. John O. Nestor's testimony, a copy of which we sent you this morning, was not clear with regard to the drug Mylicon.

We have therefore prepared the enclosed correction.

Sincerely yours,

GEO. P. LARRICK, *Commissioner of Food and Drugs.*

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Our statement with respect to the testimony of John O. Nestor, M.D., calls for a clarification on Mylicon.

We stated that the drug was promoted in 1961 for infantile colic without a New Drug Application, and that when the company's attention was drawn to this, the drug was completely withdrawn from the market. The withdrawal was with respect to use for infant colic. This is the condition in which Mylicon's safety was not established. This is the condition about which Dr. Nestor testified.

Mylicon remains on the market for use in adults and children over 12. Its labeling contains the statement: "Children under 12 years; as directed by physician." No infant uses are recommended or suggested.



## EXHIBIT 147

## SUBCOMMITTEE CORRESPONDENCE WITH FOOD AND DRUG ADMINISTRATION, INVITING ADDITIONAL REACTIONS TO TESTIMONY RECEIVED AT MARCH 20-21 HEARINGS

Subsequent to the present set of hearings, Senator Humphrey, chairman of the subcommittee, invited the Food and Drug Administration to convey any reactions it wished to the testimony which was received. The text of the letters to and from the agency follow.

UNITED STATES SENATE,  
COMMITTEE ON GOVERNMENT OPERATIONS,  
SUBCOMMITTEE ON REORGANIZATION AND INTERNATIONAL ORGANIZATIONS,  
April 12, 1963.

THE HONORABLE GEORGE LARRICK,  
*Commissioner, Food and Drug Administration,  
Department of Health, Education, and Welfare,  
Washington, D.C.*

DEAR COMMISSIONER LARRICK: I appreciated the opportunity of meeting with you so as to review the subcommittee's hearings and the problems of the Food and Drug Administration in adjusting operations to the requirements of the new drug law.

This letter will confirm and supplement the various points which we discussed, so that we will have a complete understanding as to future procedure.

1. The subcommittee will schedule future hearings as soon as practicable. Next month, we will hear from representatives of the Second Citizens Advisory Committee on FDA. We will hear thereafter from representatives of the American Medical Association, the Pharmaceutical Manufacturers Association, and the Department of Health, Education, and Welfare, including yourself.

2. In advance of these hearings, and as soon as possible, I will appreciate receiving, as I stated in the Senate, a comprehensive memorandum from your Agency, setting forth any observations and reactions which FDA would like to convey as regards facts discussed and judgments expressed at the March 20th hearing, and, for that matter, at the March 21st hearing.

We want the hearing record to be as complete, as accurate and as fair as possible; we will be happy to consider publication of FDA's detailed analysis, just as we have published FDA's statements heretofore at great length.

3. I am advising all witnesses that, in the interest of the subcommittee's considering the main issues, we would like witnesses to reserve the time available for their *oral* presentation to those topics which are of highest priority in their, and in the subcommittee's, judgment.

Each witness will be welcome to file the most complete statement in the record.

4. I will submit in advance to yourself and to each prospective witness, as I have in the past, specific questions on which the subcommittee would appreciate detailed oral answers at the hearings.

5. Among the specific issues on which I invite Mr. B. Jones' and your testimony are these:

(a) The justification for the 1964 fiscal year appropriation for the HEW Department describes (volume 1) certain steps FDA is taking under the new drug law and regulations. What further actions does FDA plan to take, over and above the limited actions described in the justification, so as to fulfill responsibilities under the new law?

(b) The justification states (p. 28) with reference to the October 1962 Report of the Second Citizens Advisory Committee on the Food and Drug Administration, "appraisal had not been completed at the time this budget was developed." The justification states, however, that "the programs proposed in the 1964 budget are in step with the general objectives" of the Second Citizens Advisory Committee Report.

My question is: exactly what now is a frank appraisal by Mr. Jones and yourself as regards the major contents of the second CAC report?

What are your views, specifically, as to future

"Organization

"Regulatory Activities

"Program Planning and Budgeting

"A Food and Drug Institute

"Personnel Management



"Education and Information

"External Relations

"Plan of Implementation."

(to quote from the outline of the report itself) ?

(c) Or, to put the question in another way: What are FDA's present and prospective needs? How well are the needs going to be met, under existing budget proposals, as approved by the Bureau of the Budget? How can the Congress be of specific assistance in meeting FDA's needs?

A review of the overall record of the Food and Drug Administration confirms, in my personal judgment, that your Agency has, by and large, served this Nation faithfully. My intention is now, and it has always been, to strengthen the Agency and enable it to do the best possible job in the public interest. I want its employees to have the highest possible morale, based upon pride in excellence of work and in public and congressional esteem for such excellence.

Thus, the subcommittee seeks to enhance the scientific and professional status of FDA. It is essential, as I see it, that your Agency have modern equipment, laboratories and other facilities. It is even more essential that the Agency be staffed by the most competent of professional and technical people and that they be adequately compensated and their competence respected.

We have been examining the record on New Drug Applications of the past in order to ascertain the soundness of Agency procedures, including the process of decision-making on whether a product is or is not a "new drug." Our subcommittee continues to be primarily interested in the administration of the Food, Drug, and Cosmetic Act and its amendments, in the organizational structure of FDA and in interagency coordination.

Our goal has been and remains, therefore, to look ahead and plan ahead for specific improvements. Your Agency has a tremendous responsibility under the Drug Amendments of 1962. The proper administration of that important law is a matter of deepest mutual interest to the Congress and to your Agency.

Certain past issues, which will indicate guidelines for the future, can be clarified only in the light of factual information in FDA files. For that reason, I confirm what I stated in the Senate—I have asked the staff to examine pertinent FDA files and to request pertinent extracts and summaries. The staff will do so, as it has in the past, in a way which will prove convenient to the Agency and which will impose the least possible burden upon your staff's other obligations.

Again, my thanks for coming over to discuss the problems of FDA and sharing with me some of your thoughts as to how we may accomplish our common objectives.

Sincerely,

HUBERT H. HUMPHREY, *Subcommittee Chairman.*

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,  
FOOD AND DRUG ADMINISTRATION,  
Washington, D.C., May 22, 1963.

DEAR SENATOR HUMPHREY: Thank you for your letter of April 12, 1963, confirming and supplementing the various points we discussed at our last meeting.

The enclosed statement, which you requested, gives our observations on the testimony which your subcommittee heard in March.

We appreciate your willingness to let us have in advance, the specific questions on which the subcommittee would like detailed oral answers when we testify.

It was very reassuring to find in your letter a statement of views which we already understood you hold with respect to our operations—that by and large our agency has served the Nation faithfully, and that it is your intention to strengthen the agency and enable it to do the best possible job in the public interest. I am sure you know that it is our sincere desire to continue to discharge our trust faithfully and effectively.

It was indeed pleasant to meet with you and discuss the steps which we can take to accomplish our common goals. We look forward to continued pleasant associations.

Sincerely yours,

GEO. P. LARRICK,  
*Commissioner of Food and Drugs.*



OBSERVATIONS OF THE FOOD AND DRUG ADMINISTRATION ON TESTIMONY PRESENTED TO THE SUBCOMMITTEE ON REORGANIZATION AND INTERNATIONAL ORGANIZATIONS, COMMITTEE ON GOVERNMENT OPERATIONS, U.S. SENATE, ON MARCH 20, 1963

Before commenting on the specifics of the March 20 testimony, it seems important to bring into focus the legal provisions under which the actions discussed were taken.

First, all drugs that are placed on the market do not have to be approved by us. Some drugs do. These are new drugs, certain of the antibiotics, and all insulin-containing preparations. For brevity this discussion refers to "new drugs."

When substantially all of the events discussed before your committee occurred, we were operating without the important and far reaching provisions of the Kefauver-Harris Drug Amendments of 1962. A "new drug" was defined in objective terms as any drug the composition of which is such that it "is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof."

Under the definition, Congress permitted the drug manufacturer to reach his own conclusion whether his product required preclearance. If he decided that his drug was generally recognized by qualified experts as safe for its intended use, he could proceed with his marketing plans. Our remedy, in the event we disagreed with the marketing decision, was to initiate regulatory action. The burden devolved upon us then to prove that the drug was not generally recognized as safe.

(The Kefauver-Harris drug amendments changed the definition to include products not generally recognized as effective for their intended use. The grandfather clause makes this inapplicable for a period of 2 years to products that have been subject to preclearance on considerations of safety.)

Second, the law before the recent amendments authorized us to withdraw a "new drug" from the market on a showing that the application contained an untrue statement of a material fact or on a showing that new tests or "clinical experience" with the drug had proved it unsafe. Thus a drug would be excluded from the market on a finding that its safety was not adequately established, but once the application became effective the heavier burden came into play and a positive showing that the drug was unsafe was necessary.

(The Kefauver-Harris drug amendments authorized withdrawal on a reasonable doubt about safety or effectiveness, and improved in other ways the reporting of clinical experience to us and the means of dealing with a drug of doubtful safety or effectiveness. Again, the grandfather clause has postponed actions based on effectiveness for a period of 2 years from October 10, 1962.)

Corrective action generally took the form of contacting the drug manufacturer for any labeling improvements that were shown by clinical experience to be needed. And when we found promotional excesses, we had the choice of enforcement action based on claims that had never been cleared or of proceeding against the New Drug Application for its suspension on the basis of false statements in the application. In cases of urgent need, we resorted to public warnings and voluntary recall procedures.

Most firms do voluntarily come to us before putting a new product on the market to determine whether in our opinion it is subject to the new drug requirements. Since 1938, when the new drug legislation was first written into the law, we have given our opinion in response to such inquiries. Recently we have established a special branch, the New Drug Status Branch, in the Division of New Drugs, Bureau of Medicine, to handle inquiries of this type.

These comments as to the status of a product under the new drug section of the law are not waivers. We do not have authority to, and we have not waived the new drug requirement of the law for any product which we concluded fell within the definition of a new drug. We do give our opinion as to the applicability of that section of the law to the drug. We believe that this is good administration and is preventative enforcement.

Not only may a manufacturer place a new drug on the market without FDA approval, but he may fail to abide by the conditions of approval after having received it through the new drug procedure. Therefore, we must have a surveillance unit to keep abreast of marketing practices. Before passage of the recent amendments, we were severely handicapped in our inspection authority and there were no requirements that the drug manufacturers report to us either



on clinical experience or marketing practices. We had to pick up clinical experiences from the medical literature and our very limited adverse reactions program, and we had to follow promotional practices by inspectional means.

Our decisions to approve or withdraw approval of an application were based on the best scientific evidence available to us at the time. Decisions which were quite sound when made sometimes required change with the emergence of new facts from the medical sciences. Doctors, like scientists in all fields, recognize that some of their earlier beliefs are not tenable in the light of present scientific knowledge.

We have given priority to correction of imminent hazards to health. If necessary we defer action on lesser problems while dealing with the ones that may involve serious danger to the public health.

For a group of medical officers, inspectors, chemists, and other scientists, clerks, and other supporting personnel to administer a complex law like the Pure Food and Drug Law, there must, as you know, be administrative leadership. We rely upon the chemists for chemical facts, upon the pharmacologists for pharmacological facts, upon the nutritionists for nutritional facts, upon the medical officers for medical facts, and upon attorneys for the law. There are occasions when scientists do not reach complete agreement, and it becomes necessary to have some method of reaching a decision that will represent the best judgment of all our people. For example, it happens occasionally that a physician may have one view while other physicians hold a different view. The Acting Director of the Bureau of Medicine is the physician who determines the medical consensus and advises the Commissioner of the ultimate decision of the Bureau of Medicine when a controversial medical question arises.

Our medical staff informally consults leading experts throughout the United States very frequently. Often it becomes desirable to have more formal advice or assistance from experts outside the FDA on matters involving medical or other scientific evaluations. At such a time, it is our practice to convene a group of nationally recognized experts as an advisory committee to consider the problem under discussion and make its recommendations. The use of expert outside advice is a procedure that the subcommittee has recommended in the scientific area. We are employing scientific advisory committees with increasing frequency as the decisions we have to make become more complex. We expect to accelerate this program.

When scientists have given their views, this does not mean that the FDA can always take the action that the scientists recommend. We must proceed within the guidelines set down by Congress in the Food, Drug, and Cosmetic Act.

A case in point is the MER/29 NDA which we would have preferred to suspend in November 1961. At that time, before the Kefauver-Harris Drug Amendments of 1962, FDA had to prove that a new drug was unsafe in order to suspend an application. When the medical officers presented all the available evidence, our administrative and legal staff examined it, and reached the conclusion that we did not have, in November 1961, proof which would establish that MER/29 was unsafe. We did all that could be done under the existing law. We required warnings in the MER/29 labeling and required the manufacturer to send a letter to every physician warning of the questions that had arisen about the drug. When more evidence became available, the firm withdrew the application in April 1962, and we issued our suspension order in May 1962.

Additionally we called the attention of the Congress to the very serious loophole in the law which made it impossible to suspend the application in November 1961 when there was substantial doubt as to the product's safety. The loophole was closed in the Kefauver-Harris drug amendments enacted in October 1962.

When the medical officers or other scientists give us the scientific facts and when the lawyers tell us that the law applies, there is still another step that is involved in sound administration. We have to decide what type of corrective action to take and how vigorously to pursue it. It is not necessary to issue a drug warning letter to doctors or a press release to laymen or to recall a drug from the market every time some labeling change is required. We do resort to one or more of these steps where they are needed to safeguard health. But many changes can be brought about without jeopardy to the public health with less drastic and less precipitous measures.

The case of vitamin pills containing minute amounts of menadione on which you have heard testimony illustrates some of the complexities of administering the Pure Food and Drug Law. Menadione is a synthetic vitamin, also called vitamin K<sub>3</sub>. It may be administered to the pregnant mother by injection before



childbirth, or to the infant shortly after childbirth, to control bleeding; it has also been employed in multiple vitamin preparations which are classified as dietary food supplements.

After menadione had been used by injection for some time, physicians began to notice that in some cases injection was followed by adverse effects in some infants. This was new information not previously available to the scientific community or to FDA. It raised a question as to the desirability of allowing small amounts of menadione to remain in multiple vitamin capsules to be consumed orally. This question was raised because of the transition procedures authorized by Congress in the Food Additives Amendments.

In connection with this consideration, we sought medical advice from the Bureau of Medicine. There had been no FDA decision at this point. We were in the decision-making process.

The Bureau of Medicine sought the views of three medical officers. They said the data available did not establish the safety of menadione in prenatal vitamin capsules. Other units of FDA set about determining what course of action to take with respect to the nutrient.

The first thing that had to be determined was whether the presence of minute amounts of menadione then allowed in vitamin pills constituted an "undue risk to the public health." (The Food Additives Amendment provided for continued use of food additives while their status was under consideration where this involved "no undue risk to the public health.")

In January 1962 we had to decide whether to allow menadione to continue to be used in dietary supplements during that year (and whether to allow continued use of hundreds of other food additives under consideration). The Bureau of Medicine and Dr. Nestor of that bureau concurred in the view that the year's extension would not constitute undue risk to the public health. Some months later Dr. Nestor changed his mind. He concluded that the extension constituted undue risk, and recommended that the extension be terminated and stocks of menadione-containing products be recalled from the market. His new conclusion was not shared by other scientists in FDA, including medical officers.

We then decided to seek the advice of a panel of outside experts. We asked the American Academy of Pediatrics to name outstanding experts who could offer informed advice. The experts were selected, they studied the available evidence and they concluded in December 1962 that the Food Additive Petition should be denied because of inadequate evidence of safety. This conclusion paralleled that reached by the scientists of FDA. However, the advisory committee did not conclude that the presence of menadione in multiple vitamin preparations on the market constituted an undue risk to the public health. It did not find that menadione in prenatal capsules causes brain damage, spasticity, or other serious conditions in either the mother or the unborn child.

In January 1963 we advised the petitioner of the findings of the panel of experts and gave the firm an opportunity to submit additional evidence or withdraw the petition. At the end of 60 days, which we allowed for response, in the absence of either additional information or withdrawal of the petition, we published an order in the Federal Register denying the request for approval for use of menadione in prenatal vitamin capsules. The order also terminated the extension of the effective date of the Food Additives Amendment then in effect.

As a result of testimony presented to your subcommittee in March, many women became unnecessarily alarmed about the hazards associated with the presence of small amounts of menadione in multiple vitamin preparations. The facts do not show the need for and we do not plan to take legal actions against stocks of vitamin pills which were marketed legally under the terms of the food additives extension.

With respect to other statements made in testimony before your subcommittee on March 20, 1963, we refer to the summary in the testimony of our employee.

Points number 1 and 6 in Dr. Nestor's summary are in many respects the same. They assert that three new drugs should not have been permitted on the market. These are Entoquel, MER/29, and Altafur. The decisions to permit these drugs to go on the market were medical decisions reached by medical officers. In the case of one of these drugs, MER/29, we have already explained the loophole in the law then in effect which made it impossible to suspend the application as rapidly as we wished, when substantial doubts arose as to safety of the product.



Clinical experience with Entoquel after it was placed on the market raised questions as to its safety. Inspection revealed among other things that the drug was being promoted for conditions that had not been authorized by the effective New Drug Applications. We seized stocks accompanied by the unwarranted labeling. This resulted in a prompt recall of all stocks of the Entoquel-containing drugs. The New Drug Applications were suspended at the firm's request.

Altafur also presented a situation in which clinical experience with the drug after it was marketed raised a question as to its safety. FDA advised the firm that in its opinion the drug should be removed from the market. The firm did not agree, and as the law provides it was given a hearing at which evidence was presented by the Government and by the firm. On the basis of the hearing record the New Drug Application was suspended. The product was withdrawn from the market.

This also covers the second point in the summary—that needless delays should not have been tolerated in withdrawing MER/29 and Altafur from the market. We must act in accordance with the procedures set forth in the law. When a firm is entitled by law to a formal hearing on suspension of a New Drug Application (Altafur) and when prompt action is impossible because of a loophole or limitation in the law (MER/29), there is inevitably a loss of time.

As you know, the Secretary is now empowered by the Kefauver-Harris Drug Amendments of October 10, 1962, to suspend the approval of a New Drug Application immediately when he finds that there is an imminent hazard to the public health. We did not have this authority for immediate suspension before the Kefauver-Harris drug amendments.

The third point, involving menadione, has been discussed.

The fourth point of the summary is that there have been new drugs on the market that never were subjected to the necessary preclearance procedure of a New Drug Application to demonstrate safety. The four drugs mentioned are Mylicon, Paremycin, Formulase, Coldaid.

In each case the manufacturer elected to enter the market with claims that in our opinion classified the product as a new drug. In each case corrective action has been taken and the drug is either off the market or the labeling has been modified by removing the therapeutic claims that caused the product to be considered a new drug.

The fifth point in the summary is that at least one new drug, PRN, was permitted to go on the market before the necessary chronic toxicity tests were performed on animals. The active ingredient in this drug, phenyltoloxamine, an antihistamine, had been on the market for some years in lower dosage. We received a New Drug Application for PRN in higher dosage in 1957. The application included toxicity tests performed on dogs. Both our Division of Pharmacology and our Bureau of Medicine agreed that the application could be made effective on these data. The medical officer requested that some additional studies be performed on rats, but did not consider it necessary to hold up the effectiveness of the application while these studies were performed. There is no clinical evidence that the drug caused harm. However, the new dosage form was not a commercial success and has not been produced since 1957 nor distributed since 1961. The New Drug Application has been recalled by the manufacturer. The lower dosage form, cleared for other uses under New Drug Applications, remains on the market.

We have already covered point number 6.

The seventh point in the summary is that adequate recognition has not been accorded to the problems of drug therapy in infants and children. For years the FDA medical officers have recognized that extra care must be taken in dealing with infant preparations. In March 1957 the Bureau of Medicine issued a policy statement with respect to the directions for use or warning statements that were required on a number of drugs in the interest of children's health.

The subcommittee will also be interested in an excerpt from a speech that our Dr. Ralph G. Smith, now Acting Medical Director, made last June before the Drug and Allied Products Guild, Inc., which was published in a nationally distributed law journal. With respect to drugs for children Dr. Smith stated:

Experts in the field of pediatrics have pointed out that infants and children may react to drugs differently from adults. Incompletely developed enzyme systems may result in impaired metabolism from drugs or, conversely, drugs may impair normal enzymatic processes to a greater degree



in children than in adults. It is no longer considered safe to derive children's doses from safe adult doses by an age or weight formula. Safety of new drugs for infants and children must be shown by actual use in the various age groups.

The eighth point in the summary is that certain New Drug Applications contained data suspected of being fraudulent.

In any instance in which we suspect fraud or misrepresentation at the time a New Drug Application is under review a prompt investigation is made before the application is approved. In case fraud or misrepresentation are suspected after the application is approved, a prompt investigation is made looking to withdrawal of approval if there is confirmation of the suspicions. The new investigational use regulations will greatly improve the quality of the data to support New Drug Applications.

The ninth point in the summary is that panels of consultants have not been made readily and easily available for advice and opinion necessary to avoid wrong decisions. Interestingly enough, the witness later referred to instances in which he consulted outside experts for advice in connection with his review of New Drug Applications. Such consultation is a routine procedure by our medical officers. They have free access to outside advice, and, as we have said, we are now working with the Department in efforts to expand greatly the use of outside consultants.

With respect to point number 10 in the summary, we have for many years re-evaluated drugs—both prescription and nonprescription—whenever the need became apparent. The Kefauver-Harris drug amendments will bring to us on a current basis all clinical and other experience to facilitate any needed determination whether the New Drug Application should be withdrawn.

In summary, most of the points made before your committee relate to matters arising under a law that has been extensively revised. As to the drugs and the vitamin specifically discussed, actions were taken in accordance with the law applicable at the time.



BIOGRAPHICAL SUMMARY OF CHARLES D. MAY, M.D.

Senator HUMPHREY. Now I want to ask Dr. Charles May to come to the chair and the witness stand. Dr. May, you have been very patient. I do not believe that it is necessary to present to individuals in this room the detailed summary of your distinguished professional background. I am, however, going to ask that the biographical summary of your eminent career, which has been circulated to the subcommittee, be placed in the transcript of this record at this point.

(The biographical sketch referred to follows:)

EXHIBIT 148

BIOGRAPHICAL SUMMARY ON CHARLES D. MAY, M.D.

The following is a summary of the professional career of Charles D. May, M.D.

BIOGRAPHICAL INFORMATION, CHARLES D. MAY, M.D.

*Positions*

Professor of Pediatrics, School of Medicine, New York University, New York City.

Career Investigatorship, Health Research Council of the City of New York.

Visiting Physician, Bellevue Hospital, New York City.

Attending Pediatrician, University Hospital, New York.

*Relevant Special Experience*

Editor of Pediatrics, journal of the American Academy of Pediatrics, 1954-61.

Member of Council on Drugs of the American Medical Association, 1961-63.

Member of Committee on Public Health, New York Academy of Medicine, 1961-63.

Chairman of Committee on Nutrition, American Academy of Pediatrics, 1956-59.

Member of The Physicians' Council, Inc., 1957 to present.

*Education*

Massachusetts Institute of Technology 1927-29.

Harvard College 1929-31.

Harvard Medical School 1931-35.

*Postgraduate Training*

Children's Hospital, Boston, Mass., 1935-38.

Commonwealth Fund Fellow, 1941.

*Academic Appointments*

Harvard Medical School : Assistant Professor, 1947.

University of Minnesota Medical School : Associate Professor, 1947-52.

State University of Iowa College of Medicine : Professor and Chairman of Department of Pediatrics, 1952-57.

Columbia University College of Physicians and Surgeons : Clinical Professor, 1957-61.

New York University School of Medicine : Professor of Pediatrics, 1961 to present.

*Professional Societies*

Member of American Pediatric Society, Society for Pediatric Research, American Academy of Pediatrics, New York Academy of Medicine, and others.



*Awards*

From American Academy of Pediatrics for outstanding research in 1949 and for noteworthy research in nutrition in 1958.

*Publications*

50 articles in medical literature.

Senator HUMPHREY. I asked you, Dr. May, to interrupt your busy schedule to visit with us today. We would like to get the benefit of your great insights, which we know you can give us, as regards the best future program for FDA, and, in particular, its Bureau of Medicine.

We know you have considered FDA's problems with great care. Moreover, you have considered the problems of clinical testing and other crucial policy issues, which are of interest to other Federal agencies, such as the National Institutes of Health.

Since time is unfortunately short, we know that you will be so kind as to highlight your prepared statement. You had kindly prepared this very important statement at length just as we had asked you to do. Its full text will be printed in the transcript, but we are anxious to submit as many oral questions to you as possible and to receive as many answers as possible.

Therefore, Dr. May, I am going to ask you to proceed as you see fit and give us the benefit of your advice and counsel. We surely appreciate your coming.

**STATEMENT OF CHARLES D. MAY, M.D., PROFESSOR OF PEDIATRICS,  
SCHOOL OF MEDICINE, NEW YORK UNIVERSITY**

Dr. MAY. Thank you, Senator Humphrey.

Mr. Chairman and members of the subcommittee, I am very pleased to have the opportunity to be here and to join with you in this constructive endeavor to take maximum advantage of laws and regulations which are now at our disposal to promote the distribution of the soundest possible products concerned with the health of the people.

In your opening remarks you suggested that the witnesses might be invited to comment upon remarks of other witnesses. I wonder if you would care for me to make a few remarks concerning Dr. Nestor's testimony before proceeding with my own.

Senator HUMPHREY. I would be very pleased if you would. You are now going to comment on some of the testimony of Dr. Nestor?

Dr. MAY. If I may.

Senator HUMPHREY. Please go ahead.

Dr. MAY. First of all, may I say I join with the others in admiring the courage of Dr. Nestor in making these remarks. Courage is something most of us admire, but hope we will never have to exhibit. I think he is particularly to be congratulated in being specific in what he has to say. It is remarkable that much of what he has to say and what I have to say have a considerable relationship to one another, although we have had no previous communications.

In fact, I had not met Dr. Nestor before today and had no knowledge of what he might be saying.



## CONSIDER THE ATMOSPHERE IN WHICH DECISIONS WERE MADE

One thing, I believe, is important: That in the analysis of what he has said a very careful distinction be made between those things which might be called abuses or failures in duty and those things which reflect the atmosphere of the times, when some of the decisions were made.

It is this consideration which I shall come back to again in my own remarks; namely, that the total atmosphere in which action must be taken is a very important consideration. That is, the degree of excellence which is generally embraced will determine, to a considerable extent, the force with which a person may take a stand. A regulatory agency is not a simple, literal, unimaginative, police operation. It is a matter of bringing to bear the soundest information available at the time in the best and most judicious possible manner so as to be fair to those persons upon whom the agency is exercising this judgment.

If they are going to observe the sensitivity and the creativity of the free enterprise system, they must bring to bear upon industry only those attitudes which are justified, not only by the evidence and by the judgment, but by the circumstances which exist at the time.

Now, these circumstances have changed enormously, and they need to change even more. My statement will be primarily concerned with the dynamic process whereby the atmosphere of excellence may be constantly maintained at a high level so as to support the officials who are working in behalf of the public interest, and to protect them from the perfectly natural pressures that come from private enterprise.

As a matter of fact, I suppose that if historians were to look at the situation on this planet and noted it became evident that slaves should be free and should enjoy equal rights, that on that day all should have received those benefits. Yet, we are aware of the fact that this atmosphere had to be developed to the point where we could all join hands in achieving the highest possible attainment in this respect.

## THE ISSUE OF GENERAL READINESS TO ACHIEVE EXCELLENCE

It was Thomas Jefferson who made it a habit to refrain from action until the public mind was brought to a state of readiness. Fortunately, we now have a state of readiness on all fronts to achieve the excellence in drugs and foods which the public health demands. It is in this manner that I believe Dr. Nestor's comments should be judged, that is, what portion reflects the faults of all of us.

Mind you, the profession, itself, has only addressed itself to some of these problems in recent months. Pediatricians had not given sufficient attention to the problems of the special actions of drugs with relation to the newborn. Just a couple of years ago I served as editor on a medical journal, and I had to seek out someone to comment on this subject, and, in addition, to suggest to him what he might have to say in order that the subject might receive due attention from the profession. Professional persons who are endeavoring to express professional excellence must somehow bring to a state of readiness the ideas and the ideals of the medical organizations of which they are a part, before they can join hands with anyone in achieving the standards to which we all aspire.



I say this not to discount in any way any specific charges which Dr. Nestor may have made, but to make it possible for us to be judicious and fair, as I know this committee and all the public wishes to be, about those public servants who have endeavored to enforce the laws of the land through the regulatory agencies of the FDA, who, whatever else may be said, can be given credit for the present excellent state of our drugs and foods.

In short, what we are aiming at is improvement, to be sure; not condemnation in toto. But, more than that, a system whereby we can maintain this excellence at all times, and not have to depend upon occasional Senate hearings to stir us all to a greater state of excellence.

It is in this way that I formulated my thoughts in the beginning, and I am pleased to see that they are a natural sequel to what Dr. Nestor has put before us.

Because Senator Humphrey said I may abbreviate what is put forth in the prepared statement to allow time for possible elaboration on certain points, I shall highlight certain portions of the statement.

First of all, my comments are stimulated by certain requirements of the Drug Amendments Act of 1962.

I wish also to say parenthetically that I hope that everyone will give careful attention to the opening paragraphs in which I pay tribute to Senator Kefauver and his associates for their contribution, and to Senator Humphrey and his associates for the contributions which they are in the process of making. This is not mere praise in an effort to "spike guns before the battle," but this is a sincere appreciation of your efforts.

Senator HUMPHREY. Thank you very much.

#### SUBSTANTIAL EVIDENCE IN NEW DRUG APPLICATION

Dr. MAY. I am concerned with those provisions in the new law that call for presentation of substantial evidence in behalf of any drug which is to be placed upon the market, before approval is given for marketing. This clause of the law says that this evidence shall be presented and it shall also be evaluated. Because these two portions of the endeavor are both vitally important, they must be viewed together and cultivated simultaneously.

The term "substantial evidence" is given some substance, by virtue of the fact it is stated in the law to mean evidence obtained from well-controlled investigations conducted by persons qualified by suitable training and experience. In other words, definition of "substantial evidence" is not going to be left entirely to legal quibbling, although it will certainly leave room for a conflict of opinion. But it is expressly stated that we are obliged to somehow find a means whereby this substantial evidence will be the kind derived from well-controlled investigations in the highest sense of scientific excellence.

The law further calls for mention in the promotional and informational material of the side effects or adverse reactions of drugs, which calls for a clear commitment in this respect.

Manufacturers are also directed to supply the description of a drug, the package insert, so called, to any physician who requests information about the product. In other words, whatever else may be sent him in response to such a request, this must also be included. It is important to notice that he must request something before he gets anything.



Although my statements relate especially to collection and evaluation of scientific data and informational activities, other major obligations of the FDA must be kept in mind, including inspections and enforcement, and with proper regard for the welfare of the industry, as well as of the people.

#### ASSURE FREE EXCHANGE OF AUTHORITATIVE OPINION

In this respect, again, we must come back to Dr. Nestor's testimony and realize that this problem of who shall overrule whom is not a simple one. When the larger issues are at stake, it is not always a matter of saying that one discipline is sacrosanct; neither the politician (or should I call him a political scientist) nor the members of a consumer group necessarily assume the paramount position.

What we need is a methodical and open means of bringing out the differences of opinion so that the truth may be hammered out where we can all hear and see it, and not wait until it has to be smoked out by some sort of investigative procedure.

Senator HUMPHREY. Doctor, I hesitate to interrupt, but the very problem that you are referring to has been brought to light in another area of the Senate Committee on Government Operations.

There is a bit of difference between the Secretary of Defense and some of his advisers on a little matter called the TFX, where certain people were overruled.

Dr. MAY. As I understand it, the most desirable arrangement is to control the budget, if you are going to be the person who can overrule everybody else.

Senator HUMPHREY. That helps a great deal.

Dr. MAY. Although the Food and Drug Administration is often characterized as a regulatory agency, in practice, the sort of regulation called for is actually judicious evaluation of the best available evidence in the tradition of fine, scientific, and scholarly endeavor.

I use this term "scholarly" advisedly, because the idea of the scientist is often that he works in a fume-filled room with test tubes and boiling cauldrons and flashing lights. But much of intellectual endeavor takes place under quieter circumstances, and is a legitimate part of the evaluatory process, and must be provided for, as surely as the more classic and orthodox scientific arrangements.

In other words, the Food and Drug Administration can fulfill expectations in a *sound* and *fair* fashion only with the aid of personnel capable of evaluation of highly complex data, and when the evidence placed before them is gathered by methods and investigators meeting the best of current standards.

Furthermore, there must be developed simultaneously a program to improve methods and to produce a sufficient supply of personnel trained to collect and evaluate the necessary data, and, by these means, promote steadily rising standards.

I should like to make it clear that I believe that whatever is done should be done in such a way as to preserve the creativity of science and to foster the productivity of industry and protect the rights of productive enterprise to a just reward. There can be no successful civilization in a bankrupt state of affairs.



I should like to comment upon certain aspects of the present situation, and then follow with what I consider to be particular remedies that might be explored.

We can consider this in two phases: the phase prior to the approval of the drug for marketing, and the phase after the drug is marketed.

Prior to approval for marketing, obviously the situation calls for the accumulation of sound evidence and the appraisal of this evidence by the most capable people who can be assembled. In the process someone will be called upon to exercise a judgment which will be in favor of the public interest, as well as fair to the industry concerned.

#### THE NEEDS IN CLINICAL INVESTIGATION

I am not going to try to review the enormous documentation which would describe the lack of adequate facilities to accumulate the evidence called for, or to train the people who can evaluate this evidence. I do believe it might be worthwhile to emphasize from my statement a few words quoted from Dr. Louis Goodman, who may be considered one of the outstanding pharmacologists in the country, author of a most important text on the subject, a man who has had enormous experience and a reputation for sound judgment and forthright expression of opinion. He stated before the Senate hearings prior to the adoption of the Drug Amendments Act of 1962:<sup>30</sup>

Everyone is agreed, I believe, that a major bottleneck in the long chain of events from the first laboratory discovery of a new chemical with potential therapeutic value to its ultimate successful use by the practicing physician is the early clinical trial in patients. The number of properly trained clinical investigators interested in assessing the properties of new chemicals and the number of suitable hospital and outpatient facilities are limited. This may seem strange, in view of the large number of university physicians and clinics in the United States, but it is a fact. Pharmaceutical industries often have to stand in line to obtain the services of recognized experts for the early clinical tests of their new products in patients. All of us who have seen the mass of laboratory and clinical information submitted to the FDA, even by the very best drug houses, in support of New Drug Applications are repeatedly dismayed by the welter of anecdotal case reports and uncontrolled clinical studies by physicians who are not equipped with the training and facilities for meaningful pharmacological and toxicological studies of new drugs in patients. All this is very expensive and very time consuming, adds to the cost of drugs, and doesn't provide the necessary information for the proper evaluation of a candidate drug.

We urgently need more good clinical pharmacologists, more first-rate clinical testing outlets, and more unrestricted financial support for properly controlled, objective, early clinical evaluation of new drugs prior to review by the FDA \* \* \*.

Dr. Nestor has already given you insight into the difficulties experienced within FDA, both in terms of receipt of adequate data and in terms of the attracting of personnel to aid in the task of evaluation. Statements circulated in behalf of the drug industry expressed the same dissatisfactions and agreed that steps must be taken to eliminate the deficiencies as soon as possible. Medical schools and medical organizations are cognizant of the woeful lack of facilities and qualified personnel for evaluation of drugs, but apparently cannot provide substantial resources without undermining equally vital obligations. To

<sup>30</sup> (EDITOR'S NOTE.—Dr. Goodman's testimony will be found in Senate Committee on the Judiciary, Subcommittee on Antitrust and Monopoly, Hearings on Drug Industry Antitrust Act, pursuant to S. Res. 52 on S. 1552, 87th Cong., pt. 1, "AMA and Medical Authorities," p. 211 ff.

(Additional notes by the editor of this volume follow.)



be sure, enormous sums are being spent to support medical research and education by both private and Government sources.

The plain fact remains that the area of medical science of greatest concern to the FDA and others concerned with drug therapy, namely, clinical pharmacology, is deplorably underdeveloped.<sup>31</sup>

#### RELATIVE INACCESSIBILITY OF CLINICAL INFORMATION TO THE PRACTITIONER

Now let's turn to the phase of circumstances after the drug has been approved and is being distributed on the market.

The plight of physicians striving to keep informed about the abundant flow of new drug preparations and health products has become common knowledge. No one will deny that systematic help is needed from trustworthy sources.

The complete descriptive material included in the package with new drugs is the result of the best efforts of the FDA and the drug industry. Unfortunately, at the moment of prescribing, this literature usually lies out of convenient reach in the package stored in the pharmacy, and so the busy doctor commonly does the best he can with fragmentary information he has gathered here and there.

It just occurred to me yesterday to go down to the hospital pharmacy, and there I pulled out of the wastebasket a small pile of package inserts which accompany new drugs. These were taken from packages from which prescriptions were filled, sent to the hospital wards, and the same would have been true had the package been given to the patient. Package inserts were removed and dropped in the wastebasket, so that the physician did not have this information at his elbow. Everybody has commented upon the fact that there is something unsatisfactory about this system, whatever its merits may be.

#### ONE WAY TO REDUCE ADVERSE REACTIONS

Collection of data on adverse reactions to drugs<sup>32</sup> and other health products is a necessary part of monitoring the consequences of widespread use. However, counting the casualties should be kept secondary to preventing them by adequate testing before approval for marketing. One way of lessening adverse reactions is to encourage discrimination in prescription of drugs by better guidance on the usefulness and hazards of drug therapy, and so reduce consumption of potentially harmful agents for dubious reasons.

#### EXPAND AND REORIENT FDA SCIENTIFIC ACTIVITIES

Now let us turn to certain practicable solutions. First of all, as to the scientific program of the FDA:

More is involved than simply attracting trained personnel and calling for application of known methods—the former are too scarce and almost no facilities exist that could be integrated into a scheme for

<sup>31</sup> See pt. 4 (soon to be published) for related comments by Walter Modell, M.D., and for exhibits on the problems of clinical pharmacology. See also pt. 2, exhibit 83, p. 528, for a report on the subject by the New York Academy of Medicine.

<sup>32</sup> For additional comments over a period of years on the issue of compilation, evaluation, and dissemination of information on adverse drug reactions, see exhibit 157, p. 1079.



proper testing of drugs, training of specialized personnel, and development of more adequate methods. There is no choice but to devise new arrangements for furnishing comprehensive solutions to old and new problems.

In my opinion, a promising approach is to expand and reorient the scientific activities within the FDA and couple these with new centers for investigation of drugs in medical institutions. Without spelling out details, although I am prepared to do so, this means supporting research and scholarly activities within the FDA to an extent which will enable direct participation by all suitable and interested personnel.

In addition, it means that abundant resources would be made available for distribution through the scientific staff of FDA in support of specially organized centers for clinical pharmacology on a continuing basis. It is suggested that these arrangements be set up under the auspices of the scientific staff of the FDA, rather than as an independent enterprise or a function of some other Government agency, for the following reasons.

1. It is inconceivable that sufficient competent scientists can ever be attracted to the FDA if their principal duties are predominantly administrative or regulatory in nature. Sound and fair regulation is inseparable from scientific and scholarly occupation. Capable people seek challenge, stimulation, significance, and prestige from their work as much as monetary reward. These elements have held university faculties together against tempting pecuniary offers. Vicarious and spasmodic contact with research in other places is not enough. Investigators within the FDA would undoubtedly accept an appropriate blending of research activity with administrative and regulatory duties, just as university investigators devote a considerable fraction of their time to serving on committees and reviewing boards in addition to teaching.

2. Through the development of the scientific programs, there could hardly be a better way to provide for training of the urgently needed specialized personnel.

3. The FDA could become a focal point for scientific and scholarly activities through the ties with centers of investigation established under a systematic plan for supporting extramural research. This will give the character and prestige that draw capable people.

4. Cooperation and integration of the Government services with the activities in the medical centers and in industry would be a natural outcome among like-minded people pursuing common interests. Cooperation and integration without mutual respect is virtually impossible to achieve by command.

#### STRENGTHEN SCIENTIFIC INFORMATION PROGRAMS

A vital program of acquisition and centralized storage of sound information is an important phase in development of better means to keep physicians and consumers well informed.

Expansion and reorientation of scientific and scholarly activities of the FDA may require alterations in the administrative and organizational structure. I believe this could be done without dislocating the entire operations or creating pockets of isolated activity unintegrated with the whole.



Another item of concern after the drug has been approved for marketing is the matter of dissemination of information to licensed prescribers.

#### MAKING PACKAGE INSERT INFORMATION MORE ACCESSIBLE

The very least information the prescriber should have at his elbow at all times is the descriptive material approved by the FDA to accompany the product as a package insert. The inserts certainly should be in the packages for obvious reasons, but the same information should be provided to the prescriber in a more convenient form. If the package insert for every drug on the market was reprinted in a single volume, the bulk and fineness of print would probably render it useless. Criteria for inclusion could be adopted to keep the volume to manageable proportions and still be of enormous value to prescribers. The mailing list could be maintained automatically by obtaining addresses from the licensing bureaus for physicians, and others.

I shall be glad to expand on that point, if you so desire.

I might say in passing that these descriptions of products in the package inserts are really quite well done, extremely useful, and yet it is horrible to relate that many physicians are not in the habit of using them—because of inconvenience, not out of willful neglect.

Senator HUMPHREY. Isn't it true, Doctor, first of all that the provision was knocked out of the Kefauver bill which would have required the sending of the package inserts to the doctors or even a modification of the package inserts?

It is also my understanding that Food and Drug has given a good deal of attention to the improvement of the package insert descriptive material, but the trouble is that the package insert descriptive material comes to the pharmacist.

Dr. MAY. That is so.

Senator HUMPHREY. He has it on his shelf. The doctor sits off in his office or the clinic and prescribes; the pharmacist gets the prescription, he reaches up and picks it off the shelf and throws the box away, throws the insert material away, or at best checks with the prescription to see whether or not the dosage that has been recommended or the unit, pill, or amount of elixir or liquid conforms with the package insert directions.

So the doctor doesn't really see—unless he goes out of his way to do so, and he is a very busy man—this highly developed, concise, package insert descriptive material and dosage direction. Is that correct?

Dr. MAY. That is correct, sir. Now even if he had the diligence which we might all suppose he ought to have to make a complete collection of all the inserts of products which he is using or is apt to use, one of the unfortunate things is that they come in very many sizes and shapes.

Senator HUMPHREY. Yes.

Dr. MAY. And I can't imagine a more inconvenient mass of material to file or to use.

Senator HUMPHREY. It would be hopeless.

Dr. MAY. I don't believe that any educator thinks there is any advantage to make it difficult to learn.



## PACKAGE INSERTS RECEIVED WITH DETAILERS' SAMPLES

Senator HUMPHREY. Of course, he does get what we call the detailing service from the pharmaceutical house in which samples, for lack of a better phrase, are presented to the doctor, in which the descriptive material is to be found.

Dr. MAY. Yes.

Senator HUMPHREY. But again, this material pours in, and where are you going to file all the samples? I would like to take you on a little tour even of the medical facilities of the U.S. Senate, take you down to the pharmacy establishment there, and you will find it is rather difficult to keep track of these inserts.

Dr. MAY. Yes. Now, in my opinion, none of this is really a reflection upon either the industry, the profession, or the FDA. It is an accidental byproduct of our civilization, gradual separation of functions, of the pharmacist on the one hand and the physician on the other.

Whereas once he may have done his own prescribing, may even have done his own mixing of herbs, et cetera, now the product is manufactured in one place, stored in another, and dispensed, or rather prescribed, in still another place.

So the historical development of things has presented us with a problem which does not seem to me could really exhaust our ingenuity, but nevertheless must be corrected.<sup>32a</sup>

Senator HUMPHREY. I think it ought to be stated that there are instances, and many of them, in which the doctor and the pharmacist do consult on these insert matters.<sup>33</sup>

Dr. MAY. Oh, yes.

Senator HUMPHREY. I mean in the smaller communities in particular where there is an intimate relationship. The doctor and the pharmacist frequently meet and discuss a new product that may be detailed in the community by a specialist from one of the drug houses, and they go over the package insert—I have seen this happen many times. But when you get into one of these huge urban centers where people are numbers instead of personalities, and where you walk into one of these massive clinics or go into one of these big pharmacies, and nobody knows you are coming or going, you doubt that you are really going to have very much consultation.

Dr. MAY. Yes. I would like to come back to a specific proposal in this connection later, if you have time.

Senator HUMPHREY. Good.

## PROPOSED SURVEILLANCE PROGRAM ON ADVERSE REACTIONS

Dr. MAY. Another matter which must receive attention after the drug has been marketed is that of collecting data on adverse reactions. In my opinion, the Food and Drug Administration should maintain its own system for collecting information on adverse reactions to drugs and other occurrences after health products are marketed. Volunteer

<sup>32a</sup> See exhibit 161, p. 1159, for results of a survey on physicians' preferences for dissemination of package inserts and related information.

<sup>33</sup> See exhibit 164, p. 1176 for a trade press editorial on cooperation between physician and pharmacist.



reporting is undependable. Committees on safety of drugs and on adverse reactions which become organized in the wake of a calamity have unpredictable futures. Information collected by others may never reach the FDA, or be slow to do so. The FDA must have a sustained and dependable system of direct surveillance, which would welcome supplementary efforts. Intimate involvement of the scientific staff of the FDA in problems of adverse reactions would sharpen the ability to detect ominous drugs before approval for marketing, and appropriate warnings would accompany the product.

#### COMPILING INFORMATION FROM FEDERAL HOSPITALS

Senator HUMPHREY. Doctor, just on that particular subject, this is a matter we have discussed at length in other hearings. I am sure you are aware of that. That is something about which I have been very concerned.

The problem always has been raised; well, "it is rather difficult to set up this kind of surveillance, this kind of control of information collection, because so much of the medical practice and the pharmaceutical practice is in the private sector"; the private hospitals, clinics, and pharmacies, and so forth, are involved.

But we do have a large number of Government beds and Government clinics where the FDA could have a very good, tightly organized system of reporting on efficacy, safety, reactions to drugs; is that not true?

Dr. MAY. That is correct; yes, sir. It is necessary to arouse a suitable climate of opinion, so that people recognize the urgency, and thereby the willingness to cooperate is engendered.

Senator HUMPHREY. Of course, the Congress has never provided FDA with the means to do this job.

Dr. MAY. I am sure that the means could not have been equal to the job, which has assumed such enormous proportions with such an increasing tempo.

Senator HUMPHREY. Your suggestion is very worthwhile.

#### PROFESSIONAL AND CITIZEN CONSULTATION FOR FDA

Dr. MAY. Now I would like to come to the question of providing consultants to the Food and Drug Administration, realizing full well we cannot house all the experts in the land in this agency. Some methodical means must be provided whereby all the parties concerned, the manufacturer and those concerned with the prescription and the ingestion of foods and drugs might have an opportunity to, on the one hand, be assured that their interests were being properly safeguarded, and on the other, that any grievances that they might possess could receive a sensible and unemotional audition.

I believe that permanent advisory councils concerned with all activities and relations of the FDA and meeting regularly with officials of the FDA and other Government officials would at least provide for methodical communication. Perhaps one advisory council should be made up of scientists, technologists, and administration specialists and the members selected for competence without concern for representation of one faction or another.



A second advisory council would be essentially a citizens' group and serve primarily as assurance to the consumer that his interest would be foremost and that a regular mechanism existed to call any of the parties to public account—Government, industry, profession, or lay groups. This council could lend its influence to programs for a well-informed public.

I think it is particularly important that it should be provided that the officials of the FDA shall meet with the councils regularly on a fixed schedule, and not just if and when someone chooses to convene the group.

Senator HUMPHREY. This would follow somewhat along the Advisory Councils that meet with the NIH?

Dr. MAY. Yes, sir.

Senator HUMPHREY. The NIH Institutes?

Dr. MAY. Yes. They have a National Advisory Council in terms of broader policies, et cetera; they also have the study groups which constitute smaller groups of consultants, and both of these are vital elements in an on-going and dynamic program, especially one that is involved in the public service.<sup>34</sup>

Senator HUMPHREY. Indeed.

Dr. MAY. Would you care for me to read the summation? It is rather short. I would like to drive home the atmosphere or the summation of this report.

Senator HUMPHREY. Please go right ahead.

Dr. MAY. A disservice is done to the FDA when it is referred to as a regulatory agency in the sense of police action. Scientific leadership is incompatible with this concept. By that I mean, without a respectable function, the capable scientist will not participate in the operation. Sound and fair regulation is inseparable from scholarly appraisal of adequate data acquired by excellent scientific procedures.

Throughout I am making it emphatically clear that sound evaluation and fair evaluation are inseparable, and there is as much concern that the industry receive a fair deal and not have a product unfairly excluded as that the public not be in any way harmed by the approval of a product inimical to their health. We must be aware of the fact that soundness represents the only road to fairness.

The staff of the FDA would be left in an untenable position without this fusion of functions. If they become totally absorbed in regulation, they will certainly be lost to the world of science. As they become totally absorbed in basic scientific research, they will certainly not fulfill the expectations to be made of them regarding safeguards to the food and drugs of the people.

Scientific leadership is exercised only by working scientists truly occupied in the mainstreams of investigation. Membership in the scientific staff of the FDA cannot be made appealing simply by furnishing ringside seats to exciting research carried on in other arenas. This refers particularly to proposals that I have heard about allowing them to have occasional visits to active centers or joint appointments in institutions several miles or more away. These are what I would refer to as vicarious and highly unsatisfying participation in scientific effort.

<sup>34</sup> For a chronology of excerpts of various opinions during the years 1955-63 on consultants for FDA, see exhibit 138, p. 978.



## NEED FOR EXTRAMURAL NETWORK OF INVESTIGATIVE CENTERS

A substantial intramural program of research and scholarly endeavors should be coupled with an extramural network of investigative centers in medical institutions to create an atmosphere of mutual respect and shared pride and prestige. Merely adding or redirecting the resources administered by other agencies as a means of promoting research in clinical pharmacology does not seem a promising way to enhance the scientific appeal and leadership of the FDA.

In other words, any system for the acquisition of sound data on drugs must be developed with consideration of the other basic problem, namely that of enhancing the scientific program of the FDA, making the FDA appeal to capable persons who will both evaluate and sit in judgment upon these data.

Assuming the majority still believe our Government should do only what cannot be, or is not, done by private agencies, the present situation and probable trends seem to call for a magnitude of resources and effort far beyond the capacities of any combination of private enterprises. In other words, this is not a situation which calls for some sort of abbreviated or patching efforts. We are going to have to look at this problem in all of its bold outlines and take equally vigorous action. Otherwise we will be faced with a complete collapse, not only of the FDA, but of the entire system of safeguarding the food and drugs of the people of this country.

Furthermore, the nature of the problems requires leadership from a source concerned primarily with the public interest and beyond the reach of any faction too bent on self-interest. By that I mean beyond the reach of self-centered scientists who might like to pursue their way completely unmolested, as well as from any vested interest that would like to gain control of the operations. We are asking for a balanced consideration of all of the assets and the frailties of each group involved.

## NEED FOR FDA TO SET EXAMPLE OF EXCELLENCE

The ultimate goal is to have the FDA set an example of excellence and so draw the best from all who are served, thereby reducing the need for regulation. The surest, if not the shortest, road to cooperation and enlightenment is via persuasion—not compulsion. Only convincing competence will lure the wary up this steep path.

## SECURING JUDGMENT OF FDA'S CAREER OFFICIALS

Finally, I would like to make a personal plea that anyone attempting to plot the future course should listen attentively to those who have labored long with the complex concrete operations of the FDA, and with no small success—I refer to the present staff of dedicated public servants.

And whatever omissions they may have had or whatever derelictions they may have shown, they are in the same boat as the rest of us, of mankind.

If all of the physicians who do not measure up to the qualifications of Sir William Osler were eliminated from the profession, the ranks would be remarkably thin. I daresay that the Congress might not be



quite so populated if we insisted on the qualifications described in Plato's description of the philosopher king.

Thank you very much.

Senator HUMPHREY. Congress is not too populated anyway.

#### EXHIBIT 149

#### STATEMENT PREPARED BY CHARLES D. MAY, M.D., FOR THE SUBCOMMITTEE ON REORGANIZATION AND INTERNATIONAL ORGANIZATIONS

There follows the prepared text of the statement submitted by Charles D. May, M.D., for the Subcommittee on Reorganization and International Organizations.

#### STATEMENT PREPARED BY CHARLES D. MAY, M.D., PROFESSOR OF PEDIATRICS, SCHOOL OF MEDICINE, NEW YORK UNIVERSITY <sup>35</sup>

A cursory review of events which precipitated the establishment of a Federal Food and Drug Administration and preceded each major improvement in the original act might influence one to believe that scandal and calamity are the main springs of legislative progress. Such a conclusion would be wrong and unfair. The unfortunate and dramatic episodes may have served to arouse more widespread concern, but turbulent feelings could not have been gathered into coherent action unless sensible direction had been available. Each step in development of laws aimed at securing proper foods and drugs for the people was preceded by prolonged efforts to appraise the needs and devise solutions.

Recent events bear this out. A band of Congressmen under the leadership of Senator Kefauver had been investigating and studying the manufacture, marketing and prescribing of drugs, and improvements in existing laws had been formulated and placed before the Congress. Any uncertainty about the need for new legislation was swept away by the thalidomide calamity. Surely the measures adopted were better because of the diligence and dedication of those who had long been striving to devise means for elimination of the imperfections their investigations had delineated. The indispensable aid of many must be acknowledged: the staffs of congressional committees; consultants from industry, Government agencies and the professions; journalists; and citizens committees, to name a few.

And all the while, whether in the limelight or ignored, praised or condemned, the persons who operate the Food and Drug Administration have gone steadily on with the daily work—too seldom the object of solicitous interest.

Against this background the present hearings of this congressional committee pertaining to the Food and Drug Administration assume special significance. The purpose seems to be to find the best means of taking full advantage of the laws and regulations on hand, to facilitate a continuous excellence and efficiency in operation of the agency, and to originate plans and procedures that will enable the agency to keep pace with demands of the changing times. Particularly gratifying is this effort to bring us closer to prevention of calamities by far-sighted planning, and to promote maximum cooperation among all agencies contributing to the public health through foods or drugs. Undoubtedly specific recommendations will be forthcoming, helpful to the FDA and deserving support from Congress where necessary.

#### CERTAIN REQUIREMENTS OF DRUG AMENDMENTS ACT OF 1962

This preliminary statement is directed at certain topics brought into prominence by requirements recently imposed on the FDA and others, namely:

1. Before a new drug may be marketed, "substantial evidence" must be *presented* and *evaluated* regarding the effectiveness claimed for the drug under the proposed conditions of use.

<sup>35</sup> (Note by the witness: Dr. May is meeting with the subcommittee through unsolicited invitation from the chairman to present personal comment on the matters under consideration. Responsibility for the facts and opinions herein (or to be presented in the course of the hearing) is accepted by the author solely as an individual, and they should in no way be construed as being endorsed by or representative of the views or positions of any organization or group with which Dr. May may be associated—in the past, present, or future.)



2. The term "substantial evidence" is stated to mean evidence obtained from well-controlled investigations conducted by persons qualified by suitable training and experience.

3. Promotional and informational material disseminated regarding drugs must include a summary of known side-effects (or adverse reactions).

4. Manufacturers must supply the description of a drug product (package insert) approved by the FDA to any licensed practitioner who *requests* information about the product.

Although these particular requirements relate especially to collection and evaluation of scientific data and informational activities, other major obligations of the FDA must be kept in mind, including inspections and enforcement. All the functions of the agency must be in balance, and integration of one division must have a salutary effect on integration of the overall operation. The present law and regulations do not pose new problems, but bring into sharper focus the imperative need for solutions. These must be sought and applied with a sense of urgency.

Although FDA is often characterized as a regulatory agency, in practice the sort of regulation called for is actually judicious evaluation of the best available evidence in the tradition of fine scientific and scholarly endeavor. In other words, the FDA can fulfill expectations in a sound and fair fashion only with the aid of personnel capable of evaluation of highly complex data, and if the evidence placed before them is gathered by methods and investigators meeting the best of current standards. Furthermore, there must be a simultaneous program designed to improve methods and to produce a sufficient supply of personnel trained to collect and evaluate the necessary data, and by these means promote steadily rising standards.

To bring the benefit of all the foregoing activities to bear on the health of the people obviously calls for commensurate measures for dissemination of information and facilitation of discriminating habits in the prescription of drugs and the use of foods.

Whatever is done must stimulate the creativity of science and industry and protect the rights of productive enterprises to a just reward. The greatest contributions to the public health will emerge from harmonious relations between the elements in industry, the Government, and the professions which undertake to provide only health products of proven worth. The ultimate goal is to cultivate voluntary excellence in preference to a monstrous system of external regulation.

#### THE PRESENT SITUATION

##### A. Prior to approval for marketing

Numerous analyses and impassioned pleas have appeared that describe the inadequacies and handicaps now obstructing acceptable evaluation and use of products proposed for the preservation of health or cure of disease. All of the voluminous documentation need not be reviewed here but one succinct, representative statement deserves quotation. A well-informed pharmacologist, Dr. Louis Goodman, made the following remarks during the congressional hearings from which the Drug Amendments Act of 1962 was developed:

Since so much depends on the scientific value of the early clinical studies on a new drug prior to submission of data and claims to the FDA in support of a New Drug Application, many persons have given serious attention to the problem of how to improve this phase of the investigational program. Under the new law, this phase would be crucially important. If means can be found to assist the pharmaceutical companies in this stage of drug development, all stand to gain, and the task of the FDA would thereby be made easier.

Everyone is agreed, I believe, that a major bottleneck in the long chain of events from the first laboratory discovery of a new chemical with potential therapeutic value to its ultimate successful use by the practicing physician is the early clinical trial in patients. The number of properly trained clinical investigators interested in assessing the properties of new chemicals and the number of suitable hospital and outpatient facilities are limited. This may seem strange, in view of the large number of university physicians and clinics in the United States, but it is a fact. Pharmaceutical industries often have to stand in line to obtain the services of recognized experts for the early clinical tests of their new products in patients. All of us who have seen the mass of laboratory and clinical information submitted to the FDA, even by the very best drug houses, in



support of New Drug Applications are repeatedly dismayed by the welter of anecdotal case reports and uncontrolled clinical studies by physicians who are not equipped with the training and facilities for meaningful pharmacological and toxicological studies of new drugs in patients. All this is very expensive and very time consuming, adds to the cost of drugs, and doesn't provide the necessary information for the proper evaluation of a candidate drug.

We urgently need more good clinical pharmacologists, more first-rate clinical testing outlets, and more unrestricted financial support for properly controlled, objective, early clinical evaluation of new drugs prior to review by the FDA \* \* \*.<sup>36</sup>

To this may be added extracts from a report describing difficulties as seen from within the FDA:

\* \* \* the physicians of the FDA are in something of an untenable position \* \* \* they must within short periods of time make decisions one way or another, and their decisions affect the health and safety of many citizens \* \* \* the information which they need to reduce almost to zero the risks of an incorrect decision too often is unavailable to them, because of weakness in research methods.<sup>37</sup>

The difficulties of the FDA have been aggravated by lack of success in attracting enough capable physicians and scientists to cope with the kind and amount of the work required of the agency, according to reliable sources.

Statements circulated in behalf of the drug industry express the same dissatisfactions and agree that steps must be taken to eliminate the deficiencies as soon as possible.

Medical societies and the medical schools and hospitals are cognizant of the woeful lack of facilities and qualified personnel for evaluation of drugs but apparently cannot provide substantial resources without undermining equally vital obligations. To be sure enormous sums are being spent to support medical research and education by both private and Government sources.

The plain fact remains that the area of medical science of greatest concern to the FDA and others concerned with drug therapy, namely clinical pharmacology, is deplorably underdeveloped.

This recitation of flaws is not grounds for gloom or despair. The food and drug supply of the United States is probably the best in the world. The point is, that to keep it this way the FDA which has served so faithfully and well must be furnished with men and methods and evidence equal to the needs now and in the years ahead.

#### *B. After marketing*

The plight of physicians striving to keep informed about the abundant flow of new drug preparations and health products has become common knowledge. No one will deny that systematic help is needed from trustworthy sources. The complete descriptive material included in the package with new drugs is the result of the best efforts of the FDA and the drug industry. Unfortunately at the moment of prescribing, this literature usually lies out of convenient reach in the package stored in the pharmacy, and so the busy doctor commonly does the best he can with fragmentary information he has gathered here and there.

Collection of data on adverse reactions to drugs and other health products is a necessary part of monitoring the consequences of widespread use. However, counting the casualties should be kept secondary to preventing them by adequate testing before approval for marketing. One way of lessening adverse reactions is to encourage discrimination in prescription of drugs by better guidance on the usefulness and hazards of drug therapy, and so reduce consumption of potentially harmful agents for dubious reasons.

### PRACTICABLE SOLUTIONS

#### *A. Scientific program*

More than simply attracting trained personnel and calling for application of known methods is involved—the former are too scarce and almost no facilities exist that could be integrated into a scheme for proper testing of drugs, training

<sup>36</sup> (Note by editor of this volume: Hearings before the Senate Committee on Judiciary, Subcommittee on Antitrust and Monopoly, July 18, 1961, pt. 1, pp. 214-15.)

<sup>37</sup> (Note by editor of this volume: Report to meeting of FDA officials on Oct. 4, 1961, edited by Shelby T. Grey, Director of Bureau of Program Planning and Appraisal, FDA.)



of specialized personnel, and development of more adequate methods. There is no choice but to devise new arrangements for furnishing comprehensive solutions to old and new problems.

In my opinion, a promising approach is to expand and reorient the scientific activities within the FDA and couple these with new centers for investigation of drugs in medical institutions. Without spelling out details, this means supporting research and scholarly activities within the FDA to an extent which will enable direct participation by all suitable and interested personnel. In addition, it means that abundant resources would be made available for distribution through the scientific staff of FDA in support of specially organized centers for clinical pharmacology on a continuing basis. It is suggested that these arrangements be set up under the auspices of the scientific staff of the FDA, rather than as an independent enterprise or a function of some other Government agency, for the following reasons.

1. It is inconceivable that sufficient competent scientists can ever be attracted to the FDA if their principal duties are predominantly administrative or regulatory in nature. Sound and fair regulation is inseparable from scientific and scholarly occupation. Capable people seek challenge, stimulation, significance, and prestige from their work as much as monetary reward. These elements have held university faculties together against tempting pecuniary offers. Vicarious and spasmodic contact with research in other places is not enough. Investigators within the FDA would undoubtedly accept an appropriate blending of research activity with administrative and regulatory duties, just as university investigators devote a considerable fraction of their time to serving on committees and reviewing boards, in addition to teaching.

2. There could hardly be a better way to provide for training of the urgently needed specialized personnel.

3. The FDA could become a focal point for scientific and scholarly activities through the ties with centers of investigation established under a systematic plan for supporting extramural research. This will give the character and prestige that draws capable people.

4. Cooperation and integration of the Government services with the activities in the medical centers and in industry would be a natural outcome among like-minded people pursuing common interests. Cooperation and integration without mutual respect is virtually impossible to achieve by command.

5. A vital program of acquisition and centralized storage of sound information is an important phase in development of better means to keep physicians and consumers well informed.

Expansion and reorientation of scientific and scholarly activities of the FDA may require alterations in the administrative and organizational structure. I believe this could be done without dislocating the entire operations or creating pockets of isolated activity unintegrated with the whole.

#### *B. Information for licensed prescribers*

The very least information the prescriber should have at his elbow at all times is the descriptive material approved by the FDA to accompany the product as a package insert. The inserts certainly should be in the packages for obvious reasons, but the same information should be provided to the prescriber in a more convenient form. If the package insert for every drug on the market was reprinted in a single volume, the bulk and fineness of print would probably render it useless. Criteria for inclusion could be adopted to keep the volume to manageable proportions and still be of enormous value to prescribers. The mailing list could be maintained automatically by obtaining addresses from the licensing bureaus for physicians et al.

#### *C. Collecting data on adverse reactions*

The FDA should maintain its own system for collecting information on adverse reactions to drugs and other occurrences after health products are marketed. Volunteer reporting is undependable. Committees on safety of drugs and on adverse reactions which become organized in the wake of a calamity have unpredictable futures. Information collected by others may never reach the FDA, or be slow to do so. The FDA must have a sustained and dependable system of direct surveillance, which could welcome supplementary efforts. Intimate involvement of the scientific staff of the FDA in problems of adverse reactions would sharpen the ability to detect ominous drugs before approval for marketing, and appropriate warnings would accompany the product.



*D. Consultants and councils*

Products of manufacturers in a highly competitive trade, where matters must be kept confidential, present thorny obstacles to liberal consultation outside the FDA. Somehow these must be dealt with so as to take full advantage of experts wherever they may be found. An expanded extramural research program would build up a nucleus of properly oriented consultants. Formal study groups could certainly aid in exploring general problems and methodology.

Permanent advisory councils concerned with all activities and relations of the FDA and meeting regularly with officials of the FDA and other Government officials would at least provide for methodical communication. Perhaps one advisory council should be made up of scientists, technologists, and administration specialists and the members selected for competence without concern for representation of one faction or another. A second advisory council would be essentially a citizens' group and serve primarily as assurance to the consumer that his interest would be foremost and that a regular mechanism existed to call any of the parties to public account—Government, industry, profession, or lay groups. This council could lend its influence to programs for a well-informed public.

It should be provided that the officials of the FDA shall meet with the councils regularly on a fixed schedule, and not just if and when someone chooses to convene the group.

## SUMMATION

A disservice is done to the FDA when it is referred to as a regulatory agency in the sense of police action. Scientific leadership is incompatible with this concept. Sound and fair regulation is inseparable from scholarly appraisal of adequate data acquired by excellent scientific procedures. The staff of the FDA would be left in an untenable position without this fusion of functions.

Scientific leadership is exercised only by working scientists truly occupied in the main streams of investigation. Membership in the scientific staff of the FDA cannot be made appealing simply by furnishing ringside seats to exciting research carried on in other arenas. A substantial intramural program of research and scholarly endeavors should be coupled with an extramural network of investigative centers in medical institutions to create an atmosphere of mutual respect and shared pride and prestige. Merely adding to or redirecting the resources administered by other agencies as a means of promoting research in clinical pharmacology does not seem a promising way to enhance the scientific appeal and leadership of the FDA.

Assuming the majority still believe our Government should do only what cannot be, or is not, done by private agencies, the present situation and probable trends seem to call for a magnitude of resources and effort far beyond the capacities of any combination of private enterprises. Furthermore, the nature of the problems requires leadership from a source concerned primarily with the public interest and beyond the reach of any faction too bent on self-interest.

The ultimate goal is to have the FDA set an example of excellence and so draw the best from all who are served, thereby reducing the need for regulation. The surest, if not the shortest, road to cooperation and enlightenment is via persuasion—not compulsion. Only convincing competence will lure the wary up this steep path.

Finally, anyone attempting to plot the future course should listen attentively to those who have labored long with the complex concrete operations of the FDA and with no small success—I refer to the present staff of dedicated public servants.

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Senator HUMPHREY. Doctor, we are indebted to you for your reasoned and thoughtful and very helpful statement, and I want to thank you very much. It is a statement that is constructive and it gives us some good suggestions for future consideration and I hope action.

I would be derelict if I did not make note of the fact that in your biographical information you have been kind enough to cite that you were an associate professor of pediatrics at the University of Minnesota from 1947 to 1952. If you had nothing else to qualify you except that, you would have been an outstanding witness.



Dr. MAY. Sir, may I say I beg your forgiveness for not capitalizing on that throughout.

Senator HUMPHREY. Yes; you should at least have underlined it, but you really did not need to.

Doctor, I want to ask a few questions of you, and I know Senator Gruening does.

#### THE REPORT OF THE SECOND CITIZENS ADVISORY COMMITTEE ON FDA

I know that you have studied the report of the Second Citizens Advisory Committee on the Food and Drug Administration, and I want to invite you to comment on this report, particularly on those issues where you may have some difference of opinion with the Advisory Committee's views, if that is the case.

I have not had an opportunity to discuss this matter with you, so I will just submit inquiries to you in the hopes that I can elicit detailed response. Let me make one comment of my own on the citizens' report.

I thought the report made many valuable recommendations and contributions. I particularly like its suggestion, for example, for the establishment of a Food and Drug Institute. This was one of its many suggestions.

It did also point out certain deficiencies in the Food and Drug Administration insofar as its administrative setup was concerned, such as the limited Adverse Drug Reporting Program, and you have commented here in your statement on this.

At the time that the report was made public, I commented upon it in the main favorably. There is, however, one aspect of it that has disturbed me throughout, and I would be appreciative of your comment on it.

#### OPPOSITION TO PROPOSAL FOR INDUSTRY "SELF-REGULATION"

I was concerned over the fact that the regulatory aspect of the report was not too strong. The advisory committee indicated that the FDA could virtually abandon to the private industry the responsibility of regulation, a sort of self-regulation.

This has been commented upon in some journals. One of them was the publication of Consumers Union, an article in the March 1963 issue of Consumers Reports.<sup>38</sup> This article elaborates on the issue of the citizen committee's failure, as they put it, to provide for adequate protection of the consumers' interests. I was disturbed and am disturbed over that aspect of the report relating to the self-regulation of the drug industry. What are your reactions to that report, Doctor, particularly the part on the regulation?

Dr. MAY. Sir, I thought it was a most praiseworthy report. Certainly anyone who is faced with the assignment of making this kind of an investigation within the time limits, within the facilities, could well be proud to achieve so much. It is inevitable that in a report of this scope some items might receive more emphasis than others by the persons involved.

<sup>38</sup> See exhibit 150, p. 1049.



I am afraid it is also possible that anyone who reads it may be guilty of interpreting it somewhat differently than the committee may have intended.

#### LACK OF REFERENCE TO NEEDS OF CLINICAL TESTING

My only reactions were really very much centered about two points. One was that I was struck by the fact that no comment was made about the matter of systems for collecting sound evidence to present before the FDA.

As I have pointed out, to sit there in the FDA with the most competent persons in the world, but to feed them inadequate data is about like having a Cadillac and no roads. In other words, you just simply cannot solve the problem without solving both facets simultaneously.

I don't think for a moment the committee was unaware of this, or really for all I know, upon examining every paragraph, there may be some mention of it, but as I read it, there failed to be an impression of an emphasis on this aspect commensurate with the emphasis upon the scientific personnel of the FDA.

Senator HUMPHREY. Are you saying now that the investigative standards and process were inadequately dealt with in the report?

Dr. MAY. Especially as far as resources outside of the FDA are concerned.

Senator HUMPHREY. That is what I mean, outside of the FDA.

Dr. MAY. Yes, sir.

Senator HUMPHREY. And of course we depend largely on resources outside of the FDA for the information that the FDA uses to make its judgments on a new drug.

Dr. MAY. Right. The other part of the report to which I reacted pertained to the Drug Institute and to other administrative matters, and again I think it is a matter of being quite clear what one intends by a Drug Institute.

Certain administrative structures may be very vital insofar as how these ideas might be developed. I would like to spend a moment on the problem of administrative structure of the Food and Drug Administration as it pertains to the scientific program. For that purpose I have prepared a little outline<sup>39</sup> and I believe that there are copies available for the committee and others, of the diagrammatic representations of major elements of the organization of the Food and Drug Administration, to facilitate development and integration of the scientific program.

These are to be compared with exhibits B-4 and B-5 in the Citizens Advisory Committee Report.

Senator HUMPHREY. This is in your statement on the treatment centers?

Dr. MAY. There are several items there together. Perhaps we can enter as an exhibit the single sheet, the diagrammatic representations of the administrative organization of the FDA.

Senator HUMPHREY. We have your outline of administration, and we do not have with us right now the citizens committee report.

Dr. MAY. Assuming that is readily available to you, I have indicated on my diagrammatic representation those pages in the citizens

<sup>39</sup> See exhibit 155, p. 1073.



report to which my proposed administrative structure can be compared, because they took the pains in their appendixes to indicate certain organizational arrangements.

Senator HUMPHREY. I was just asking Mr. Cahn here, with reference to your prepared statement on the plan for new treatment centers—we will want all of this information which you have prepared for the committee, Doctor, if it is agreeable with you, to be made a part of this record.

Dr. MAY. Very well.

Senator HUMPHREY. Just as your whole statement is being made a part of the record.

Dr. MAY. Yes.

Senator HUMPHREY. And I am also asking that this March 1963 issue of Consumer Reports relating to the citizens committee report be made a part of the testimony today. That will be entered in the record.

#### EXHIBIT 150

#### ARTICLE IN CONSUMER REPORTS CRITICIZING THE REPORT OF THE SECOND CITIZENS ADVISORY COMMITTEE ON THE FOOD AND DRUG ADMINISTRATION

There follows the text of an article in the March 1963 (pp. 134-137) issue of Consumer Reports, as referred to by Senator Humphrey.

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#### DRUG SAFETY

THE BASIC QUESTION IS WHETHER CONTROL OF CLINICAL TESTING SHOULD BE LEFT TO THE MANUFACTURERS. AT A TIME OF WORLDWIDE CONCERN OVER DANGEROUS DRUGS, A "CITIZENS COMMITTEE" PROPOSES A SURRENDER OF PUBLIC RESPONSIBILITY

In Europe, where thalidomide was widely sold and deformed children were born by the thousands to mothers who had taken the drug during pregnancy, public anxiety over the situation has been intense and the consequences all of a piece. Ten countries, acting on a better-safe-than-sorry principle, have recently banned or inhibited the sale not only of thalidomide but of a number of other drugs as well. Here in the U.S.A., where the Food and Drug Administration had kept thalidomide off the market by refusing to certify it as a safe drug, public reaction has been less intense but more complicated.

Although not cleared for sale by the FDA, thalidomide *had* been made available to a number of consumers in this country through doctors who were conducting clinical tests of the drug for the William S. Merrell Co. This situation—a dangerous drug available while still not approved as safe—was bad enough to assure the passage of basic new drug legislation (Consumer Reports, Oct. 1962). And in the process of putting the legislation through, Congressmen wanted to know why thalidomide had been available at all; why the FDA had not acted sooner to recall all samples from the doctors; what chances there were that other dangerous drugs were being handed out in clinical tests; and what evidence there was that the FDA was truly on top of the large and very complex job of protecting the public against the distribution and sale of dangerous drugs.

Dr. Frances Oldham Kelsey, the FDA staff doctor who was awarded the Distinguished Federal Civilian Service Medal by President Kennedy for standing off the promoters of thalidomide, was but one staff member of the Division of New Drugs of the FDA's Bureau of Medicine, and she was known to be a stubborn and dedicated doctor. Suppose someone else in the FDA had been handed the thalidomide application? Could Dr. Kelsey's resistance to industry pressure be taken as a typical example of the whole agency's policy of devotion to consumer protection?

The dedication to public welfare of a regulatory agency such as the FDA is, of course, under repeated challenge from the regulated industry, whose vested interests frequently conflict with the public interest. When the industry is as large, as profitable, as tightly organized, and as well schooled in lobbying techniques as is the drug industry, the day-to-day pressures on the agency



can be massive. More than 2 years before the thalidomide incident, testimony before the Kefauver committee had led to disclosures of an unsavory relationship between Dr. Henry Welch, Director of the FDA's Division of Antibiotics, and the drug industry. Dr. Welch subsequently resigned, but not before several Members of Congress had expressed fears that the FDA's capacity to deal with industry pressure might be less than it should be. Thus the thalidomide incident, even though the FDA's record here was commendable, has served more to underscore the threat inherent in an inadequately controlled drug industry than to quiet public concern.

#### THE REPORT: ILL CONCEIVED, ILL TIMED

Last October, the very month in which President Kennedy signed the new drug laws and at the very time that Senators and Congressmen were readying probes into FDA affairs, an eagerly awaited Citizens Advisory Committee's "Report to the Secretary of Health, Education, and Welfare on the Food and Drug Administration" appeared. Few documents in history purporting to review matters of serious public concern can have been so inauspiciously timed or so poorly conceived. The report failed to mention at all the big problem in drug testing—whether it is wise to allow manufacturers to control the clinical testing of their own products. Aside from this, the report gave *as its first and most urgent recommendation that the FDA take a more lenient attitude toward industry to the end that "mandated self-inspection and self-regulation" should eventually supersede control by regulatory investigation and legal enforcement.* As one drug trade commentator put it, the pro-industry bias of the committee's report was so plain that even Congressmen out to pin something on the FDA or its Commissioner, George P. Larrick, could not use it for that purpose.

No more than 1 of the 16 members of the Citizens Advisory Committee, Miss Anne Draper of the AFL-CIO, is on record as opposing the committee's pro-industry philosophy. Nor, with the exception of Miss Draper, has anyone spoken out about the remarkable shortcomings of the report. Privately, a good many Washington officials have characterized it as a report to end all such reports. But publicly Senators, Congressmen, and the officers of the FDA and the Department of Health, Education, and Welfare have allowed the report to stand without opposition. In January the Pharmaceutical Manufacturers Association gave the report a strong endorsement.

It seems to CU that, among the several proposed investigations into the problems of drug control and the FDA's functions in this area, the Congress might well include an investigation of how a citizens' committee happened to come out with so uncitizenlike a philosophy. The role of the citizens' committee in our form of Government can be, and has been, an important and influential one. Another Citizens Advisory Committee report on the FDA appeared in 1955 (Consumer Reports, July 1956). At that time neither the Congress nor public leaders generally were aware of how dangerously understaffed the FDA was in the face of a flood of new products and new techniques flowing from a rapidly expanding chemical industry. Although problems of consumer protection had multiplied geometrically in number and complexity, there were actually fewer FDA enforcement personnel in 1955 than there had been before World War II. The 1955 Citizens Advisory Committee's report called sharp attention to the situation, and as a result some much-needed corrective measures were taken to bring the FDA's staff and annual appropriations up closer to the level of the need.

#### FDA'S INCREASING RESPONSIBILITIES

Meantime, however, the jobs for which the FDA is responsible have multiplied, too. In addition to enforcing the basic Federal Food, Drug, and Cosmetic Act passed in 1938, a series of amendments enacted in recent years has made that agency responsible for:

- Certification of antibiotic drugs and insulin.
- Reviewing evidence of the safety of food additives.
- Establishing tolerances of safety of food and drug color additives.
- Establishing tolerances for pesticide residues.

The new drug amendments passed as a result of the thalidomide incident have, of course, created still more responsibilities. And all of these regulatory responsibilities added since 1955 are *in addition to* responsibility for enforcement of the basic law plus earlier amendments (such as control over the market-



ing of oleomargarine); and *also in addition to* the administration of five related consumer protection laws: the Tea Importation Act, the Import Milk Act, the Federal Caustic Poison Act, the Filled Milk Act, and the Federal Hazardous Substances Labeling Act.

The fact is that, in relation to the number and importance of the FDA's duties, its current appropriation of \$28 million and its budgeted staff of 3,012 are both still dangerously meager. And yet this latest Citizens Advisory Committee took the position that the FDA's most pressing need was not for the means with which to work but for a new philosophy—a philosophy of yielding control to industry.

#### EVIDENCE OF INDUSTRY'S FAILURE

To be sure, the Citizens Advisory Committee was set up in late 1961, almost a year before the thalidomide tragedy became international news. None of its members could have known that events were conspiring to throw a most revealing light on its deliberations at precisely the time these would be made public. But even without the thalidomide tragedy there was available to the committee ample evidence of the failure of the industry to exercise adequate caution in the testing of drugs. Senator Hubert H. Humphrey (Minn.), Chairman of the Senate Subcommittee on Reorganization and International Organizations and one of the Senators most active in investigating the problems of the control over dangerous drugs, recently made public a startling year-old document to which the Citizens Advisory Committee had had access. This report, an inner-agency FDA document evaluating the quality of the industry data submitted in New Drug Applications, asserted that:

Apparently fraudulent reports of the results of therapy had been submitted by some doctors commissioned by a pharmaceutical company to evaluate a drug.

Well-known and accepted research techniques such as the "double-blind" control rarely appeared in the studies submitted in support of New Drug Applications.

Results were offered from tests so designed that they were incapable of affording an adequately scientific demonstration.

The choice of groups of patients to serve as controls was sometimes so poorly considered that test results were biased and exaggerated.

Against this background, it is particularly noteworthy that the Citizens Advisory Committee suggested that the FDA even withhold the names of companies whose products might be seized for violations of law.

#### THE FUNDAMENTAL QUESTION

In addition to its criticism of the FDA's philosophy, the Citizens Advisory Committee also criticized other aspects of that agency's operations—its inner organizational structure, its lack of sufficient and properly qualified scientific talent, its failure to achieve a better liaison with other regulatory agencies such as USDA and the U.S. Public Health Service, and so on. No doubt a number of these criticisms were well founded. But they dealt with relatively minor aspects of the very big problem illustrated by thalidomide. At the core of that problem lies that most fundamental question: namely, is it good public policy to permit the drug manufacturers to do or to supervise the clinical testing of their own products?

There is no hint whatsoever in the whole of the nine-chapter Citizens Advisory Committee report of any awareness of the question. CU's tests have demonstrated over the years that, with the best intentions in the world, the manufacturer of a product may be unable to take a view of his own handiwork that is objective enough to reveal the product's weaknesses. The results of this almost inescapable maker's myopia can be distressing enough in such goods as automobiles, typewriters, luggage, electric dryers, and so on. Sometimes the inability of the maker to see the product from the point of view of the user can be dangerous; shock hazard in electrical appliances is an example. With the potent drugs now coming on the market the penalties for inadequate testing are *nearly always* threatening to the patient's health or his life.

How to assure that potent drugs shall be adequately and reliably tested for safety and efficacy is a major issue before the Congress. Under present law, even as amended after the thalidomide case, the drug maker remains responsible for drug testing. The new law *does* subject his test methods and procedures to closer FDA scrutiny and review. And the Division of New Drugs in the FDA's Bureau of Medicine has been reorganized to exercise the more effective control



required by the new law. An Investigational Drug Branch has been established in the bureau to evaluate the proposed clinical tests of drugs that are to be submitted by manufacturers in their first step toward New Drug Applications. Dr. Frances Kelsey, the thalidomide heroine, has now been named director of this branch. The evaluation of laboratory and animal testing and other data and procedures is to be the responsibility of other branches. But all branches will be handling test reports that have been procured *by the manufacturers*.

#### NEEDED: AN OBJECTIVE TESTING AGENCY

The creation of a source from which to obtain an objective and reliable evaluation of drugs has not yet been considered by the Congress, the FDA, or the drug industry. As an enforcement agency, the FDA is obviously too heavily burdened to undertake the responsibility for testing as well as regulating. Perhaps a new public corporation responsible to both industry and Government is what is called for—an organization patterned after that described by President Kennedy to control Telstar.

There doubtless would be problems, grave ones, encountered in the design of such an objective testing agency, but there are even graver problems under the present setup. Aside from the basic wisdom of separating maker from tester, a particular agency empowered to be responsible for the test data submitted to the FDA might help alleviate the second biggest weakness in the present drug-testing setup—the lack of qualified testers. With each company bidding competitively for the services of physicians and scientists and, too frequently, wasting talent and time in poorly designed tests, our limited scientific resources are unnecessarily strained.

#### INTERNATIONAL COOPERATION

In Europe there seems to be more awareness of the pressing need for a new approach to drug-testing controls. This is probably due in part to the highly emotional reaction to the tragic consequences of thalidomide, which continues to mark discussions of the problem there. The various national efforts to assure drug safety through a variety of controls recently imposed on a number of drugs in addition to thalidomide illustrate another large dimension of the problem: the need for international cooperation. What happened in the case of Preludin is a clear example.

Preludin is an appetite depressant that, before thalidomide, had been generally available without prescription. A few months ago an English doctor published his doubts about that drug's safety for pregnant women. Almost immediately in country after country the sale of Preludin was subjected to restrictions.

Here in the United States the drug has remained on sale. Both the FDA and the American Medical Association believe there is no evidence that restrictive action is called for. In Canada the Minister of Health has announced that he is investigating the drug, although a member of the House of Commons has suggested a temporary ban on it.

CU's medical consultants believe, as do the FDA and the AMA, that the evidence against Preludin is not convincing. However, since the use of an appetite depressant is not a reliable and safe way to control weight, CU advises pregnant women to avoid this drug as well as *all* other drugs not considered by their own physicians to be essential to protect their health. Only in those instances where a physician feels that the known benefit from a drug is definitely worth the known (or unknown) risk to mother and fetus is any drug advisable in pregnancy.

In Europe the 16 countries which are members of the Executive Council of Europe have begun a move through that agency's Public Health Committee to exchange information on drugs and to secure harmonized legislation among its members. In the U.S. Senator Humphrey has proposed the establishment of a worldwide network of drug evaluation centers under the auspices of the World Health Organization. There is a growing realization that, as it was put in a speech reported by the British Medical Journal, "only with organized accumulation of information \* \* \* about efficacy and toxicity can we plan the necessary control measures based on factual knowledge."



## THE IMMEDIATE NEED

Meantime, what do we do? Obviously the creation of a worldwide network of drug evaluation centers and the establishment of a national organization for the objective testing and evaluation of drugs are not easily attained goals. At present we are dependent on the FDA's ability to judge the quality of drug testing data and on the FDA's integrity in dealing *as an enforcement agency* with drug manufacturers. Let us hope that FDA officials are not persuaded to a philosophy of self-regulation by business, especially by a business that has produced and marketed a number of dangerous drugs that have had to be withdrawn later. The FDA will need larger appropriations this year to meet its enlarged burden of responsibilities. It will need further amendments to the law. The amendments passed last year deal with prescription drugs only. The controls over cosmetics and drugs sold without a prescription need to be strengthened, too. Support for the FDA from consumers is called for in these demands.

This does not mean that the FDA should be shielded from criticism. On the contrary, a continuing critical review of its actions is not only desirable but essential to keep it on its toes. But the criticism that is required from the citizens of the Nation is that which will strengthen the FDA as the regulatory agency it was intended to be.

Dr. MAY. Do I understand that the outline plans for new treatment centers, which I offer as a detailed expansion of the illusion made to the subject in my statement, will become a part of the record?

Senator HUMPHREY. That is correct; yes, indeed.

## EXHIBIT 151

## MEMORANDUM FROM CHARLES D. MAY, M.D., ON A SYSTEM OF CENTERS FOR STUDY OF DRUGS

There follows the memorandum referred to by Dr. May in his testimony.

## OUTLINE PLAN FOR NEW-TREATMENT CENTERS

(Prepared by Charles D. May, M.D., March 14, 1963)

## PURPOSE

To provide for personnel and facilities assigned on long-term basis to conduct investigations in humans with new drugs prior to approval for marketing and new uses for drugs already on the market, to determine safety and efficacy and also indications and mode of usage.

The arrangements should include opportunity to investigate basic pharmacology and effects on bodily metabolism in health and diseases, while agents are undergoing clinical trial. Development of new methods of study of clinical and basic pharmacology should be encouraged. Training in these fields of investigation will be a prime objective.

The initiative for types of investigations will come from the investigators, in form of requests for support from the granting agencies through appropriate administrative channels. These will be reviewed by panels of experts.

The centers will be foci for the spread of the most discriminating practice of therapy, because students and practitioners will be exposed to refined methods for evaluation of treatment throughout their careers.

## FACILITIES

Variable according to nature of investigations contemplated.

Typically, would be part of an established medical school or institution and include a separate unit of hospital beds and/or special facilities for close observation of ambulatory persons. Laboratories to suit the clinical and research needs would have to be provided, along with suitable offices and space for adjunct activities.



The number of such New-Treatment Centers would depend on acceptable proposals that might be proffered. A few centers might be inaugurated to start, and expansion of the program be governed by their success, the apparent demand, and appraisal of the needs.

#### ADMINISTRATION

Local administration would be an autonomous responsibility of the administrative officials of the medical institutions sponsoring the New-Treatment Center. The supporting agency would be directed by a scientist administrator acting on recommendations of panels of medical scientists and clinicians who served as reviewers of proposals.

#### INVESTIGATIVE PERSONNEL

All investigative activities under the direction of a principal investigator. Additional senior investigators as indicated by the scope of the proposed studies.

Investigators may be clinicians, pharmacologists, or any specialists the studies require.

Senior statistician.

Paramedical personnel as indicated by studies.

The objective is to assemble a coordinated group to bring various skills to bear on the questions involved in evaluation of therapy and development of techniques, simultaneous with explorations of basic mechanisms. These experts are to be attracted by the prospects of a substantial career of investigation in the realm of clinical pharmacology.

Special attention will be given to arrangements for training of personnel in all of the categories represented.

#### FINANCIAL SUPPORT

The proposed New-Treatment Centers should be established from newly found resources and without any drain on the existing resources of medical institutions willing to sponsor the centers. This means meeting the full cost including overhead.

The facilities and core personnel should be supported on a long-term basis to maintain sustained operation of the centers and so keep skilled personnel intact and continuously available for investigation and training.

To insure independence of the operation of the centers in behalf of the public interest, the basic facilities and personnel should be supported by public funds.

The basic public-supported center could receive supplementary support from private sources according to clearly designated conditions—such as to a minor extent that would not jeopardize independence or control of the center by undue dependence or augmentation from extraneous sources. A firm seeking evaluation of a product could contribute some support without securing control, when investigators considered the product worthy or of interest in their investigations. The choice, control, and initiative remains with investigators adequately supported by basic grants to pursue the studies specified in the proposal for the center. Private foundations could add to the resources of a center in a similar fashion to pursue studies of concern to the foundation and of interest to the investigator. All agencies seeking the aid of the centers would be obliged to put forth products or projects deemed worthy of study by the investigators, and likewise investigators must satisfy the supporting agency that their studies continue to be significant.

#### IMPORTANT CONSIDERATION

The foregoing are a few suggestions only. Careful planning and development of policies should precede any implementation of the idea of New-Treatment Centers. This should be done by committees of experts from the areas of investigation involved. Opinion from interested parties on administrative and other relationships of the centers should be gathered.

The goal should not be obscured by pursuit of limited objectives by individuals or groups—the need is for independent, objective evaluation of therapy and development of techniques and more experts in the field of clinical pharmacology and drug metabolism—and not a machinery for getting a limitless quantity of products approved for marketing.



Senator HUMPHREY. On the citizens committee report, that is, the second citizens committee report, do you feel or do you have any observations or feelings with reference to the charge that is made that there was undue emphasis upon the self-regulatory aspects of the drug industry?

ONE EXPERT'S VIEW OF THREE STAGES OF A REGULATORY AGENCY'S  
DEVELOPMENT

Dr. MAY. Sir, again I think this impression might have been created in part by the introductory material on page 8, section 2. They quoted a prominent health regulatory official who describes three stages of development in a regulatory agency, the period of police power enforcement, the period of health education and the period of mandated self-inspection and self-regulation.

This particular committee chose to consider that the FDA had, until the present time, been largely in the first phase of development, and urged that steps be now taken to bring in the second phase.

I think in an effort to facilitate the progression along this laudable evolutionary scale, that they did give emphasis to development of those facilities other than enforcement. But I am not sure they meant to discount the responsibilities which are inescapable insofar as enforcement is concerned.

EXCERPTS FROM REPORT BY KENDALL COMMITTEE IN 1960

Another committee, I think, stated more skillfully this problem of the balance between enforcement and the development of voluntary self-regulation coupled with education of the public and the profession in terms of allowing a more excellent system to operate:

Self-regulation has its limitations, however. The first purpose of the Food, Drug, and Cosmetic Act, the Supreme Court has pointed out, is the protection of the consumer. There will always be some producers subject to the act who are unwilling to give priority in their operations to the interests of the consumer. These "fringe" producers not only fail in the faithful execution of the law—they constitute unfair competition for the rest of the industry whose costs include research and testing facilities, high quality raw materials, complex production controls, and extensive advertising. Because there are concerns that won't regulate themselves, self-regulation tends to be only partial regulation and may involve a competitive penalty for the very companies that genuinely police themselves. \* \* \* The protection of the consumer contemplated by the Congress will be provided only so long as a well-trained and dedicated staff of public servants is continuously active in the enforcement of the law. (From Report to the Secretary of Health, Education, and Welfare concerning the Food and Drug Administration of the Special Investigative Unit as of Dec. 23, 1960, Charles H. Kendall, chairman.)

Senator HUMPHREY. I personally felt that this was an area of limitation, of weakness in the citizens committee report. I just wanted to emphasize it today because I don't think we are at the stage where you can rely upon self-regulation, even though it is a fact that the Pharmaceutical Manufacturers Association did establish a commission on drug safety.

Dr. Austin Smith I believe announced it, and it is a creditable and respectable commission that can do a very good job.

I believe it needs to be buttressed by the enforcement facilities of the Food and Drug Administration, and particularly by rules and



regulations that relate to investigative procedures on new drugs and clinical analysis of those procedures or of those results.

Dr. MAY. Sir, I am quite confident when the personnel in each of the divisions of the FDA reaches a parallel degree of competence, this problem will wither away, so to speak.

#### ANALOGY OF PROMOTING EXCELLENCE IN PROFESSIONAL JOURNALS

As a matter of fact, it has not yet been eliminated from science itself. When I served as editor of a medical journal, I was obliged to bring to bear upon the author the opinions or the regulations, if you will, of fellow scientists. I could not simply open the pages up to voluntary submission of manuscripts, leaving it to each scientist to achieve the highest standards for his products. It had to pass through the hands of fellow scientists who exercised and applied to his work the highest critical faculties.

This sort of stimulus to matching the standards imposed by others, which could also be called regulation, is one of the wellsprings of our creativity and productivity. I don't think we are going to look forward to the elimination of imposition of standards from without, even though you call it regulation.

#### THE VACANCY IN DIRECTORSHIP OF BUREAU OF MEDICINE

Senator HUMPHREY. I think your information on these matters is very profound. It is a source of considerable regret to me, Doctor, that the important position of the Director of the Bureau of Medicine in the Food and Drug Administration has been vacant for almost a year. It is just incredible that this vacancy continues, in light of the number of investigations that have been conducted and hearings that have been conducted on the drug laws and the administration of those laws by the Food and Drug Administration.

The Commissioner as I understand it, Mr. Larrick, thought well enough of you, Dr. May, to nominate you to serve in that position as the Director of the Bureau of Medicine. You are not in that position. I think that is regrettable. Do you have any observations on this whole subject as to why there may have been some controversy over your nomination? If this is embarrassing in any way, I surely apologize. I don't mean to embarrass you. But I know you are a man of great professional competence and ethical standing, and I would be interested in your observations.

Dr. MAY. Sir, I am not embarrassed by a mention of this subject.

#### BACKGROUND TO CONSIDERATION OF DR. MAY FOR MEDICAL DIRECTOR POST

First of all, I think it is an exemplification of the same sort of problem that Dr. Nestor referred to; namely, that one person may well be overruled by another, and in this instance it is more than likely that the Commissioner of the Food and Drug Administration himself was overruled, so those underneath him need not feel that they have been singularly abused in this respect.

Secondly, when I was approached in regard to this position, I was happily situated in every way. I had no ambitions that needed to be cultivated.



Senator HUMPHREY. You did not seek it, we know that.

Dr. MAY. Yes. Furthermore, I do have some sense of public responsibility, and I examined myself very closely in terms of the qualifications which I possessed, and matched them against the qualifications I believed the situation demanded.

I was well aware of the fact that this was not a one-man job, but unless one could somehow attract an enormous number of persons throughout the development of such programs as I have alluded to here, one could not really accomplish much.

But because I had been successful in having substantial support from fellow scientists in a number of ventures, and because I was deeply interested in how the whole matter of the manufacture and distribution and scrutiny of drug products might influence the habits and beliefs of physicians, and because my career had thus far been one of an educator and investigator, and I had therefore a legitimate interest in what happened to the students who went through the medical schools and what happened to the products from the investigators' laboratories when they were distributed through the journals, I felt this would be a legitimate service to assist in some way in bringing a harmonious working relationship between all these elements so that not only could there be a free practice of medicine and a free enterprise system in industry, and a nobility of performance in Government, but the citizen himself might also rest content that these groups were working in his behalf more than any other faction. After examining myself in these respects, I was satisfied I was qualified.

Senator HUMPHREY. I think you are eminently qualified.

Dr. MAY. Commissioner Larrick apparently thought so, and his associates thought so, and they pursued it to the end, so if you want an explanation from those who think I am not qualified, you will have to start above that level.

Senator HUMPHREY. I gather, Doctor, you gave some testimony over here before the Kefauver committee on drug legislation, and you had some comments that were reported in the press.

I have here a copy of the Sunday Star of Washington, D.C., January 6, 1963, in which it points out that you declined this medical unit directorship after prolonged consideration had taken place. I just want to quote:

Dr. May said he withdrew his name after a meeting at which Mr. Jones made the point that some of Dr. May's past activities had made him a controversial figure in an essay entitled "Selling Drugs by Educating Physicians" and later in testimony before the Kefauver committee considering drug legislation.

Dr. May questioned the promotional practices of the drug manufacturers. He contended that guidance of physicians on the most effective treatment for various conditions should come from within the medical profession. Dr. May was formerly a member of the American Medical Association's Council on Drugs and former editor of *Pediatrics*, the official journal of the American Academy of Pediatrics.

He said he had made himself available for the FDA job out of a sense of public duty, although it would have been a financial sacrifice.

Interestingly enough, the man that was finally appointed for an interim, Dr. Kessenich, said that he took the assignment reluctantly and after a while told Mr. Larrick he wanted to leave for a job with fewer pressures, even with less pay. Mr. Larrick said he prevailed on Dr. Kessenich to stay until he could find a successor. After a considerable investigation and consultation with the Public Health Service, Mr. Larrick said he picked Dr. May—

and so on and so on.



## POSSIBLE PRESSURES AGAINST THE APPOINTMENT

Now it seems that there are all kinds of pressures brought to bear here. I don't know where those pressures are coming from, but I intend to take a look.

Dr. MAY. Sir, I thought it was rather strange that I should be approached about this position in April of 1962, and that the months would wear on, which were more than enough for the Federal Bureau of Investigation and the Civil Service Commission to exhaust my obviously short life and limited accomplishments, and yet no definite decision was forthcoming either way.

I could have understood someone saying "We have now examined you thoroughly and you are not qualified," whereupon I would respect this judgment. After all, each person in their area must be free to exercise judgment in terms of what kind of persons they wish to enlist in support of the activities for which they are responsible. This is not the question at all.

Senator HUMPHREY. Doctor, let me make it quite clear that there has never been any doubt as to your good citizenship, your loyalty, patriotism and professional competence. I just want that clear on this record.

The pressures came from less than patriotic concern; let's get that clear. I am going to look into this a little bit, because I happen to believe that the Government of the United States ought to have men of competence in these positions, and I don't think you can run the Food and Drug Administration without a Director of the Bureau of Medicine. You ought to close up shop if you don't have one.

Dr. MAY. I think it would have been easy to say "No." It could have been said much more quickly.

Senator HUMPHREY. We will come back to that. We may have to talk to you about it again. We will talk to some other people about it, too.

I want to make it clear for the record it is inexcusable that this Government does not have such a director. I don't think anybody can explain why we don't have one, unless they are simply saying that they are trying to find somebody who will satisfy every manufacturer or every outside influence, and if you find that fellow he won't be worth a hoot.

Dr. MAY. Only time will tell. I owe a great debt to someone for leaving me to my present tranquil pastures.

Senator HUMPHREY. You will be a happier man I assure you. You will live a lot longer than a lot of us worrisome souls.

## EXHIBIT 152

## ARTICLE IN THE SUNDAY STAR OF WASHINGTON, D.C., WITH REGARD TO THE VACANCY IN THE POST OF MEDICAL DIRECTOR, BUREAU OF MEDICINE, FOOD AND DRUG ADMINISTRATION

There follows the article referred to by Senator Humphrey as regards the continuing vacancy in the post of Medical Director, Bureau of Medicine, Food and Drug Administration. The article, by Miriam Ottenberg, appeared in the Sunday Star of Washington, D.C., January 6, 1963.



[From the Sunday Star, Washington, D.C., Jan. 6, 1963]

## MAY DECLINES MEDICAL UNIT DIRECTORSHIP

(By Miriam Ottenberg, Star Staff Writer)

Dr. Charles D. May, whose appointment as Director of the Food and Drug Administration's key Bureau of Medicine has been pending since last March, has withdrawn his name from consideration for the \$20,000 post, it was learned yesterday.

Dr. May, now a professor of pediatrics at New York University Medical School, was proposed for the top job in the Bureau of Medicine by FDA Commissioner George P. Larrick.

The appointment was kept under study for the next 9 months by Boiesfeillet Jones, special assistant to the Secretary of Health, Education, and Welfare for health and medical affairs.

The Bureau of Medicine, which will administer the new drug laws passed by Congress and a series of new regulations, has been under an acting director since last August.

### CONTROVERSIES CITED

Dr. May said he withdrew his name after a meeting at which Mr. Jones made the point that some of Dr. May's past activities had made him a "controversial figure."

In an essay entitled "Selling Drugs by 'Educating' Physicians" and later in testimony before the Kefauver committee considering drug legislation, Dr. May questioned the promotional practices of the drug manufacturers. He contended that guidance of physicians on the most effective treatment for various conditions should come from within the medical profession.

Dr. May was formerly a member of the American Medical Association's Council on Drugs and former editor of "Pediatrics," the official journal of the American Academy of Pediatrics. He said he had made himself available for the FDA job "out of a sense of public duty," although it would have been a financial sacrifice.

Those who opposed his appointment, he said, "had the attitude that anyone who appeared and spoke of the need for further legislation was automatically considered hostile to industry."

### CONSCIOUS OF POSITION

"I don't see how you can take a stand on any issue without someone being displeased," he added.

Asked about Dr. May's decision to withdraw his name, Mr. Jones denied that Dr. May's writings or testimony before the Kefauver committee had anything to do with delaying a decision on his appointment. Mr. Jones also denied that he had been approached by representatives of the drug industry to oppose the appointment.

"We don't question Dr. May's competence or his scientific objectivity," Mr. Jones said, "but it's perfectly obvious that he was a subject of controversy not only in industry but in scientific circles."

Mr. Jones said he did not act on the May appointment because the Citizens Advisory Committee report on FDA was imminent and he wanted to see if any changes would be recommended in the makeup of the Bureau of Medicine which would influence the choice of a director. The advisory committee's report was made public October 25.

### SALARY AN ISSUE

He said he had considered other prospects besides Dr. May. He said he was trying to find somebody "acceptable to industry, the consumers and the academic world but we're not trying to satisfy industry per se."

He acknowledged that "the kind of people we're talking about come at salary levels considerably above \$20,000."

"We want to give Commissioner Larrick an opportunity to develop a first-class organization," he said. "We're going to look over his shoulder and help him while he does it."

Commissioner Larrick briefly outlined his troubles in getting and keeping a director. He said he had a capable one but lost him because the salary wasn't large enough. After canvassing the country unsuccessfully for a successor, he said, he promoted Dr. William Kessenich from within the bureau.



Dr. Kessenich, he said, took the assignment reluctantly and, after a while, told Mr. Larrick he wanted to leave for a job with fewer pressures, even at less pay. Mr. Larrick said he prevailed on Dr. Kessenich to stay until he could find a successor.

After considerable investigation and consultation with the Public Health Service, Mr. Larrick said he picked up Dr. May. He said he wrote a letter offering the appointment to Dr. May and cleared the offer with the Secretary's office. He added that he explained to Dr. May that [he] still had to go through security clearance but described it as "perfunctory."

Dr. Kessenich left in August and Dr. Ralph Smith has been the acting director ever since.

#### FEAR AS TO "DRYING UP" OF NUMBERS OF NEW DRUGS

Senator HUMPHREY. Dr. May, over a period of years from 1938 to 1962 some 13,000 applications for new drugs remained effective. Views have been expressed in some quarters in the pharmaceutical industry that the application of stricter Federal standards prior to the approval of new drugs will, and here I am quoting their own words, "cripple the drug industry," and "curtail the prospects of discovery of new remedies." Would you like to comment on this matter as to the prospective number of new drugs?

Dr. MAY. Yes, sir, and in so doing may I introduce certain items into the record as exhibits. One is entitled "A Report of the Council on Pharmacy and Chemistry of the American Medical Association," and it appeared in the Journal of the American Medical Association 20 years ago in 1944.

Another is entitled "Too Many Drugs." It is also a report of the Council on Pharmacy and Chemistry of the AMA published in 1949.

These reports represent one of those happy moments in history when there was complete harmony between industry, the Food and Drug Administration and the American Medical Association. For this report is under the authorship of members of the FDA, Dr. Austin Smith when he was secretary of the Council on Pharmacy and Chemistry, and under the auspices of the Council on Pharmacy and Chemistry (now known as the Council on Drugs) of the AMA.

The item from the Journal of the American Medical Association in 1944 was a detailed exposition of the general principles to be observed in the investigation of new drugs before marketing. This was set forth as sort of a model toward which all would aspire, realizing that it would take time to develop it or that it might be modified in a few circumstances.

But it was set forth as a goal by, as I say, these persons who are still vexed with the problem 20 years later. It so happens that if you compare this full report with the present law and with the recent regulations of the FDA, you will find that by and large the recent legislation and the regulations of the FDA are simply measures to implement what was recommended by these parties 20 years ago.

This report is concluded by the statement:

A study of this outline for the therapeutic and toxicologic appraisal of new drugs may leave the impression that the task which has been said is far too complex and difficult, requires too much time and expenditure of energy and money and can be circumvented by briefer and less thorough investigations.

While this may be true in a few isolated instances, it is not true in a majority of cases of really new drugs. Recent history contains too many instances of disastrous results that have followed incomplete or inadequate investigations on new drugs. This outline is an objective toward which investigations of new



agents should be directed. It need not apply in all cases, but the reasons for omitting any part should be that the omitted parts are not necessary and not merely that they are troublesome.

Finally, it is necessary to exercise sound judgment in deciding whether a product deserves recognition.

I will not read the rest of this because this is simply reemphasizing that the people in the FDA must have competency to match the adequacy of the data put before them.

Now, when this original report from the Council on Pharmacy and Chemistry, prepared by officials of the FDA and Dr. Austin Smith, under the auspices of the AMA, appeared, an eminent pharmacologist, Dr. Chauncey Leake, wrote a letter to the editor in which he expressed concern about some of the minor provisions for testing the toxicology, et cetera, and he also went further to say that perhaps many of the molecular modifications could be subjected to a more cursory examination. The authors of the preceding report made this reply:

The pharmacologic properties of drugs cannot be predicted reliably on the basis of the chemical similarity to other well-known drugs [and they list examples].

There are so many exceptions to the so-called relationship between the chemical structure and the pharmacologic activity that reliance on that relationship as a shortcut to adequate investigation is extremely risky.

Now, to answer more specifically your question about crippling the drug industry or having any deleterious effect on the public health by curtailing the number of drugs, the final paragraph is particularly pertinent:

Finally we seriously doubt that the application of the criteria set forth in our paper will delay the use of worthwhile therapeutic agents. In fact, it is our belief that ill-conceived and poorly executed investigations have contributed materially to delays in the proper and widespread use of therapeutically desirable agents.

Senator HUMPHREY. Who signed that report?

Dr. MAY. This was signed by officials of the FDA at that time, Dr. Van Winkle, Dr. Herwick, and Dr. Calvery, and by Dr. Austin Smith, then secretary to the Council on Pharmacy and Chemistry of the AMA.

Senator HUMPHREY. And now is?

Dr. MAY. President of the Pharmaceutical Manufacturers Association.

My guess is that the body of evidence set forth and the conclusions drawn would be as acceptable to him today as they were then. I do not believe that his present alinements would either allow him or invite him to draw any different picture.

Senator HUMPHREY. So it is fair to say, then, that the stricter Federal standards prior to the approval of new drugs would not "cripple" the drug industry in terms of its new preparations?

Mr. MAY. Exactly not, and I think in addition the exhibit which I have asked to be entered regarding "Too Many Drugs," which is a statement from Dr. Austin Smith, points out that quite to the contrary, the profusion which existed even then, nearly 20 years ago, was already presenting a serious challenge to the effectiveness of medical care, and obviously is not less so today.<sup>40</sup>

<sup>40</sup> For additional comments on the issue of the number and variety of drugs, see exhibit 158, p. 1136.



## EXHIBIT 153

EXCERPTS FROM AMA COMMENTS IN 1944 AND 1949 AS REGARDS POSSIBLE DIMINISHING OF THE NUMBERS OF NEW DRUGS, TOGETHER WITH A STATEMENT IN 1962

There follow the series of quotations as contained in the comments by American Medical Association sources in 1944 and 1949, together with a statement in 1962 by Austin Smith, M.D. These quotations were furnished by Dr. May as an exhibit of his testimony—

REPORT OF THE COUNCIL ON PHARMACY AND CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION: LABORATORY AND CLINICAL APPRAISAL OF NEW DRUGS

(By Van Winkle, W., Jr., Herwick, R.P., Calvery, H.O. (from the FDA) and Smith, Austin (Secretary of Council on Pharmacy and Chemistry of AMA), JAMA 126: 958, 1944)

Detailed exposition of general principles to be observed in investigation of new drugs *before* marketing. Recommends many of provisions of new FDA regulations. Concluded with:

## SUMMARY

A study of this outline for the therapeutic and toxicologic appraisal of new drugs may leave the impression that the task which has been set is far too complex and difficult, requires too much time, and expenditure of energy and money can be circumvented by briefer and less thorough investigations. While this may be true in a few isolated instances, it is not true in the majority of cases of really new drugs. Recent history contains too many instances of disastrous results that have followed incomplete or inadequate investigations on new drugs. This outline is an objective toward which investigations of new agents should be directed. It need not apply in full to all cases, but the reasons for omitting any part should be that the omitted parts are not necessary and not merely that they are troublesome \* \* \*.

Finally, it is necessary to exercise sound judgment in deciding whether a product deserves recognition, and the only basis on which such a judgment can be made is by a careful appraisal of the data obtained through a systematic study. Investigations of new therapeutic agents are perhaps the most exacting of all scientific investigations since human health, and even life may depend on the thoroughness of these investigations. Furthermore failure to interpret correctly the results of the tests conducted and criteria for their evaluation may be disastrous.

CORRESPONDENCE<sup>41</sup> RE "APPRAISAL OF NEW DRUGS"

(Reply to comments by Chauncey D. Leake (JAMA, 127: 244, 1945) largely on details but questioning frequency with which thorough study required)

The pharmacologic properties of drugs cannot be predicted reliably on the basis of a chemical similarity to other well-known drugs. [Gives examples] \* \* \* there are so many exceptions to the so-called relationship between chemical structure and pharmacologic activity that reliance on that relationship as a short cut to adequate investigation is extremely risky.

Finally, we seriously doubt that the application of the criteria set forth in our paper will delay the use of worthwhile therapeutic agents. In fact, it is our belief that ill conceived and poorly executed investigations have contributed materially to delays in proper and widespread use of therapeutically desirable agents.

<sup>41</sup> JAMA, 127: 353, 1945. Signed by authors of Report of Council on Pharmacy and Chemistry, JAMA, 126: 958, 1944.



## TOO MANY DRUGS?

(Report of the Council on Pharmacy and Chemistry of the AMA. Authorized for publication during secretaryship of Austin Smith. JAMA, 139: 378, 1949)

A fundamental requirement to successful treatment is that the physician have the clearest possible understanding of the remedial agents that he prescribes. This is difficult at best, and is rendered increasingly difficult with multiplication of agents that are nearly but not quite equivalent. Each may show minor differences, which may or may not be practically important, but which are difficult to learn if he spreads his experience too widely and therefore too thinly, as he is urged to do when pharmaceutical firms introduce and promote many actual or near duplicates, with the chief purpose of profiting in a presumably lucrative field, rather than with any real consideration for the welfare of the public or of the interest of medical science and practice. A satisfactory advance has been achieved in the elimination of superfluous drugs from the Pharmacopeia, and the National Formulary has made praiseworthy strides in this direction, but the catalogs of drug houses continue to be overcrowded. The processes of natural selection and the operation of economics tend toward the final survival of the fittest and the eventual elimination of the less fit, but they operate slowly. In the meantime, as new fields open, there is the gold rush to stake out claims and make a killing while the going is still good. But it is particularly in these new and relatively unexplored fields where the harm of unnecessary duplication is greatest, where it interferes most seriously with the acquisition of the precise information that is essential to the proper evaluation of the scope and of the dangers of new medications. Two examples that come to mind are the estrogenic preparations and the "antihistaminic" drugs. In both cases, synthetic chemistry is able to produce practically numberless agents. Both fields are already crowded and overcrowded, but new agents are still being introduced at an alarming rate which makes it practically impossible to acquire the experience that is necessary to determine what advantages, if any, they possess over the older similar agents.

There is another side to the argument, however, for few if any therapeutic agents are ideal. Improvements, increased efficiency, fewer side actions and lower toxicity should be sought for. Skillful experimentation in this direction should be encouraged, not obstructed, but this thorough experimentation should precede the introduction into medical practice. It were better, much better, for medical practice and probably for financial dividends, if modifications which do not offer substantial advantages were shunted into the discard before they see publicity and add to the confusion of practitioners. As an example, it has been suggested to the council that it decline to accept further antihistaminic drugs unless they offer at least one of the following advantages over the agents already accepted: (1) that the drug have a greatly increased potency over those now available so that it would be possible to give relief to certain allergic manifestations not relievable now; (2) that the drug be much less toxic than any now available and not 10 or 20 percent less toxic; (3) that the drug be more active for a much greater duration, not just 3 or 4 hours, but for 24 hours; (4) that the drug have other than histaminic actions, such as sympathomimetic action, or some other action that in some way interferes with allergic mechanism.

The council agrees fully that some such criteria should be applied to all fields that are becoming overcrowded, but the council believes that it would be much better if this is done by voluntary action of the individual manufacturers, rather than by the fiat of any central agency. The latter could easily tend to stifle legitimate and useful competition by cooperative manufacturers, while the less conscientious would go ahead and modify or pirate without council acceptance. The council therefore refers the problem to the good sense of the manufacturers who value the respect and good will of the medical profession.

TOO MUCH MEDICINE? <sup>42</sup>

(By Austin Smith, M.D.)

It is true that new prescription products, if one considers variations in dosage forms, are entering the market to the extent of several hundred per year. It is true, too, that a great deal of effort on the part of physicians is required to keep up with the new discoveries.

<sup>42</sup> New Medical Materia, vol. 4, October 1962, p. 21.



But those who feel that this is bad have several alternatives. One is to request drug firms to discontinue sending information. Another is to cut back on medical journal reading or medical meeting attendance. A third is to push for greater "censorship" of new medicines by other than the body of medical practitioners—perhaps a Government agency. \* \* \*

What is more, the physician has a wider choice of drugs for every purpose—  
anesthetics, antihistamines, etc. \* \* \*

Competition forces each drug company, as a matter of economic survival, to dedicate itself to obsoleting its own products. Any slackening of competitive research carries with it the prospect of grave decline in future progress. \* \* \*

Senator HUMPHREY. Senator Gruening?

Senator GRUENING. I think the chairman has pretty thoroughly explored many aspects of the situation. I want to say to you, Dr. May, I think your testimony has been most valuable and stimulating. After the earlier somewhat cauterizing treatment, you seem to have applied a more or less analgesic therapy.

Dr. MAY. If not hypnotic.

#### SEEKING EFFICIENT REGULATION

Senator GRUENING. And a soothing therapy. I agree with your idea expressed on page 4 that—

although FDA is often characterized as a regulatory agency, in practice the sort of regulation called for is actually judicious evaluation of the best available evidence in the tradition of fine scientific and scholarly endeavor.

But I don't quite follow you when you think that the alternatives, where on page 5 you say—

the ultimate goal is to cultivate voluntary excellence in preference to a monstrous system of external regulation.

Why does regulation have to be monstrous? Can't we just have regulation that is sound and efficient without being monstrous?

Dr. MAY. Sir, I agree with you very precisely. It was for that very reason that I said it was preferable to a monstrous system.

This word was chosen just to make this antithesis, for the simple reason, as Senator Humphrey pointed out; namely, it would be possible for some to believe that the regulatory functions should be played down. I think they should be given a proper balance, even with the scientific activities. But I am as opposed as anyone to a monstrous system.

#### THE IMPORTANCE OF "CONTROVERSIAL" LEADERS

Senator GRUENING. I would like to say that I shared the chairman's regret that after being kept waiting for 10 months, you decided not to accept the medical directorship which I think is understandable, and I want to say that I notice that there is mention—one of the things mentioned—that you were somewhat "controversial."

It has been my experience that if a man hasn't been labeled "controversial" at least once, he is not worth his salt.

Senator HUMPHREY. You are cheating then.

Senator GRUENING. I recall from my slight knowledge of history some very distinguished controversial figures—Galileo, Darwin, Pasteur. They were all highly controversial, and somehow they have become immortal.



So I hope you will always continue to be "controversial" to the extent that you stand up for your convictions, and I know you will. I think that the Government and the public are the losers at your declination of that appointment. After being kept waiting, however, for 10 months, I can understand your feeling that maybe you weren't wanted.

Dr. MAY. Yes, and perhaps because I was possibly labeled as "controversial," it was easy to set me aside. This is what I brought out in my introductory remarks—the temper of the times is vitally important in molding the decisions.

This is not a time in which analysis of matters is welcomed. People talk about leadership and criticism, and they talk about courage. They hope somebody else will exercise these functions. Therefore, I think this would have been a much more difficult decision to be made if all of us were comfortable with the analytical point of view. I choose other than the word "critical" because the word "critic" has become so black. We might as well find a new word to designate a new breed of men.

Senator GRUENING. Thank you very much.

#### ABANDONMENT OF AMA SEAL OF APPROVAL OF DRUGS

Senator HUMPHREY. Doctor, the American Medical Association at one time had a very effective drug-evaluation program, isn't that right?

Dr. MAY. Yes, sir.

Senator HUMPHREY. What has happened to that particular program? I ask this question because, as I recall, there used to be a time when a physical seal was placed upon new drugs as approved by AMA?

Dr. MAY. Yes, sir.

Senator HUMPHREY. What has happened to that seal?

Dr. MAY. That was abandoned; I think it was around 1955.<sup>43</sup> I am not quite clear of the date. This was all explored very extensively in the previous hearings as far as precise information is concerned. But it has been abandoned for some time.

Senator HUMPHREY. Do you know why?

Dr. MAY. I don't know exactly why. It would be very easy to have this examined carefully, but I think it was a difficult program to administer.

Senator HUMPHREY. Yes.

Dr. MAY. For the simple reason, if you put a label on a product which in a sense is in terms of its worthiness, you may automatically be called up in terms of certifying the contents of the package. If there happens to be a nail in it instead of what was supposed to be in there, you may have problems.

But the point is that so long as the Council on Drugs and the American Medical Association were able to maintain a prestige which made them unassailable, this program was in no sense threatening, just as an individual can be more forthright in terms of his unassailability. So I think this is one of the problems: that the altera-

<sup>43</sup> (This and succeeding foot notes to the witness' testimony were provided, as in the case of Dr. Nestor's comments, by the subcommittee editor in order to facilitate the readers' review.) For the editorial in the Journal of the American Medical Association which announced the ending of the seal-of-acceptance program, see exhibit 159, p. 1142.



tion in the times, in the image, made them more vulnerable and, therefore, more squeamish about taking this particular stand.<sup>44</sup>

Senator HUMPHREY. Doctor, I think that they miscast you as Director of the Bureau of Medicine. You should be in the State Department. You are a great diplomat.

Dr. MAY. Thank you.

Senator HUMPHREY. I will talk to you privately about this little matter later on. I am not quite that diplomatic. I guess that is why I am in the Senate.

I have a feeling that there may be some other reasons why that program was abandoned, and I am sorry it was abandoned. I really am, because I do believe that the high standards that were established by the American Medical Association's Council on Drugs was very helpful.

Dr. MAY. Sir, they have found nothing to take its place. They lost the most valuable tool they ever had as far as being of service to the profession, and clearly appreciated by the public.

Senator HUMPHREY. Well, we are just beginning to look into these matters, so we will be back later on.

I have a couple of questions. I won't keep you much longer. It is getting a little late, but people ought not to eat too heavy a lunch anyway. I think that is another medical observation I ought to make. As a layman I say that.

#### THE VAST MAGNITUDE OF DRUG INFORMATION

You know we are publishing a print for the subcommittee entitled "The Nature and Magnitude of Drug Literature."

This print points out the almost impossible task of the private physician in trying to find, amidst literally thousands of drugs, what he needs to know about a given drug.

**You were commenting upon that earlier today, Doctor—what he needs to know in terms of its comparative safety, its comparative efficacy, and the contraindications, possibly dangerous drug combinations, and so forth.**

I note, for example, that the 1961 Physicians' Desk Reference, which is the standard publication for doctors, lists no fewer than 31 antibiotics for gastrointestinal purposes only. Do you believe that the dissemination of information to prescribers should be left exclusively to private agencies, such as the AMA or to publications such as the Physicians' Desk Reference?

Dr. MAY. Sir, I think that it is a great pity that the culmination of the best efforts, the best joint efforts of the Food and Drug Administration and of the drug industry, are so inconveniently accessible to the physician—I refer to the packaging inserts.

These are excellent documents, and they will become more thorough as the new laws and the new regulations have their effect. And I say it is a pity that they are not brought to physicians in some systematic and convenient way.

<sup>44</sup> See Senate Committee on the Judiciary, Subcommittee on Antitrust and Monopoly hearings pursuant to S. Res. 52 on S. 1552, 87th Cong., pt. 1, "AMA and Medical Authorities," p. 90 ff.



## THE PHYSICIANS' DESK REFERENCE

Let me point out for a moment how the doctor now does get some of this information. You have referred to the Physicians' Desk Reference, which is a private publication.

Senator HUMPHREY. That is the book you have there, is it not?

Dr. MAY. Yes, sir.

Senator HUMPHREY. It is generally found in most doctors' offices, isn't that correct?

Dr. MAY. It is distributed free of charge to—it says in the contents—180,000 prescribers of drugs, and made available to many others of the health team.

I should like to introduce as an exhibit in this connection statements from the introductory material, editorial comments on the Physicians' Desk Reference. I believe you have a copy of this available.

Senator HUMPHREY. Yes.

Dr. MAY. Because it points out certain aspects of the Physicians' Desk Reference which are worthy of note.

First let me say that those who conceived of the idea of publication of the Physicians' Desk Reference and who have carried out its operations have done a commendable job. This is not only an ingenious idea, but it turns out to be a most useful one. In fact, this is the book most used by doctors in America today as a source of information on drugs.

Senator HUMPHREY. It is to the doctor almost what the pharmacopeia is to the druggist, isn't it?

Dr. MAY. Exactly so, except that it does not have any official standing, of course.

Senator HUMPHREY. Yes.

Dr. MAY. In the preface it points out that this book is made possible through the courtesy of manufacturers whose products appear in the following pages. In other words, listing of drugs and descriptions of drugs are inserted in terms of whether or not the manufacturer hires space in the publication for the insertion of information.

Secondly, it is pointed out in the material, which I have given to you as an exhibit, that the copy for the material included in PDR is furnished by the manufacturer, and the manufacturer is admonished by the editors to see to it that this information is authentic.

But, nevertheless, the responsibility rests with the persons who provide the copy, and the editorial staff assumes no degree of responsibility such as screening, criticizing, or otherwise manipulating this data, insofar as the introductory paragraphs suggest.

Furthermore, on the other hand if one realizes that the majority of the descriptions really are patterned after the package inserts, one might therefore say this suffices then as a way of getting this information around.

## DISCREPANCIES BETWEEN INFORMATION IN PACKAGE INSERTS AND IN PDR

But for those inserts referred to earlier, which I rescued from the wastebasket, I also took the pains to compare with the description of PDR. And there are some very interesting differences in terms of omissions or rearrangements.



The bulk of the information is there, but since this copy was provided by the manufacturer, it is conceivable that at times what was introduced into PDR might be slightly different from what was insisted upon by the Food and Drug Administration in terms of warnings or indications for the usage of this drug.

I say that the Food and Drug Administration should have a systematic system under their own control for the delivery into the hands of the doctor of these descriptions of products contained in the approved package labeling insert.

Senator HUMPHREY. Wouldn't it be possible for the Food and Drug Administration and the manufacturers to set up a joint task force of educators to see to it that the PDR was directly related without contradiction or evasion to the inserts that are approved by the FDA?

Dr. MAY. I think every means should be explored for either direct publication, or by contract getting someone to publish all of the inserts, not just those that someone chooses to put in because they are at the moment drugs they wish to push or that are selling well, but every drug that a physician may come to use for one reason or another; and the prescriber should have this publication made available to him without charge.

Every means should be explored for cooperation with industry in terms of standardization of typography, format, and arrangement, with private publishers if necessary, or if no satisfactory cooperative scheme can be developed, then this is the least that the Government might do as a service to the profession and as a means of protecting the interests of the public.

Senator HUMPHREY. Doctor, the reference that you made to the Physicians' Desk Reference publication—this was included with the material that you had presented to the committee?

Dr. MAY. Yes, sir.

Senator HUMPHREY. For general inclusion in the record here today?

Dr. MAY. Yes, sir.

Senator HUMPHREY. All of this material is included.

#### EXHIBIT 154

##### EXCERPTS FROM 1963 EDITION OF PHYSICIANS' DESK REFERENCE

There follow the excerpts referred to by Dr. May in his testimony from the 1963 edition of Physicians' Desk Reference:

##### PHYSICIANS' DESK REFERENCE TO PHARMACEUTICAL SPECIALTIES AND BIOLOGICALS

Oradell, N.J., Medical Economics, Inc., 1963.

##### PREFACE TO SECTION FIVE

##### (Professional Products Information)

"This book is made possible through the courtesy of the manufacturers whose products appear on the following pages (section 5).

"The information concerning each product has been prepared by the manufacturer, and edited and approved by the medical department, medical director, or medical counsel of each manufacturer.

"In the course of obtaining this material, the publisher, Medical Economics, Inc., emphasized to manufacturers the necessity of describing products comprehensively so that physicians will have access to all the essential information needed to prescribe intelligently, including composition, action and uses, administration, dosage, contraindications, precautions, side effects, form in which



supplied, and other details concerning use. In addition the common name, generic composition or chemical name of each brand name prescription product will be found in the information for each product.

"In organizing and presenting the material in Physicians' Desk Reference, the publisher is providing all of the information made available to PDR by manufacturers \* \* \*."

#### PREFACE TO MANUFACTURERS' INDEX

"The manufacturers whose names appear in this index have provided information concerning their pharmaceutical specialties, biologicals, and antibiotics in section 5. It is through their patronage that Physicians' Desk Reference is made available to you \* \* \*."

Senator HUMPHREY. Now I would like to ask just two questions, and it won't take long.

#### AMA'S PROPOSED HANDBOOK OF DRUG APPRAISAL

Why can't the system for reporting adverse reactions on these drugs be done by some agency besides the FDA, such as, let's say, the American Medical Association or any other professional organization?

Dr. MAY. That question is in a sense a companion question or a derivative of the preceding one.

Senator HUMPHREY. Yes.

Dr. MAY. Namely, why can't the AMA provide this information about drugs?

As you will recall, in previous hearings the AMA committed themselves to the preparation of a handbook on drugs containing not only all of this information but an overall appraisal of the drug in terms of its position among its class of drugs.

The distribution of these package inserts is a way of distributing information, but it does not tell you which is the preferred drug for a given condition, nor should it do so if it emanates from a Government source.

In other words, the Government's job is not to tell doctors how to practice medicine, but to provide them with the true information to do so well, and then to see that they are perhaps doing so.

But the handbook on drugs was not only to meet all the considerations we had in mind, but to give in addition this overall appraisal, which is also sorely needed. This book was promised to be completely operational by 1963, this promise having been made in July of 1961.

Now, I have seen no signs of this handbook on drugs. It would be extremely important to know what the present status of its development may be, whether appropriations have been made for the hiring of staff and the preparation of dummies and when it is to be forthcoming, if ever, because it cannot be depended upon as a means of disseminating information if it is not going to exist.

Senator HUMPHREY. We have some witnesses who are coming from the American Medical Association. I hope they will testify on this.

Dr. MAY. I hope they will be able to bring us up to date.

Senator HUMPHREY. It would be very interesting to know what progress has been made on this publication.

#### THE FEDERAL GOVERNMENT'S OWN RESPONSIBILITY

Dr. MAY. But the reason the answer to this question is so important is that now, in 1963, we have a promise of a system from the AMA



for systematic reporting of adverse reactions. We would be very much more inclined to depend upon it if the previous promise had been fulfilled on schedule.

In other words, my thought is that it would be imprudent for the Government to depend upon any agency for an adverse reaction reporting program outside of the FDA, that they should develop a strong program within FDA which could cooperate with any public or private agency, including the cooperation of industry, which is certainly to be expected or desired.

I think the FDA can't afford to carry out its operations with any uncertainty of arrangement or system. At the present time I do know that the AMA has as chairman of its Adverse Reactions Program Committee one of the most eminent persons in the country in this respect. But they also had at their service a Council on Drugs, who are one of the most eminent groups of men in medicine, and who formulated the ideas and contents of the handbook on drugs.

If by any chance the handbook has been set aside, then it may well be that the adverse reactions program may dwindle to a halt at some point. It is very important to find some way of getting a firm and lasting commitment, or if we are not satisfied in this respect, not to depend on it.

#### AVOIDING "GOVERNMENT (ONLY) BY CRISIS"

Senator HUMPHREY. It seems to me that if the Federal Aviation Agency can collect adverse reactions on parts of planes, maybe the Government might be able to cooperate with the American Medical Association, the Pharmaceutical Manufacturers Association and others on the adverse reaction to drugs.

What is really needed is a continuing account of such adverse reactions. This is absolutely essential, and I don't understand how we can delay all these things forever. I keep asking myself how many people do you have to kill before somebody gets excited. We have Government by crisis in this country, not by premeditation.

#### FDA'S EXISTING PROGRAM ON ADVERSE REACTIONS

Dr. MAY. I know something of the existing program in the FDA for reporting of adverse reactions, and have been instrumental in having an arrangement to cooperate with them established in our own hospital. The FDA has a system which is fundamentally sound. What it needs is the support that it deserves in terms of the total operations.

Now, where this support should have come from, or should come from in the future, or whether it is only now that we have been brought into a frame of mind where we can appreciate its significance by reason of recent calamities, they know perfectly well what to do.

Furthermore, the FDA has a working organization which spreads throughout not only Government agencies but many private institutions as well.

I think it is also important to point out that the Food and Drug Administration is held in high esteem by the practicing physician. He is as willing to report matters that pertain to the reactions to new



drugs to a Federal agency as he is to his own medical organization. The argument that only a medical organization can get anything out of a doctor is not true as far as reporting of adverse reactions to drugs is concerned.

#### PROPOSED CENTERS FOR DRUG INFORMATION

Senator HUMPHREY. I give you my \$64 final pet question. I want you to know that as a result of asking this question now for 5 years at every meeting I have been able to get a few results.

Is there a need for a centralized system for storage and retrieval of this information on drugs?

Dr. MAY. Senator, in this respect I would not attempt to rival your eloquence in pleading for the importance of this.

I don't know, maybe sometimes we ought to resort to some sort of a dramatic episode. If one were to fire a particular question at a place that ought to have the information, it might be interesting to see how long it takes to get the answer. This would be a very convincing way to find out whether you need some system for bringing answers to questions promptly. The fact of the matter is, I can't believe that any reasonable man can deny the need in these times for a centralized agency for the storage and retrieval of information.

Now, who should do this or where it should be done is a very much larger question, and I believe that persons should be brought together to settle this now and forthwith, whether it be done by the National Library of Medicine, the National Institutes of Health, the Health Information Foundation, or whatever agency.

I cannot believe it is necessary for everybody who is interested in information to maintain some sort of gigantic system. And in this respect private interests, namely, the medical organizations themselves, and I know this matter was discussed within the halls of the AMA, and the industry must be very conscious of this problem. The Government certainly is.

Isn't this one area where we might possibly be able to develop the spirit of cooperative endeavor to which we all aspire? We could have a central agency accessible to all those who will support it and availed by others on a service basis. I think it certainly deserves the utmost urgency in attention.

Senator HUMPHREY. It would seem that the answer is quite obvious, but I must say that it sure takes an awful lot of prodding.

However, we are beginning to make some progress. I think you would be interested in knowing that in another area, at long last, the Defense Department is now cataloging and indexing all of its current research projects. It is doing this for the first time now, despite the fact that we have long since spent billions and billions and billions of dollars on research. I am happy to say that the Deputy Secretary of Defense, Roswell Gilpatric, came before this committee last year and said because of the prodding of this subcommittee and studies that had been made, the Defense Department is now undertaking an overall information system with coordinated indexing, collation and retrieval, which will save the taxpayers hundreds of millions of dollars. It will also make available to the public and to interested industries and manufacturers vast amounts of information, as well as scientific laboratories and establishments and universities.



We have information stacked up in every building, not only in Washington but within 50 miles of each side of Washington. We can't find the space to stack the stuff, and nobody, or very few people, knows what is in it.

There are hundreds of thousands of research projects that have gone on without any coordination. This subcommittee has exposed duplication that has cost the taxpayers tens of millions of dollars. But you have people who are interested in a new research project and don't even know that they have completed the last one.

We will just keep at it. Someday maybe we will get it done.

One of the great qualities that a man needs in the legislative branch is patient persistence with a degree of orneriness. It is hard to keep them in balance.

Thank you very much, Doctor. It has been a joy to have you.

Dr. MAY. Sir, may I just make one final comment?

#### ESTABLISHING A SOUND STRUCTURE FOR SCIENTIFIC DECISIONMAKING

I would like to be sure that this is entered in the record somehow. That is, I hope that the administrative structure of the Food and Drug Administration is not going to get "frozen" by all sorts of people operating upon it before a scientific administrator is selected who can have some influence on what the arrangements may be.

And also that the scientific structure or the administrative structure take into account one of the major premises in my exhibit regarding organization; namely, the placing upon a par of the scientific administrator with the others, but not necessarily calling for his immunity from any accounting to others.

Also, that the fewest possible intermediaries be placed between the scientists who are working beside the administrator and his direct path of communication with the Commissioner.

These things are all indicated in my chart of proposed administrative structure. This is one of the aspects of the citizens report about which I was concerned—as you look at their charts, and I realize that these charts may not always operate the way they look, but it looked to me as though an awful lot of people were between the ordinary worker and the man at the top.

I have a great deal of respect for the ordinary worker as being the cornerstone of the activity. And also I thought that there was an artificial division between the Bureau of Medicine and the Bureau of Scientific Activities. I think in this day and age that microbiology and medicine do not belong in separate categories, and that such administration can complicate the administration or referral of problems.

In my plan I suggest all these be brought together in such a way that they have free access to one another, and are adequately represented at a top policy level. These points I did not bring out in my introductory statement or in our discussions. They are indicated in the exhibits, but I would like to give them this emphasis, and I thank you for indulging me these few final remarks.



## EXHIBIT 155

CHART BY CHARLES D. MAY, M.D., ON PROPOSED ORGANIZATION OF SCIENTIFIC PROGRAMS IN THE FOOD AND DRUG ADMINISTRATION

The chart referred to by Dr. May in his testimony appears on p. 1074.

DIAGRAMMATIC REPRESENTATION OF MAJOR ELEMENTS OF ORGANIZATION OF FOOD AND DRUG ADMINISTRATION TO FACILITATE DEVELOPMENT AND INTEGRATION OF SCIENTIFIC PROGRAM

(Prepared by Charles D. May, M.D., Mar. 14, 1963)

TO BE COMPARED WITH EXHIBITS B-4, B-5 IN "APPENDIX OF REPORT ON FDA BY CITIZENS ADVISORY COMMITTEE," OCTOBER 1962

Essential feature is to have chief scientist on par with heads of other major divisions, and with direct and methodical access to the Commissioner. Likewise directors of scientific bureaus are on a par and each has direct access to Associate Commissioner for Science and direct access to each other.

[Exhibits B-4 and B-5 appear in Exhibit 156 below.]

## EXHIBIT 156

EXCERPTS FROM REPORT BY THE SECOND CITIZENS ADVISORY COMMITTEE ON THE FOOD AND DRUG ADMINISTRATION WITH REGARD TO PROPOSED REORGANIZATION OF SCIENTIFIC PROGRAMS

There follow excerpts from the report of October 1962 by the Second Citizens Advisory Committee on the Food and Drug Administration. These excerpts relate to the proposed reorganization of scientific programs as commented upon by Dr. May.

EXCERPTS FROM REPORT BY SECOND CITIZENS ADVISORY COMMITTEE ON FOOD AND DRUG ADMINISTRATION

## Appendix B, p. 4

## DETAILS OF RECOMMENDED ORGANIZATION PLAN

The details of the plan of organization which the committee believes would equip FDA to fulfill the responsibilities recommended in this report are presented below.

The overall plan of organization appears in exhibit B-4, on the following page. It incorporates a number of basic changes from the present plan. At the top policy level, an Assistant Secretary of HEW is proposed as a staff aid to the Secretary, with fulltime responsibilities for keeping informed of FDA and PHS activities, and for providing a more effective channel of communications between the Secretary and the Commissioner. This Assistant Secretary would have no line operating authority over FDA; rather, he would be the Secretary's specialist for this agency and for PHS, and would aid in channeling the Secretary's attention to major FDA and PHS problems and relationships, to ensure consistent policy application. He also would be the staff aid for promoting coordination of functions between FDA and PHS to the extent desirable.

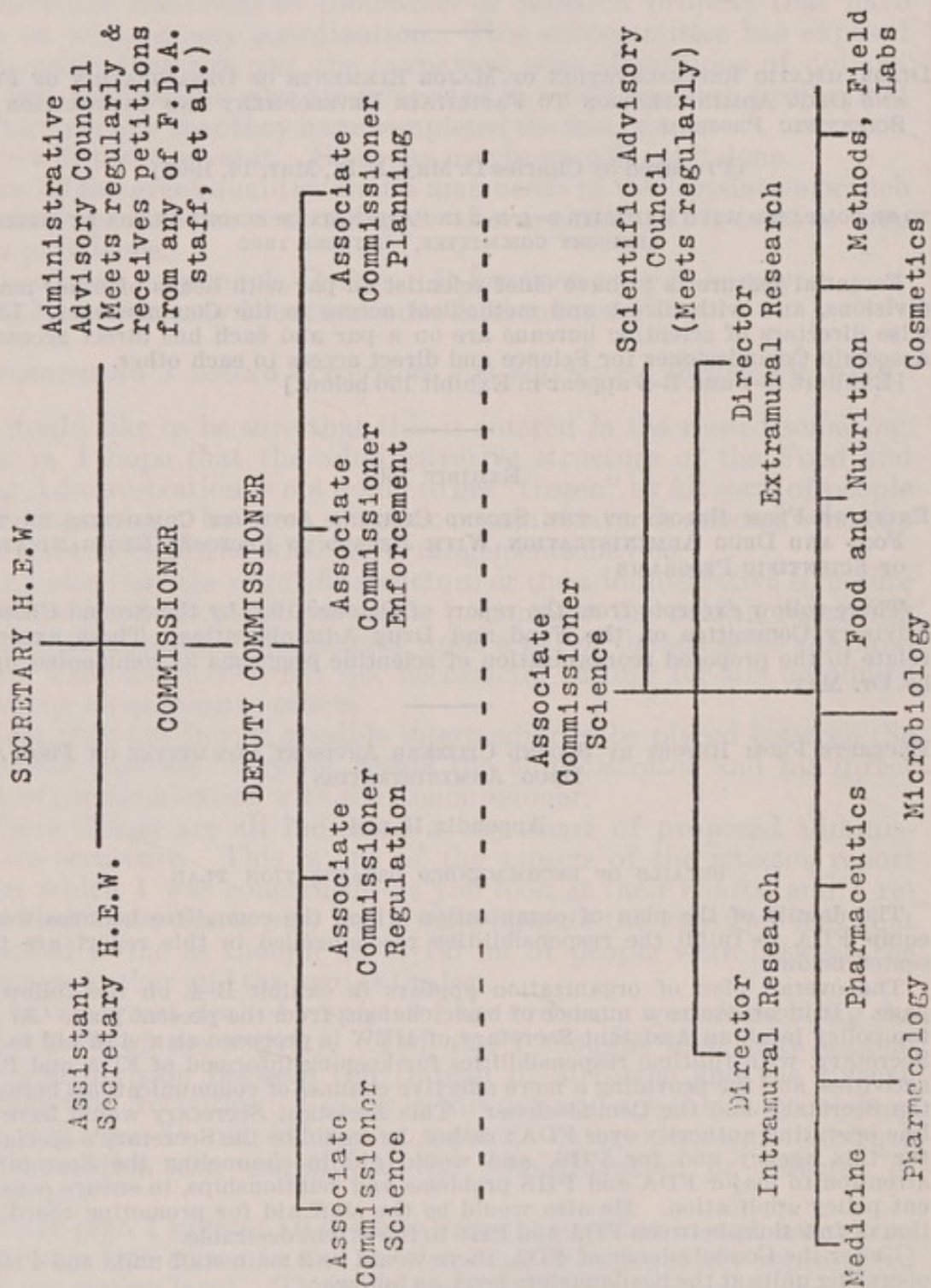
Under the Commissioner of FDA, there would be 2 main staff units and 4 main operating units at the headquarters level, as follows:

- Staff Headquarters Activities
  - Deputy Commissioner for Planning
  - Deputy Commissioner for Operations
- Line Headquarters Operations
  - Food and Drug Institute
  - Bureau of Education and Information
  - Bureau of Enforcement and Inspection
  - Bureau of Administration

The major duties and the organizational details of each of these units are described below, together with the basic changes these would represent.

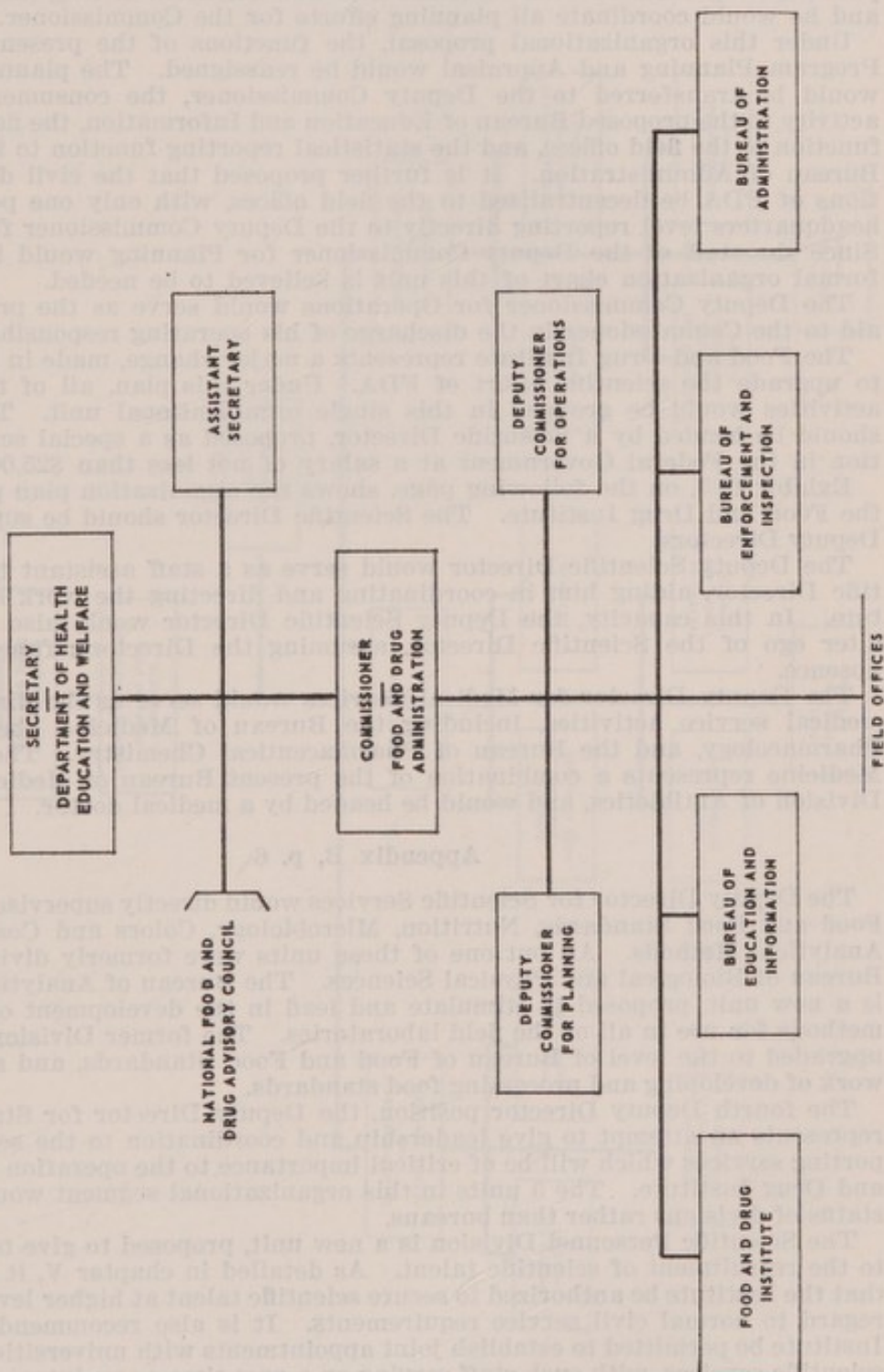


(Chart furnished by Charles D. May, M.D., on proposed FDA Scientific Organization)





**EXHIBIT B-4**  
**FOOD AND DRUG ADMINISTRATION**  
**PROPOSED ORGANIZATION**  
**HEADQUARTERS**





## Appendix B, p. 5

The Deputy Commissioner for Planning is a new position, established to furnish leadership for the long-range planning function at the highest possible level. This Deputy Commissioner would not be expected to perform personally all of the future planning for FDA, but he would see to it that each of the principal operating units devoted sufficient time and attention to long-range planning, and he would coordinate all planning efforts for the Commissioner.

Under this organizational proposal, the functions of the present Bureau of Program Planning and Appraisal would be reassigned. The planning function would be transferred to the Deputy Commissioner, the consumer consultant activity to the proposed Bureau of Education and Information, the field appraisal function to the field offices, and the statistical reporting function to the proposed Bureau of Administration. It is further proposed that the civil defense functions of FDA be decentralized to the field offices, with only one person at the headquarters level reporting directly to the Deputy Commissioner for Planning. Since the staff of the Deputy Commissioner for Planning would be small, no formal organization chart of this unit is believed to be needed.

The Deputy Commissioner for Operations would serve as the principal staff aid to the Commissioner in the discharge of his operating responsibilities.

The Food and Drug Institute represents a major change, made in an endeavor to upgrade the scientific effort of FDA. Under this plan, all of the scientific activities would be grouped in this single organizational unit. The institute should be headed by a Scientific Director, proposed as a special scientific position in the Federal Government at a salary of not less than \$25,000 per year.

Exhibit B-5, on the following page, shows the organization plan proposed for the Food and Drug Institute. The Scientific Director should be supported by 4 Deputy Directors.

The Deputy Scientific Director would serve as a staff assistant to the Scientific Director, aiding him in coordinating and directing the work of the Institute. In this capacity, the Deputy Scientific Director would also serve as an alter ego of the Scientific Director, assuming the Director's functions in his absence.

The Deputy Director for Medical Services would serve as the director of the medical service activities, including the Bureau of Medicine, the Bureau of Pharmacology, and the Bureau of Pharmaceutical Chemistry. The Bureau of Medicine represents a combination of the present Bureau of Medicine and the Division of Antibiotics, and would be headed by a medical doctor.

## Appendix B, p. 6

The Deputy Director for Scientific Services would directly supervise 5 Bureaus: Food and Food Standards, Nutrition, Microbiology, Colors and Cosmetics, and Analytical Methods. All but one of these units were formerly divisions of the Bureau of Biological and Physical Sciences. The Bureau of Analytical Methods is a new unit, proposed to stimulate and lead in the development of analytical methods for use in all of the field laboratories. The former Division of Food is upgraded to the level of Bureau of Food and Food Standards, and assigned the work of developing and processing food standards.

The fourth Deputy Director position, the Deputy Director for Staff Services, represents an attempt to give leadership and coordination to the scientific supporting services which will be of critical importance to the operation of the Food and Drug Institute. The 5 units in this organizational segment would have the status of divisions rather than bureaus.

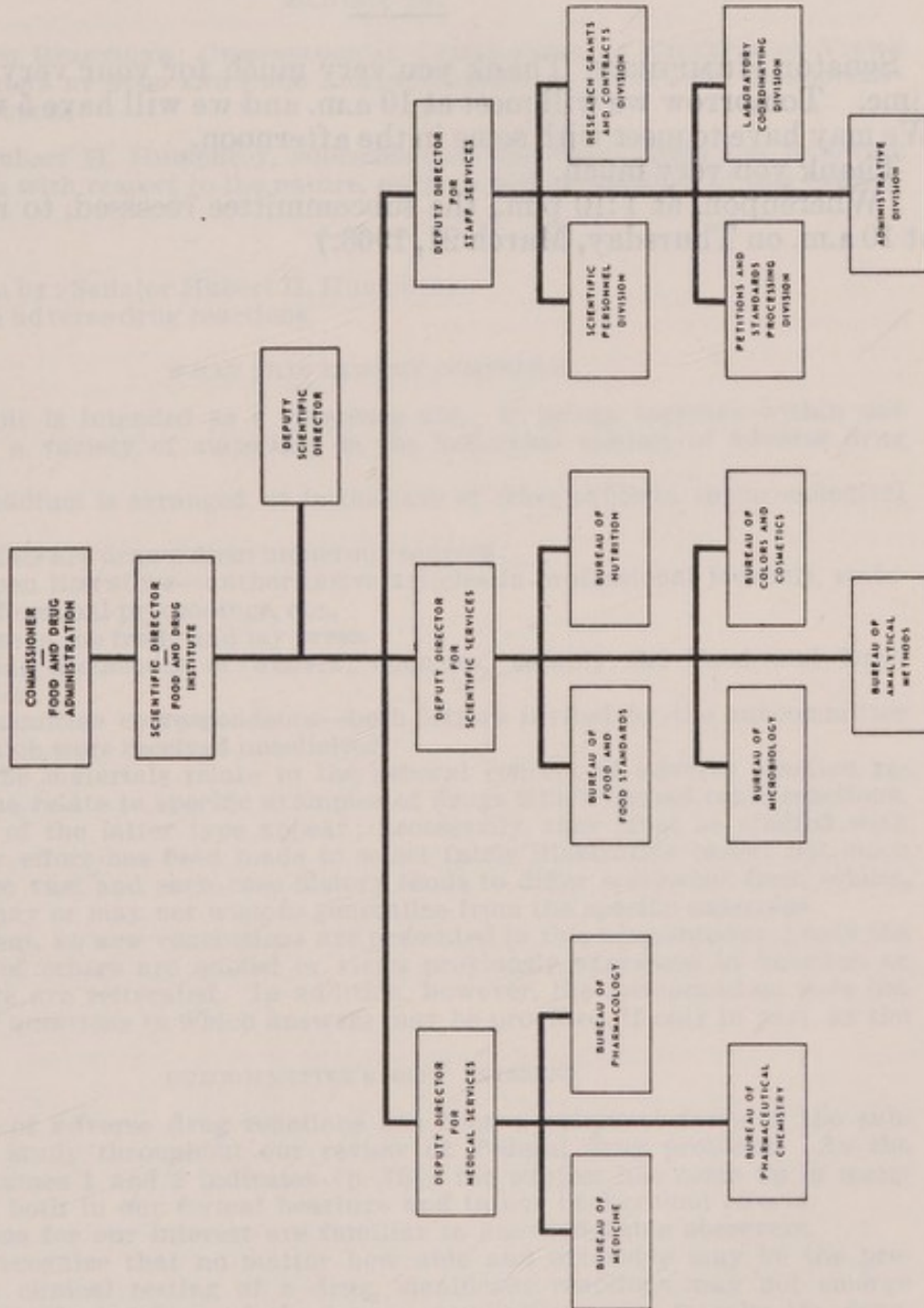
The Scientific Personnel Division is a new unit, proposed to give top attention to the recruitment of scientific talent. As detailed in chapter V, it is proposed that the Institute be authorized to secure scientific talent at higher levels, without regard to normal civil service requirements. It is also recommended that the Institute be permitted to establish joint appointments with universities and other scientific services, with such staff serving on a part-time or an intermittent basis.

The Research Grants and Contracts Division is also a new unit, intended to review and approve FDA grants and contracts for scientific work by other institutions. The details of this arrangement appear in chapter V.

The Petitions and Standards Processing Division represents a combination of all present services concerned with the processing of petitions and standards. Some of these are now located in the Commissioner's office (all of the functions of the Assistant Commissioner for Regulatory Matters) and others are in the various scientific bureaus.



EXHIBIT B-5  
FOOD AND DRUG ADMINISTRATION  
PROPOSED ORGANIZATION  
FOOD AND DRUG INSTITUTE





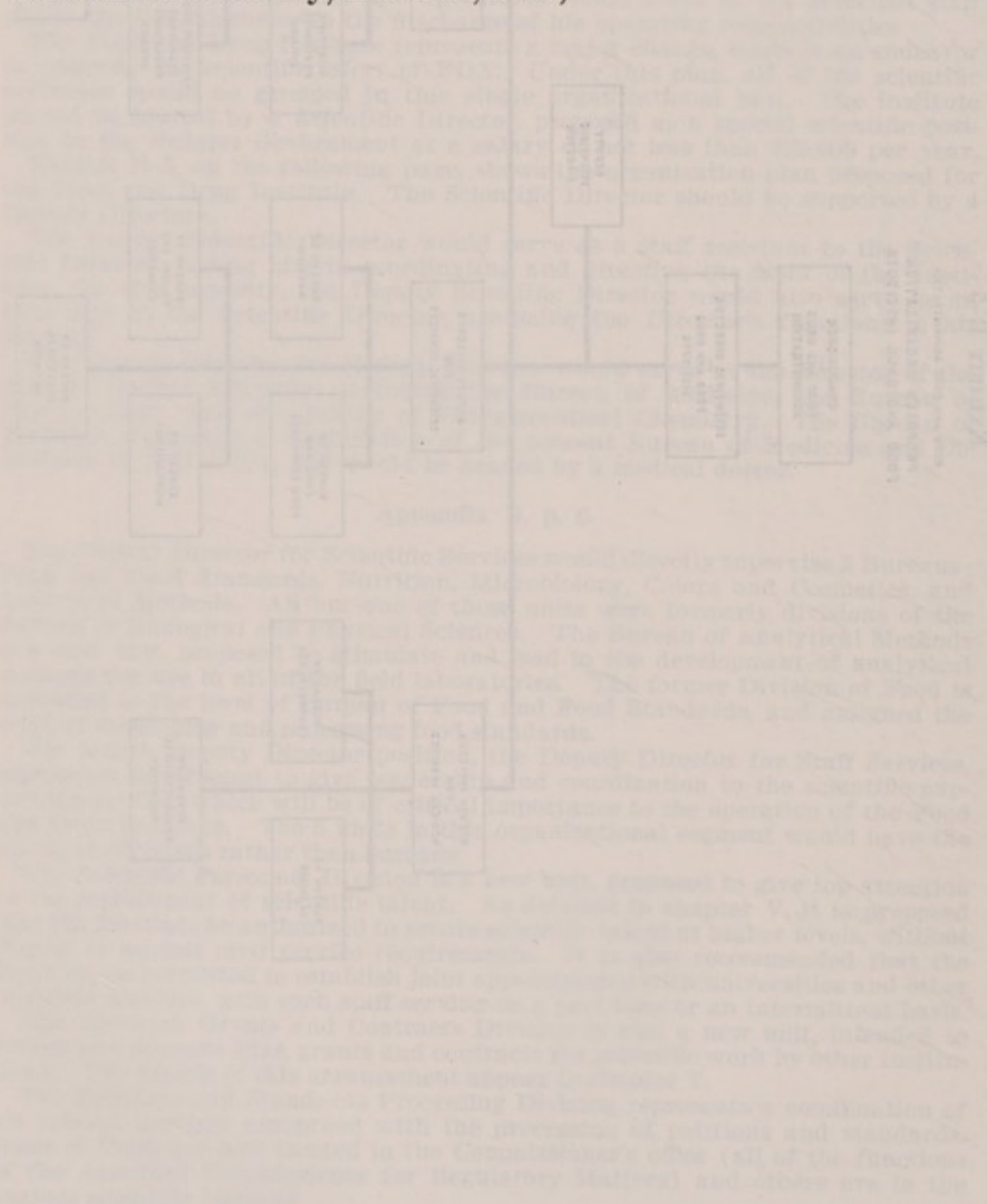
The Laboratory Coordinating Division is designed to give leadership to the coordination of headquarters and field laboratories, to develop the specific role of each, and to aid in the development of field laboratory capabilities. The field laboratory management function of the present Bureau of Field Administration should be transferred to this unit.

The Administrative Division is designed to provide budget and management services to the Institute, because it is believed that an organization of this size needs a small administrative group to aid it in these functions.

Senator HUMPHREY. Thank you very much for your very valuable time. Tomorrow we will meet at 10 a.m. and we will have 5 witnesses. We may have to meet with some in the afternoon.

Thank you very much.

(Whereupon, at 1:10 p.m., the subcommittee recessed, to reconvene at 10 a.m. on Thursday, March 21, 1963.)





EXHIBITS ON ISSUES REFERRED TO BY DR. CHARLES D. MAY

EXHIBIT 157

ADVERSE DRUG REACTIONS: CHRONOLOGICAL COMPILATION OF EXCERPTS OF VIEWS AND DECISIONS BY FOOD AND DRUG ADMINISTRATION AS WELL AS BY NONGOVERNMENTAL SOURCES

Senator Hubert H. Humphrey, subcommittee chairman, offers the following memorandum with respect to the nature, purpose and background of this exhibit.

Memorandum by: Senator Hubert H. Humphrey.  
Re exhibit on adverse drug reactions.

WHAT THIS EXHIBIT COMPRISES

This exhibit is intended as a reference aid. It brings together within one compendium a variety of materials on the important subject of adverse drug reactions.

The compendium is arranged, as in the case of other exhibits, in chronological form.

The materials are drawn from numerous sources:

- (a) the open literature—authoritative articles in professional journals, statements in professional proceedings, etc.,
- (b) articles in the trade and lay press,
- (c) internal documents of Federal agencies, notably the Food and Drug Administration,
- (d) subcommittee correspondence—both letters invited by the subcommittee and those which were received unsolicited.

Some of the materials relate to the general concept of adverse reaction reporting; some relate to specific examples of drugs which caused toxic reactions. Only a few of the latter type appear; necessarily, they must be studied with care. Every effort has been made to select fairly illustrative cases; but since the field is so vast and each case history tends to differ somewhat from others, the reader may or may not wish to generalize from the specific examples.

In any event, no new conclusions are presented in this memorandum; only the conclusions of others are quoted or views previously expressed in hearings or in the Senate are reiterated. In addition, however, the memorandum does list a number of questions to which answers may be provided, if only in part, by the exhibit.

SUBCOMMITTEE'S DEEP INTEREST

The topic of adverse drug reactions has been a principal focus of the subcommittee's study throughout our review of Federal drug problems. As the index to volumes 1 and 2 indicates (p. 761) the subject has come up in many connections, both in our formal hearings and in our background efforts.

The reasons for our interest are familiar to knowledgeable observers.

Experts recognize that no matter how able and extensive may be the pre-clinical and clinical testing of a drug, significant reactions may not emerge until considerable numbers of the human population begin to take the drug. There has, therefore, always been agreement within the healing arts on this principle: a sound system of adverse drug reaction reporting is an important tool in medical science.

The key word is "sound." Experts whose views are quoted herein and in other subcommittee publications stress, for example, that reports of adverse reactions must be evaluated with particular competence, lest the "tool" be misused.

The aim of the process is, of course, to help maximize the benefits from safe and efficacious drugs and to minimize avoidable hazards.



## SIGNIFICANCE OF UNPUBLISHED INFORMATION

To the subcommittee, one of the many facets of interest of this topic is that it illustrates the role of unpublished information.

For years, the subcommittee has pointed out that, as massive as the open literature of science may be, still more massive is the amount of information which does not reach the open literature. This latter information ranges in quality and significance from the most unfounded and trivial to the most reliable and consequential.

One type of largely unpublished information consists of adverse reactions. As the American Medical Association points out herein (May 1963 release), most reactions are definitely not reported in professional journals. A variety of reasons account for this nonreporting—some of these reasons are good, others are not so satisfactory—the subcommittee has been told.

Whatever the reasons, medical science increasingly recognizes that a sound system does require compilation, abstracting, indexing, cross-referencing, evaluation, and dissemination of both the published and the unpublished segments of information on adverse reactions.

Since the unpublished segment, by definition, does not undergo the scrutiny of the critical referee system within journals, it must be evaluated, as earlier indicated, with particular discretion.

## VARIED SIGNIFICANCE OF CONTENTS

Each reader—layman or professional—will tend to see in the chronology which follows some one or more phases pertinent to his particular area of interest. Generally, however, the contents may help provide answers to two particular types of questions:

- (a) Questions involving fact and principle.
- (b) Questions involving judgments as to various programs.

## QUESTIONS INVOLVING FACT AND PRINCIPLE

Among the factual questions which the quotations and documents may help to answer are these:

- (a) What is actually meant by adverse drug reactions?
- (b) What are the various factors which may be responsible for adverse reactions?
- (c) What, then, is the medical significance of adverse reaction reporting systems?
- (d) How long have such systems been in operation within the Federal Government, by the American Medical Association and by other sources?
- (e) How extensive are adverse reaction reporting systems?
- (f) What are the respective roles in such systems by the general practitioner, the medical specialist, the pharmacist, nurse, researcher, and other members of the health team?

## QUESTIONS INVOLVING EVALUATION OF ACTUAL PROGRAMS

More important are answers which may be provided as regards those issues involving evaluation of adverse reaction reporting itself. For example, the following are but a few of the questions which should be asked and answered, based upon the documents which follow, but also on many more materials, as well:

- (a) Has the Food and Drug Administration effectively discharged its obligations with respect to an adverse reaction reporting system?
- (b) Have other Federal agencies fulfilled their responsibilities with respect to adverse reaction reporting?
- (c) Has the medical profession, including medical specialty organizations, fulfilled their responsibilities?
- (d) Have the allied healing arts done all that might be reasonably expected of them?
- (e) How complete, how useful, and effective are present systems of adverse reaction reporting:
  - 1. With respect to case histories?
  - 2. With respect to coverage of the literature?



(f) To what extent are the various programs of adverse reaction reporting coordinated with one another? To what extent should they be so coordinated?

(g) Have pharmaceutical companies adequately cooperated with the Food and Drug Administration with respect to adverse reaction reporting:

1. Under the old law when companies were required to furnish such information only with respect to drugs on which New Drug Applications or supplements thereto were pending?

2. Under the new law, since October 1962, wherein the aforementioned distinction is eliminated and adequate records with respect to adverse reactions must be maintained and must be furnished to the U.S. Food and Drug Administration promptly, whether or not an NDA is pending.

#### CONCLUSION

The present exhibit offers only a small portion of materials necessary to answer the preceding questions. The exhibit may, however, serve as a useful starting point for review of a subject which is of such vast significance. Other exhibits within this volume may offer additional helpful background as regards adverse reaction reporting on specific drugs.<sup>1</sup>

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1952. Council on Drugs of the American Medical Association becomes "concerned with the problem of hematotoxicosis from the ever-increasing number of therapeutic agents.<sup>2</sup> The council's former Committee on Research recommends that a Registry on Blood Dyscrasias be formed".

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1952-1954. A 2-year pilot study is conducted on the problem by the Council on Drugs.

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July 1954. Registry on Blood Dyscrasias is established.

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June 8, 1955.

David P. Barr, M.D.:<sup>3</sup>

"First of all, be sure you do no harm: *Primum non nocere*." In all ages this admonition has been fundamental to the practice of medicine. It applied to the use of all the empirical drugs of ancient and medieval times. \* \* \*

Today, when multitudes of new and relatively untried diagnostic and therapeutic procedures form an integral part of the practice of medicine, the admonition "Be sure you do no harm" applies more than ever before. \* \* \*

In the lists of 1953, more than 140,000 medicaments were available to practitioners, and 14,000 new preparations were added during the year. Accretion is still far greater than deletion. \* \* \*

\* \* \* accidents, risks, and dangers may be regarded as the price that we, as responsible physicians, must pay for the inestimable benefits of modern diagnosis and therapy. They are the hazards to which, with best intent and most correct practice, we must occasionally subject our patients. In the following discussion about the price we must pay for modern management of disease, care has been taken to exclude from consideration all examples of carelessness, misconduct, malpractice, as well as the use of nostrums, patent medicines, and other unacceptable or condemned remedies. It is believed that all the herein-cited accidents and misfortunes may result on occasion even with enlightened thoughtful use of diagnostic and therapeutic measures by conscientious and well-informed physicians earnestly trying to help their patients. Since even a list of possible dangers would be too cumbersome, examples have been chosen arbi-

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<sup>1</sup> See, for example, references for MER/29, as indexed in the concluding portion of this volume, p. 1266.

<sup>2</sup> "Registry on Blood Dyscrasias, Report to the Council," Journal of the American Medical Association, Mar. 17, 1962, vol. 179, p. 888.

<sup>3</sup> "Hazards of Modern Diagnosis and Therapy—The Price We Pay," Frank Billings Memorial Lecture, before Section on Internal Medicine, American Medical Association, Atlantic City, N.J., reprinted in Journal of the American Medical Association, Dec. 10, 1955, vol. 159, pp. 1452-1456.



trarily as illustrative of the extent and variety of hazards in our daily work. For orderly presentation, they have been arranged under headings representative both of types of unfavorable responses and of special accidents that may arise in the use of single agents or groups of agents having similar actions.

#### ACCIDENTAL DRUG INTOXICATION

One of the great hazards in the use of potent drugs is their inherent toxicity that, with wide individual variation, will develop intoxication in any patient if the dose is large enough. \* \* \*

#### MODIFICATION OF INTERNAL ENVIRONMENT

Although the homeostasis of the body is modified by a vast number of drugs in ways but vaguely appreciated, it is most strikingly changed by parenteral injection of fluids of variable composition and by agents that modify the rate of excretion of water, electrolytes, and other substances through kidneys or intestine. Modifications that can be produced by these measures are alarming in variety and degree and only partially predictable. \* \* \*

#### INTRODUCTION OF INFECTION

Entry by needles or other instruments into tissues, vessels, or cavities of the body always involves some risk of infection. \* \* \*

#### ALLERGIC REACTIONS

More than 500 separate drugs are known to cause allergic reactions.<sup>1</sup> The unfavorable effects may be expressed by simulation of serum sickness, by the more violent reactions of anaphylaxis, or by affection of one or more of the organs of the body: the skin, bone marrow, lungs, liver, or kidneys. There is great variety and separateness in the response of individual patients to individual drugs. While many drugs cause reactions, there are only a few ways in which the body can react. \* \* \*

#### SPECIAL INSTANCES OF INTOXICATION

*Antibiotics.*—Because of the enormous usage of antibiotics, intoxication assumes a prominent role even though it may be statistically infrequent. No antibiotic has as yet been found free from hazards or disadvantages. \* \* \*

*Cortisone, Hydrocortisone, and Corticotropin (ACTH).*—Unfavorable reactions from the long-term administration of cortisone, hydrocortisone, and corticotropin (ACTH) are well known. \* \* \*

*Antihistaminics.*—The antihistaminic agents, of which there are now no less than 20, must be regarded as serious causes of intoxication, more particularly since their use is chiefly among patients who are not seriously ill. Several fatalities have been attributed to them. Their side-effects, especially those observed on the nervous system, are so numerous and sometimes so severe as to suggest that their use is actually more hazardous than that of sulfonamides and antibiotics employed for the most part in treatment of infections that might otherwise result in death.<sup>2</sup>

*Phenylbutazone and Chlorpromazine.*—Phenylbutazone is a congener of aminopyrine, and its toxic effects, particularly on bone marrow, are reminiscent of the unfortunate experiences with aminopyrine. Side-effects are numerous and sometimes serious; they include edema, eruptions, and unfavorable actions on the gastrointestinal tract, hematopoietic system, central nervous system, and heart.<sup>3</sup>

<sup>1</sup> Brown, E. A., "Problems of Drug Allergy," JAMA 157: 814 (Mar. 5), 1955.

<sup>2</sup> Wyngaarden, J. B., and Seever, H. H.: "The Toxic Effects of Antihistaminic Drugs," JAMA 145: 277 (Feb. 3) 1951.

<sup>3</sup> Hemming, A., and Kuzell, W. C.: "The Pharmacologic and Clinical Characteristics of Phenylbutazone (Butazolidin), Antibiotics & Chemother." 3: 634, 1953. (Original footnotes.)



## HIDDEN AND GENERAL DANGERS

The history of new drugs indicates that not all their potential dangers are immediately apparent. \* \* \*

## DANGERS FROM MULTIPLE PROCEDURES

The danger in diagnostic and therapeutic procedures comes not so much from the use of individual tests or drugs as from the multiplication of these measures now commonly used in so-called diagnostic surveys and therapeutic regimens in which each symptom receives some remedy. For patients in a diagnostic clinic or in the ward of a modern hospital, the application of 20 or 30 diagnostic tests is not uncommon. Many of these tests may be repeated on several occasions. *A seriously ill patient or one who has been subjected to a major operation may receive 20 to 40 different drugs in addition to numerous mechanical procedures.* His management may actually require use of anesthetics, sedatives, narcotics, antibiotics in variety, phenylephrine (Neo-Synephrine) hydrochloride, arterenol, digitalis, diuretics, bishydroxycoumarin, cortisone, transfusions, infusions, and finally antihistaminics, either for the correction of symptoms of his disease or to combat the toxic manifestations of other drugs. Since such combinations of measures and medicines are frequent, it is not surprising that iatrogenic disturbances are frequent.

In a medical service in a great hospital, over a period when approximately 1,000 patients were admitted, more than 50 major toxic reactions and accidents consequent to diagnostic or therapeutic measures were encountered. Many of the incidents and accidents took place before the patient's admission to the hospital and provided the occasion for hospitalization. Others developed in the course of diagnosis and treatment in the wards. The survey was not systematic or complete, and some instances of major intoxication may have been omitted from the list. The survey took no account of such factors as inconvenience and expense to the patient, prolongation of hospitalization, minor intoxications, or hidden and delayed reaction. \* \* \*

## CONCLUSIONS

It is realized that such concentration on toxic and unfavorable actions of diagnostic and therapeutic measures creates a distorted picture that can be corrected only by detailed recitation of simultaneous benefits. The discussion has been offered without nihilistic intent and with grateful recognition of the triumphs of modern diagnosis and therapy. Choice of topic developed from an ever-growing conviction of the extent and variety of dangers intrinsic in the medical practice of today and from a desire to suggest that discriminating selection of measures may be more important than unreflective completeness. It is suggested that it may be as useful to the patient that his physician know when not to treat as when to treat and that the use of potentially dangerous agents for trivial or inconsequential complaints may not be justifiable. Only by such discipline and understanding may we, as physicians, avoid doing unnecessary harm and minimize the price we and our patients pay for modern management of disease.

July-August 1955.

American Society of Hospital Pharmacists:\*

## (RESOLUTION)

## INVESTIGATIONAL DRUGS

Whereas the Food and Drug Administration has approached the American Association of Medical Record Librarians and the American Society of Hospital Pharmacists with a request to explore the establishment of some form of reporting sources where drugs are subject to continuous use, investigation and evaluation, and

Whereas the Society is of the opinion that such a service would be a valuable public health service to the Nation,

Be it resolved that the executive committee be requested to explore further this suggestion through a meeting of representatives of the Food and Drug

\*The Bulletin, American Society of Hospital Pharmacists, vol. 12, No. 4, p. 401.



Administration, the American Association of Medical Record Librarians and this Society, and

*Be it further resolved* that the executive committee be empowered to take such action as is recommended to foster the development of this program on a voluntary basis in the teaching hospitals of the Nation.

October 5, 1955.

Helen M. Traugott, C.R.L., Chief Medical Record Librarian, The Western Pennsylvania Hospital, Pittsburgh, Pa.:<sup>5</sup>

The need for developing a more adequate and accurate method of reporting adverse reactions of pharmaceuticals, antibiotics, and the powerful new drugs has been recognized by various medical disciplines for some time. The introduction of antibiotics, commercially available in 1941, announced a new era in medicine. Experience with these new drugs should therefore be followed closely to discover any serious untoward effects so that necessary safeguards can be taken to protect the patient, the physician, the hospital and the drug manufacturer.

Sporadically, reports from the literature have revealed that many of the so-called harmless drugs and antibiotics when used in large doses, when used over long periods of time, or when administered to a hyper-sensitive patient have exhibited serious untoward effects and allergic reactions.

In 1953 Dr. Ethan Allan Brown of Boston, wrote an article, "Drug Allergy," which appeared in the March issue of *The Quarterly Review of Allergy and Applied Immunology*, designed to help the general practitioner thread his way through the maze of drug allergies, and at the same time make available to the specialist an index of those drugs most frequently the cause of allergic reactions.

In March 1954, a nationwide survey was made and published in *Antibiotics and Chemotherapy*, June 1954 issue, entitled "Blood Dyscrasias" by Drs. Henry Welch, C. N. Lewis, and I. Kerlan of U.S. Food and Drug Administration.

At the 1954 AAMRL Annual Conference in Detroit, Dr. Albert H. Holland, Jr., Medical Director, Food and Drug Administration, presented a paper on "Drugs, Records and You," and stressed the need for developing better reporting methods. This need was cited in view of the fact that several serious incidents of severe drug reactions had occurred within the past few years. Recognizing that the problem could only be attacked by defining the seriousness and extent of the problem, a pilot study was suggested, as a possibility, with a sufficient number of hospitals of all sizes, types, and localities, enabling us to obtain a cross section of the country by various size hospitals and states. This study would rely to a great extent on hospital medical records for the factual data.

Toward this end the FDA enlisted the cooperation of the AAMRL and a special committee was appointed by our president. In June 1955, this committee held its first conference in Washington, D.C., with the FDA and other interested participants. At this gathering the FDA initiated, in cooperation with the AAMRL, the American Society of Hospital Pharmacists, and the American Medical Association, a pilot study on adverse reactions to drugs. This study was started on August 1, 1955, in the five hospitals of the medical record librarians on this committee. These are as follows:

Marjorie L. Balmer

Oakwood Hospital, Dearborn, Michigan

Elizabeth Bingham

St. Joseph's Hospital, Providence, Rhode Island

Madeline L. Brown

George Washington University Hospital, Washington, D.C.

M. Loyola Voelker

U.S. Public Health Service Hospital, Baltimore, Maryland

Helen M. Traugott

Western Pennsylvania Hospital, Pittsburgh, Pennsylvania

At the present time this pilot study has been in operation for 10 months and the response has been most gratifying. While it is too early at the present time to make any deductions from the information gleaned from the hospitals under

<sup>5</sup> "The Recording and Reporting of Drug Reactions," presented as part of a panel discussion of the annual meeting of American Association of Medical Record Librarians, Chicago: reprinted in *Journal of the American Association of Medical Record Librarians*, vol. 27, No. 5, June 1956, p. 141.



study, we can say that the initial results are proving to be interesting beyond our expectations.

March 12, 1956.

F-D-C Reports—"The Pink Sheet":<sup>6</sup>

\* \* \* \* \*

The development of side effects which manifest themselves only after widespread use of an important drug is a problem facing FDA as well as everybody in the pharmaceutical industry. These side effects often fail to show up in the premarket testing and clinical evaluation on which FDA bases its NDA action. In recent years, virtually all important drugs have gone through a similar cycle—lavish praise by the medical profession on introduction, then after widespread use the publication of papers reporting side effects. When the latter are not reported in the lay press, they don't usually have too much effect on the market position of a drug—unless the side effects are very serious.

\* \* \* \* \*

June 1956.

Albert H. Holland, Jr., M.D.,<sup>7</sup> Director, Bureau of Medicine, Food and Drug Administration:

\* \* \* \* \*

In the first place, the well-informed doctor wants accurate, prompt information about drugs. They are one of his major professional tools. Without detailed knowledge of their use he is at a loss to employ them effectively or even safely. These "facts of life" are well recognized by the drug manufacturer and he takes great pains to see that this information is put in the doctor's hands. This information—this knowledge—comes only from actual experience with the drug, however, whether it be from animal or human studies. Hence, it becomes important to have prompt reporting of clinical experience with a new drug. Particularly is this so with respect to its untoward, unusual, or unexpected effects. Physicians learn and profit from each others' experience. This is one of the reasons why medical literature continues to command so much of the physician's attention. Likewise the manufacturer appreciates the many reasons why he must himself be concerned with obtaining prompt and accurate information on his drug products and then place it in the hands of his customers—the doctors.

Now there seems little doubt that a central repository for drug injury information is desirable. Here are some of the reasons. It would serve to provide information in support of necessary law enforcement actions. It would provide a source of up-to-date information of great importance to both doctor and patient. It could provide a source of information of great advantage to the manufacturer. Pharmacists, students, nurses, and other members of the health team would also have occasion to benefit from the prompt availability of the results of actual clinical experience.

The ever-increasing numbers of new and more effective drugs for which we must all be so thankful demands that we now take cognizance of the magnitude and importance of this problem.

There are a variety of circumstances which lend to the present inadequacy and difficulties in obtaining information. The medical journals are almost swamped with papers for publication. Rarely does a paper appear in the literature within 6 months from the time it was written. Often the lapse is much longer. Nor are all cases reported. This would be an impossible burden, obviously. It is often hard to predict, however, when the one, two, or three cases that have occurred sporadically may provide the important clue to a better understanding of a drug's therapeutic benefits as well as its potential liabilities. There is also the problem, which cannot be ignored, of how to interpret the significance of a few case reports properly. I believe there is no pat answer to this question. Rather, it is a matter for the best efforts of all members of the health team to contribute cooperatively and to assess constantly our progress in safe, effective therapy.

<sup>6</sup> Vol. 18, No. 5, p. 12.

<sup>7</sup> "The Pilot Study and Its Scope," *Journal of the American Association of Medical Record Librarians*, vol. 27, No. 5, June 1956, pp. 142-144.



There are, as you know, medicolegal complications which always require careful evaluation in the preparation of any report. Time is perhaps another factor with which the reporting physician must reckon. Time is indeed for all of us a precious possession and a fleeting commodity. No less is the time of the busy physician.

There is yet another aspect of the difficulty in obtaining information with which you are intimately familiar. It is the problem of good record keeping. While I probably could never satisfactorily run a record room, I say this because all endeavors in life seem to be fraught with their fair share of problems. I suspect medical records are no different.

As some of you will recall, I had the privilege of addressing your annual meeting last year in Detroit. At that time I suggested that we would be happy to explore the feasibility of a cooperative pilot study with a committee representing this association. I am happy to report that your officers accepted this suggestion and with their excellent cooperation a group of 6 medical record librarians met with us in Washington on June 20, 1955. The group was under the able chairmanship of Miss Helen Traugott. Prior to this meeting we prepared a background statement, part of which I should like to read to you.

Scientific and technical advances during the past 20 years have given us many potent and effective therapeutic agents whose full potentialities for harm as well as good frequently cannot be fully determined until they have been used widely for a considerable period of time after initial laboratory and clinical investigation. Experience with new drugs should therefore be followed closely to discover any serious untoward effects so that necessary safeguards to protect the patient, the physician, the hospital, and the drug manufacturer may be applied promptly. Several unfortunate experiences with new drugs have within recent years pointed up the need for close and continuing surveillance. Concern extends not only to the identity, quality, purity, and potency of drugs, but also to their packaging and labeling. To be informative in the interest of the user, the manufacturer, and the medical profession, adequate information as to the clinical indications, contraindications, side effects and their management, as well as warnings or cautions against misuse should be provided.

Protection of the public in the use of these agents is not a one-sided affair. The medical profession and industry share in this responsibility, and cooperate actively with the administration. This sense of mutual responsibility has been strongly evident in the past in a number of instances in which drugs, hitherto unsuspect, became associated with serious untoward effects after prolonged use. Exchange of information among all concerned led to appropriate action, resulting either in the removal of the drug from the market or the cautioning of physicians about the hazards involved through direct communications to them and revisions in labeling and related medical literature.

This informal pattern of reporting has been in operation for many years; however, the present accelerated rate at which new drugs, pesticides, and food processing chemicals are being introduced creates a need for up-to-date techniques for following more closely the immediate and long-range effects of such articles.

The medical record pilot study was designed to assess the value of the above approach to the development of information on adverse reactions to drugs. It is concerned more with methodology for selecting, reporting, coding, evaluating, and disseminating data than with their immediate application to the resolution of medical and administrative problems under the law. The small sample represented by the study would preclude such application generally.

It will be conducted for a period of at least 9 months, beginning last August 1, in each of the five hospitals at which are employed as heads of their medical record departments the five members of the special committee set up by the American Association of Medical Record Librarians to study the problem.

Although the concern of the Food and Drug Administration extends to other commodities under its jurisdiction such as devices, cosmetics, processed foods, pesticides, and household chemicals, the present study will be limited to drugs.

The American Society of Hospital Pharmacists is aware of the significance of this problem to their profession and to the hospitals of the country. At their meeting in May 1955 a resolution was passed favoring a tri-partite project with the Food and Drug Administration and the American Association of Medical Record Librarians.

As a result of the June 20 meeting, your committee agreed to undertake a 1-year pilot study program with five cooperating hospitals for the purpose of



gaining experience with the mechanics of this type of a reporting program. The pilot study will also afford us an opportunity to determine how best to handle the information, both mechanically and professionally, once it is received by the Food and Drug Administration. And finally, at the end of the study we hope to be able to reach a conclusion in cooperation with your committee as to whether or not this type of reporting is realistic, feasible, and does in fact provide the information we all would like to have. I hope that we will have the good fortune to be able to answer all of these questions in the affirmative when the pilot study is completed.

*June 1956.*

George F. Archambault,<sup>8</sup> Ph. C., D.S.C., LL.B., Chief, Pharmacy Branch, Division of Hospitals, Bureau of Medical Services, U.S. Public Health Service; then immediate Past-President, American Society of Hospital Pharmacists:

For the task at hand, this continuous gathering and reporting of information on adverse drug reactions from the hospitals and clinics of the Nation, the FDA, in my opinion, has chosen wisely in requesting your group to serve as key individuals in the administration of this difficult reporting project. If you, as individuals and as a professional group, with the "know-how" on medical record reporting cannot entrench this program into the reporting systems of key hospitals, then I'm sure no other professional group can do the job. That you will be performing a valuable public health service function goes without saying. In my opinion, this project is a most needed one; one wherein its participants will truly be fulfilling the obligations of public trust vested in them by their professions.

As president of the American Society of Hospital Pharmacists, I made the following statement in my presidential address in April 1955:

"Food and Drug Administration.—This past year your society has been approached by the Food and Drug Administration to explore the feasibility of some type of a cooperative Food and Drug-hospital liaison to obtain valid information on untoward effects, allergies, sensitivities, and other side reactions and new uses of drugs, old and recent. The American Association of Medical Record Librarians as well as the American Society of Hospital Pharmacists is interested in this project and it may well be that this tripartite project—The Food and Drug Administration, the AAMRL, and the ASHP—will develop a valuable service for the public health of the Nation. Obviously, some reporting sources need to be established in places where drugs are subject to continuous use, investigation and evaluation. What place is more appropriate than certain selected hospitals of the Nation."

As a result of my remarks, the ASHP, which incidentally has a membership of over 2,300, voted the following resolution at its Miami Meeting: "Investigational Drugs.—Whereas the Food and Drug Administration has approached the American Association of Medical Record Librarians and the American Society of Hospital Pharmacists with a request to explore the establishment of some form of reporting sources where drugs are subject to continuous use, investigation and evaluation, and Whereas the society is of the opinion that such a service would be a valuable public health service to the Nation, Be it resolved that the executive committee be requested to explore further this suggestion through a meeting of representatives of the Food and Drug Administration, the American Association of Medical Record Librarians and this society, and Be it further resolved that the executive committee be empowered to take such action as is recommended to foster the development of this program on a voluntary basis in the teaching hospitals of the Nation."

In early June, Dr. Irvan Kerlan, Chief, Research and Reference Branch, Division of Medicine, Food and Drug Administration, invited our group to attend the June 20 conference to lay the groundwork for the pilot study you are hearing about today. Miss Gloria Niemeyer, secretary of the society and myself attended this meeting.

Our national journal, the Bulletin of the American Society of Hospital Pharmacists carried the following news item about that meeting in the July-August number:

<sup>8</sup> "The Role of the Pharmacist and Pharmacy Committee in Aiding the Study," Journal of the American Association of Medical Record Librarians, vol. 27, No. 5, June 1956, pp. 144-146.



"Drug Reactions To Be Studied.—A pilot study on reporting adverse reactions to drugs is being carried out by the Food and Drug Administration, Division of Medicine, and the American Association of Medical Record Librarians, Committee on Reporting of Drug Reactions. Also cooperating are the American Medical Association, the American Society of Hospital Pharmacists and the pharmacy and drug therapeutics committees of five hospitals in different parts of the United States.

"At a meeting of representatives of the sponsoring groups on June 20, Dr. George F. Archambault, past-president, and Miss Gloria Niemeyer, secretary represented the ASHP. At that time the scope of the problem was discussed and plans outlined for the development of information on adverse reactions to drugs. The pilot study will be concerned more with methodology for selecting, reporting, coding, evaluating, and disseminating data than with their immediate application to resolution of medical and administrative problems under the law. The small sample represented by the study would preclude such application generally.

"Five hospitals will participate in the pilot study. In each of these hospitals, the head of the medical record department is a member of the special committee set up by the American Association of Medical Record Librarians to study the problem. \* \* \*

From this short background presentation, you will note that the ASHP and hospital pharmacists are thoroughly convinced of the need for and value of this project.

I can assure each of you that the ASHP and its members will gladly cooperate with any committees set up by your hospital or society in connection with this study.

So much for the position of the ASHP. And now for some specific approaches and techniques that, in my opinion, will help insure active physician and dentist participation in this reporting program.

I am sure we all agree that even though an excellent methodology is developed, it is worthless unless active participation of physicians and dentists is had. How then, can we best obtain this participation?

I shall speak of an approach, which if properly presented, should aid materially in the success of this study at the individual hospitals. I refer to the use of the pharmacy committee. The chief pharmacist is a voting member of the pharmacy and drug therapeutics committee in most hospitals. The presence of this committee is one that is checked by the inspectors of the Joint Commission on Accreditation of Hospitals. An active pharmacy committee insures additional accreditation points to the hospital. There are now 1,700 hospitals with such committees. The purpose of this committee is stated as follows in the Minimum Standard for Pharmacies in Hospitals:

1. To develop a formulary of accepted drugs for use in the hospital;
2. To serve as an advisory group to the hospital pharmacist on matters pertaining to the choice of drugs to be stocked;
3. To evaluate clinical data concerning drugs requested for use in the hospital;
4. To add to and to delete from the list of drugs accepted for use in the hospital;
5. To prevent unnecessary duplication in the stock of the same basic drug and its preparations; and
6. To make recommendations concerning drugs to be stocked on nursing units and other services.

Note in particular item three—"To evaluate clinical data concerning drugs requested for use in the hospital."

Considering that most large hospitals have pharmacy committees, whose membership, incidentally, usually consists of chiefs of services or senior staff men and, considering the functions of the committee, as just cited, it appears to me, that here is an excellent place to start the implementation of the reporting program.

May I suggest that those of you that undertake this study work closely with your administrator, with the chairman of the pharmacy committee, and its secretary. As you introduce this program, make this pharmacy committee your advisory board to work with your medical record committee. It would be wise to suggest that all apparent side effects, contraindications and previously unreported reactions be channeled first to this committee through the chief of the service involved, for clinical evaluation. Members of this committee, I'm sure, will be enthusiastic participants in the program. In addition, such



methodology might well stimulate better pharmacological evaluations and incidentally produce papers for publication of credit to the hospital.

What better or more appropriate means exist to gain support for this project in your hospital? None that I know of. To go directly to the staff would, in my opinion, but dilute your efforts. To first enlist the support of the pharmacy committee is to enlist the aid of a vitally interested group of clinicians, individuals concerned with pharmacological evaluations. These physicians will, through their reporting system on drugs to the staff, do much to enlist total staff support of the program. Further, the secretary of the pharmacy committee by reason of his office, is often the first to be alerted to the adverse type reactions in which we are interested.

\* \* \* \* \*

(Illustrative Article in Trade Press)

December 17, 1956.

F-D-C Reports—"The Pink Sheet":<sup>9</sup>

Epilepsy drug volume and toxicity figures should be reported by pharmaceutical mfrs., Harvard's Dr. William G. Lennox said in his acceptance speech after receiving the Am. Pharmaceutical Mfrs. Assn. (APMA) scientific award for 1956 in NYC Dec. 11 for his work in the epilepsy field. Lennox said that "pharmaceutical cos. are reticent about the volume output of their anticonvulsants, so that physicians are in the dark about how many of our million or so epileptics are receiving modern therapy." He also commented that "mfrs. do not put their own information" re fatalities "into medical circulation."

Lennox urged mfrs. to report both volume and fatal toxicity figures re their anticonvulsants "in order to give patients some idea of the risk they run \* \* \* information, even if only partial, about the frequency of deaths in relation to the number of persons being treated." He did not say how or to whom the reports should be made. Lennox also asked that mfrs. of new epilepsy drugs "share the extra cost of laboratory testing and close personal followup of guinea pig patients, measures that might lead to earlier discovery of toxic effects." Lennox predicted eventual success v. epilepsy via discovery of a drug which will remedy a brain biochemistry deficiency.

(Illustrative Cases Involving One Drug)

April 14, 1958.

F-D-C Reports—"The Pink Sheet":<sup>9a</sup>

Hoffmann-LaRoche Marsilid pick-up of all packages on the market with old labeling was undertaken late Friday (April 11) via telephone instructions, confirmed by telegrams, to all of the company's district men and its entire field force. The decision to remove from the market all packages with old labeling was made in cooperation with the Food and Drug Administration (FDA). It followed press publicity given to the verdict of a San Francisco coronor's jury in the death of a woman who had been taking the drug since January. The death was attributed to jaundice.

The San Francisco coronor fingered both FDA and the company in a comment made to the press following the jury's verdict, and the resulting publicity triggered the pick-up program. Prior to the publicity last week, FDA apparently had been satisfied with the efforts of Hoffmann-LaRoche to inform M.D.'s of Marsilid's potential side effects and to provide data on a new and lower dosage schedule.

Marsilid (iproniazid, a relative of isoniazid) has been under intensive clinical investigation since 1950 by the Veterans' Administration and other leading groups. In March 1955, FDA cleared a New Drug Application (NDA) covering its use for TB in large dosages—2 to 4 milligrams per kilo of body weight, about 300 milligrams per day. Curiously, the jaundice side effect did not show up when the drug was used in high dosages in over 300,000 TB cases.

An amended Marsilid NDA was cleared by FDA in March 1957 following the discovery that the drug had therapeutic effects against psychic depressions

<sup>9</sup> Vol. 18, No. 45, pp. 17-18.

<sup>9a</sup> Vol. 20, No. 15.



hitherto untouched by other therapeutic agents. Some of the leading mental health researchers, both in and out of Government, regarded it as a significant breakthrough in the psychotherapeutic field—the drug that opened up the important psychic energizer area. The March 1957 NDA provided for a 150-milligram dosage, and the package was heavily labeled with warnings to the M.D., including: "This is a potent drug to be used under the careful supervision of a physician."

The jaundice side effect began to show up after the drug had been in use as a psychic energizer for less than a year. On January 14, Hoffmann-LaRoche made a mailing to M.D.'s calling the situation to their attention, and on February 3 proposed a supplement to its NDA changing the brochure and labeling to lower the dosage and provide stronger cautions on jaundice. The new dosage started with 50 milligrams per day—taken at one time—for ambulatory patients and was scaled down to 10–25 milligrams for continued therapy. The NDA supplement was cleared by FDA on March 14; shipment of new packages was started immediately, and old packages were removed from company warehouses.

Jaundice reports have been recorded with FDA in 64 out of the more than 200,000 mental cases in which the drug has been used—with 14 deaths. The company made a second mailing to M.D.'s on February 19, and similar messages have been carried in its journal ads and by its detail men. With FDA's blessings, the new packages will remain on the market and will continue to be shipped.

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*April 21, 1958.*

F-D-C Reports—"The Pink Sheet":<sup>9b</sup>

Roche's Marsilid pick-up program to remove all old-labeled packages from the market ("F-D-C" April 14) was augmented by an April 15 letter from the company to all pharmacists. They were urged to return all pre-March 15 packages of the drug which had not been picked up by the Roche field force. Pharmacists were told to differentiate between the old and new packages as follows: Old-labeled Marsilid has dosage statements on the label proper; the new package has no dosage recommendation on the label, but dosage instructions are included in an accompanying 8-page package insert. A copy of the insert was sent to all pharmacists. Roche also sent another letter on Marsilid's jaundice effect to all MD's on April 15.

Government mental health researchers at the National Institutes of Health (NIH) and the Veterans' Administration (V-A) supported the judgment of Roche and the Food and Drug Administration (FDA) that the product was so important in the treatment of certain mental health cases that it should remain on the market, despite its incidence of side effects. After the publicity on Marsilid, V-A first considered sending its own warning letter to its MD's, but decided against this in view of the actions taken by Roche and the fear that such a message might prevent the use of the drug, even when indicated in specific patients. Earlier, Marsilid had been praised in a statement filed by National Institute of Mental Health Director Felix with the House Blatnik subcommittee.

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<sup>9b</sup> Ibid., pp. 19–20.



April 23, 1958.

Drug Research Reports.<sup>10</sup>

MARSILID INCIDENT IN SAN FRANCISCO, SPOTLIGHTED BY LAY PRESS, POINTS UP LONG-TERM PROBLEMS FOR MEDICAL RESEARCH AND PRACTICE

The Marsilid (iproniazid) incident in San Francisco 2 weeks ago, spotlighted by lay press coverage of a coroner's jury verdict linking the drug with the death of a woman, points up forcefully a number of long-term problems facing medical and pharmaceutical research—and, in fact, the entire field of medical practice.

These problems arise from the fact that research is producing a steady stream of highly potent and useful drugs, some of which hold promise of benefits in hitherto incurable illnesses.

Many of these drugs have potential side effects which impose greater responsibility on the practicing physician to inform himself fully before determining the "calculated medical risk" in ordering their use.

The San Francisco coroner, in announcing the jury's verdict, fingered both the Food and Drug Administration (FDA) and Roche Laboratories (Roche), a subsidiary of Hoffman-LaRoche (H-LaR), the company that markets Marsilid. The death was attributed to acute hepatic necrosis.

PATIENT ON MARSILID THREE MONTHS; SAW DOCTOR TWICE

The ambulatory patient, according to reports from San Francisco, had been using Marsilid since January but had seen her doctor only twice between the time he prescribed the drug and the day in April when she was rushed to the hospital in serious condition. The patient is also reported to have been treated with estrogens, vitamins, and reserpine for an endocrine complaint.

The jury's verdict and the coroner's additional public statement made newspaper headlines which resulted in a decision by Roche, in cooperation with FDA, to have its field staff pick up all outstanding packages of Marsilid which had been shipped before March 15. Roche had started to ship Marsilid packages containing new labeling and a new brochure on March 15.

Shipment of the new packages was started by Roche immediately after FDA cleared the changes in the dosage recommendation, the labeling, and the brochure for doctors. Roche had applied to FDA for the clearance and had filed its data February 3 with the Government agency.

Roche had mailed a letter to doctors January 14 calling attention to the jaundice side effect resulting from the use of Marsilid. This was followed up February 19 with a second letter to doctors, and similar messages were carried in medical journal advertisements and by Roche detail men in their visits to physicians.

The pre-March 15 packages had recommended a 150-milligram dosage on the label, but the accompanying medical brochure included numerous cautions to physicians on the use of the drug. Included in the warnings was the following: "This is a potent drug to be used under the careful supervision of a physician."

The post-March 15 packages do not have any dosage recommendations on the

<sup>10</sup> Vol. 1, No. 14, pp. 3-5.

See pt. 2, exhibit 81, p. 517, for an FDA chronology on Marsilid and exhibit 90, p. 564, for comments by the Veterans' Administration on use of the drug.



label, but dosage information for the doctor is included in the brochure. The dosage recommendation for ambulatory patients was reduced from 150 to 50 milligrams a day, the latter to be scaled down to 10-25 milligrams for continued therapy.

Roche followed up its pickup instructions to its own field force with a letter dated April 15 to all pharmacists and all doctors. The company sent pharmacists copies of its letter to physicians and of its new medical brochure. Pharmacists also were asked to return any pre-March 15 packages which had not been picked up by Roche's field force.

#### VA DECIDED AGAINST SPECIAL CAUTION TO ITS HOSPITALS

The April 15 letter to doctors called Marsilid a "highly potent compound" and warned that it "should be employed in the right way, in the right dose, and in the right patient." The letter urged that the drug's use "should be restricted to those patients who have not responded to milder central nervous system stimulants—patients who are sufficiently depressed to warrant administration of this potentially toxic compound."

A copy of the new medical brochure was included in the letter to doctors, and attention was called to the possibility of hepatitis. Roche explained that the brochure was being sent even though it is enclosed in every package of Marsilid because the company realized doctors "do not always have an opportunity to see such packages."

When the Marsilid publicity first broke in the lay press, Veterans' Administration (VA) topside doctors at first considered sending a warning of their own to all VA hospitals, but later decided against doing this for two reasons: (1) The prompt and effective action taken by Roche in cooperation with FDA, and (2) The possibility that such a letter might scare VA hospitals off the drug even when its use was indicated in specific patients.

Originally developed as a TB drug, Marsilid has been the subject of clinical evaluation since 1950. FDA cleared its use for TB in large dosages—about 300 milligrams a day—in 1955. The jaundice side effect did not show up when the drug was used in 300,000 TB cases, a fact that has been labeled as a "medical mystery" by Government researchers.

FDA cleared the use of Marsilid as a "psychic energizer" in March 1957. The side effects started showing up after its use in psychotherapy, and it is understood that reports have been compiled on more than 100 hepatitis cases, about 20 percent fatal. Including TB patients, it is estimated that Marsilid has now been used in more than 500,000 cases.

Under sponsorship of the NIH Psychopharmacology Service Center (PSC), Dr. Nathan Kline of Rockland State Hospital, Orangeburg, N.Y., is conducting one multidrug study in which Marsilid is included. PSC has an application pending to evaluate Marsilid, and this was expected to be acted on by its advisory committee which met in Washington early this week (April 21-22).

Marsilid also may be included in another multidrug study proposal which PSC expects to receive in the near future. Dr. Benjamin Passamanic is understood to be studying the drug at Ohio State University without grant support from NIH.

VA has not included Marsilid yet in its coordinated mass clinical evaluations of psychotherapeutic drugs, but some of its individual hospitals have been doing work on the drug. Three or four research designs for controlled studies are being drawn up, and VA is interested in a controlled study of all the new energizing and antidepressant drugs. This probably will not get under way for some months.

#### ONE BIG PROBLEM: GETTING BUSY M.D. TO READ

The National Heart Institute on April 4 issued a press release summary of an article that appeared a week earlier in the journal *Science*. The article indicated that the effectiveness of Marsilid in treating depressed mental states may be due to the fact that this drug protects the neurohormones, serotonin and norepinephrine, from monoamine oxidase, an enzyme that normally destroys them in the brain.

The VA decision not to warn its hospitals, and informal comments from National Institutes of Health (NIH) officials, indicate Government researchers generally join in the Roche-FDA judgment to continue the drug on the market because its potential usefulness outweighs the possibility of harm from side effects.



Among the long-term problems pointed up by the San Francisco Marsilid incident are the following:

Bridging the gap between the medical researcher or clinical evaluator and the average, busy practicing physician.

Getting the busy practicing physician to read. Medical research and the pharmaceutical industry can, and frequently do, supply mountains of information on potent new drugs, but all of this goes to waste if the busy practicing doctor does not have the time or inclination to read.

Calculating the medical risk on a national basis in determining whether a potent drug is to be released for use by physicians generally. First responsibility for this judgment rests with the pharmaceutical manufacturer.

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*(Letter from official New York City file)*

June 26, 1959.

Harold Jacobziner, M.D.; Assistant Commissioner of Health, New York City Department of Health:

Dr. HARRY D. KRUSE,

*Executive Secretary, Committee on Public Health,*

*New York Academy of Medicine, 2 East 103d Street, New York, N.Y.*

DEAR DOCTOR KRUSE: The Department of Health is very much concerned with the problem of unethical advertising of pharmaceutical products, i.e., the exaggerated claims made by some pharmaceutical manufacturers relating to their products; also some of the implications often made that the product is safe because it does not contain a certain ingredient, such as the non-barbiturate sedatives; also the lack of accurate information in the literature disseminated to physicians by pharmaceutical manufacturers relating to side reactions of drugs, and particularly new drugs.

The Department of Health feels that it will be desirable for physicians to report any side reactions which they observe, particularly with regard to the use of new drugs, so that more may be learned about the ill effects of drugs which may be widely used in therapy. The use of unsafe and toxic drugs would thus be restricted.

In speaking to Dr. Herbert Pollack at the annual meeting of the American Medical Association, he thought that the reporting of side reactions by physicians is an excellent idea and stated that the misuse of insulin, for example, by inexperienced personnel in hospitals has resulted in many injuries and fatalities.

He then expressed the opinion that this whole area of both iatrogenic accidents and side reactions of drugs is one which should be taken up with the various specialty societies so that their combined experiences should be forwarded to a central agency for indicated action.

Physicians may be assured that all information will be treated very confidentially. The Department of Health is naturally very concerned and intends to study this problem in all its phases.

Knowing of the Academy of Medicine's interest in this problem of information and education of the physician, we are wondering whether the Academy of Medicine would not like to study this problem jointly with the Department of Health?

It is hoped that on the basis of the accumulated knowledge, we would be in a better position of informing physicians and the public on the safer use of drugs.

I am sending a similar letter to Dr. Robert Craig of the Committee on Medical Education and to Dr. Iago Galston, Executive Secretary of the Committee on Medical Information.

Sincerely yours,

HAROLD JACOBZINER, M.D., *Assistant Commissioner.*



August 24, 1959.

George P. Larrick, Commissioner, Food and Drug Administration:<sup>11</sup>

\* \* \* \* \*

The pharmacist frequently is the first individual informed of adverse reactions from drugs. On several occasions we have been able to secure the prompt removal of dangerous stocks of drugs from the market because an alert pharmacist called our attention immediately to untoward results from the drugs or to some abnormality he observed in the product when it was first received. We are developing a program with a number of hospitals whereby they will inform us routinely of drug reactions that come to their attention. We would like to develop a similar program with the Nation's pharmacists.

\* \* \* \* \*

May 27, 1960.

Harold Jacobziner, M.D., Assistant Commissioner of Health, New York City Department of Health:

THE CITY OF NEW YORK,  
DEPARTMENT OF HEALTH.

From: Harold Jacobziner, M.D., Assistant Commissioner.

To: Poison Control Officers.

Subject: Reporting of Adverse Drug Reactions.

The Department of Health is very much concerned about the lack of accurate information available to the physician in the literature disseminated by pharmaceutical manufacturers relating to adverse drug reactions and contraindications, especially to the ever increasing number of newer drugs.

Though new drugs are evaluated for safety by the Food and Drug Administration prior to release for general use, wider clinical use may uncover adverse effects which were not observed in the trial investigations.

In order to protect the public from the possible use of harmful drugs and to obtain accurate information promptly, the Health Department requests all physicians and hospitals to report to the New York City Poison Control Center, not only "poisonings" but all side reactions and effects of overdosages, i.e., any untoward reaction from the use of a drug.

Only by means of such wide reporting to a central agency will it be possible to accumulate, promptly, accurate information about previously unknown hazards and to determine whether a drug is safe for specific use. The information and knowledge thus obtained will be analyzed and the results widely publicized so that physicians will be alerted to the possible dangers and the need for preventing harmful effects. Physicians may be assured that all information which they submit will be treated very confidentially.

The New York Academy of Medicine, through its Committee on Public Health, endorsed the action of the Department of Health in establishing a system for the reporting of side reactions and urged that the data thus assembled be disseminated among physicians as part of an educational program directed toward the reduction of hazards from drugs.

Poison Control Officers are therefore requested to report in detail every side reaction to any drug and any reaction from an overdose to the Poison Control Center. Specially designed forms are available for this purpose and may be forwarded to you on request. Reports may also be submitted, however, on the regular 45VX discharge form.

HAROLD JACOBZINER, M.D.,

Assistant Commissioner,

Medical Director, Poison Control Center.

HARRY W. RAYBIN,

Technical Director, Poison Control Center.

<sup>11</sup> "Pharmacy at the Crossroads," presented at the Pharmacy Education-Industry Forum of the National Pharmaceutical Council, Princeton, N.J., p. 2.



June 6, 1960.

George P. Larrick, Commissioner of Food and Drugs:<sup>12</sup>

\* \* \* \* \*

"Untoward effects may be due to overdosage (therapeutic, accidental, or homicidal), intolerance, side effects, secondary effects, allergy, or idiosyncrasy or error in compounding, labeling, or packaging, or from some deficiency in the manufacture of the drug, or in its preparation for use."

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June 27, 1961. Subcommittee on Antitrust and Monopoly, Senate Committee on the Judiciary, reports on Administered Prices—Drugs, Senate Report 448, 87th Congress. Chapter 12 is devoted to "The Special Problem of Side Effects."

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*(Internal Agency Documents on a Particular Case)*

October 17, 1961.

To: Office of the Director, Bureau of Medicine.

From: John D. Archer, M.D.

Subject: Flexin.

As we discussed, this memorandum is to organize the more pertinent features of the failure of McNeil Laboratories adequately to furnish this Administration with their information on hospitals from Flexin as such information was accumulating. This summary is largely repetitious of information in the various related documents which are attached to some copies of this memorandum, or which in any event are present in the application. However, the information is somewhat scattered in these documents. Also, since they were prepared at different times as our knowledge of the subject was developing, some statements are superseded and modified by others.

The following conclusions are based upon Dr. C. Wingard's careful review of the NDA's as they existed in early August 1961, and upon my review of the information submitted by the manufacturer on October 3, 1961. Undoubtedly, occasional minor inaccuracies will occur in this analysis; much of our information is sketchy. For example, Dr. Kieffer furnished a report on only one case, but the McNeil memorandum associated with this makes it appear that there was still another case. It is entirely possible that an occasional case actually was a coincidental occurrence of liver disease from some other cause. For example, one patient had cirrhosis of the liver, and the death may not have been actually from Flexin. Occasionally, administration of other drugs leaves some question of the etiology of the hepatitis. In addition, two or three cases apparently did not progress to frank jaundice although liver involvement occurred. In fact, gaining adequate insight into this subject actually requires reading the reports, as viral hepatitis often was a consideration in the differential diagnosis. With these limitations, though, the following represents a substantially correct analysis.

The original application for Flexin was submitted on November 14, 1955. No hepatitis was reported in the clinical trials.

The application contained a report from Dr. Bernard Alpers of a series of patients. On December 2, 1955, the firm received a report from Dr. Alpers by telephone that a patient receiving Flexin subsequent to his earlier report had developed hepatitis and had died. The possibility of toxic hepatitis was considered. At this time, the application for Flexin was under review by the Food and Drug Administration. An amendment of substance was submitted on December 27, 1955. On January 10 and 12, 1956, the firm discussed details of labeling with the Administration. We have found no indication that the Administration was informed about the case of hepatitis on any of these occasions.

(The animal studies did indicate some liver damage. Apparently, this was not considered of particular significance in view of high dosage and inconsistent findings. I might add that even in retrospect, these pharmacological results appear of doubtful significance to the clinical situation that eventually occurred.)

<sup>12</sup> Senate Committee on the Judiciary, Subcommittee on Antitrust and Monopoly, hearing on S. Res. 238, 86th Cong., pt. 22, "Administered Prices—Drugs (Food and Drug Administration: Mr. Henry Welch)," p. 12122.



The application became effective on January 13, 1956. The labeling contained a list specifically denying that certain toxic reactions had been reported; jaundice was included in that list.

On August 14, 1956, a supplement was submitted for a new dosage form. The list of reactions that had not been reported was retained in the labeling, but jaundice was quietly deleted from it without explanation. (Kidney damage also was deleted.) By this time, the firm had received reports of 9 or 10 additional cases of liver involvement, usually with jaundice, associated with the drug. Some of these were reported by investigators who had cooperated in the firm's research program with Flexin (although the reactions occurred subsequent to the effectiveness of the application). Some patients had been rechallenged with the drug with evidence of recurrence of liver involvement. Some cases had developed almost immediately after the drug was instituted; in fact, one patient had a biopsy diagnosis of acute hepatitis immediately following a single tablet. One additional death had occurred, but the cause of death was and is obscure; the jaundice had subsided by the time of death, and the information suggests that something else was the cause. None of this information was submitted in conjunction with the supplemental application.

On May 10, 1957, the firm submitted original applications for Flexilon and Flexilon-HC. These, of course, relied upon the Flexin application for support of the safety of Flexin in these combination dosage forms. The firm still did not inform this Administration, nor the prescribing physician through the labeling, about the occurrence of hepatitis. However, by now the cases exceeded 20. (It must be pointed out that all cases were not necessarily considered at the time of reporting to be caused by Flexin. However, they were cases reported in conjunction with use of the drug in which the possibility at least was specifically raised.)

On June 10, 1958, a supplement was submitted providing for use of the drug in gout. This was the first time that jaundice was mentioned in the labeling. A paragraph in the section titled "Side Effects, Toxicity, and Precautions" read: "During the 3 years that Flexin has been in use clinically there have been occasional reports of patients who have developed jaundice while receiving Flexin. After careful inquiry into these cases it has usually been concluded that the possibility of a viral hepatitis as the cause, rather than a drug-induced hepatitis, could not be excluded. The possibility exists that Flexin in rare cases may produce hepatitis and jaundice."

The section containing the above statement was introduced by another statement reading, "Flexin has produced no irreversible toxic reactions when administered to patients daily for periods of over 6 months. Individuals receiving Flexin for prolonged periods have been carefully checked with \* \* \* liver function tests \* \* \*." In view of this introductory statement, together with the highly qualified paragraph on the hepatitis itself, it is easy to see that this information could be accepted by the Administration at face value without appreciation that a major problem existed. However, the firm by this time had reports of approximately 30 cases, including some fatal ones, and they did not submit them. (Neither did they call attention to the article that had just been published on hepatitis in two patients receiving Flexin.) It also should be borne in mind that the stated single purpose of this supplement was to add gout to the therapeutic indications; any added precautionary information in the labeling ostensibly was merely coincidental. From currently available information, though, it is apparent that much of the other needed precautionary information also was understated or omitted.

On September 28, 1959, again in conjunction with a labeling supplement primarily for other purposes, the firm furnished us with the first actual information on the hepatitis that had occurred. This was in the form of a brief summary which could only be interpreted as indicating that but two deaths had occurred, and the etiology of the hepatitis was questioned. The statement was made that there had been only 32 cases. In reality, there had been about 40 cases of some degree of liver involvement reported, and these included about a dozen deaths.

On January 6, 1960, the original application for Triurate was submitted. No further information about the hepatitis accompanied this submission, although 2 more cases had been reported to the firm.

Finally, on July 13, 1961, the firm informed us verbally of 54 cases with 15 deaths. (This followed closely two published cases in medical journals having wide circulation.) On July 26, 1961, they submitted pertinent written infor-



mation on the subject, but it was only in the form of incomplete, summarized information. This was in conjunction with a proposal to revise the labeling and to send a letter to physicians calling attention to hepatitis from Flexin. However, the proposed letter and labeling were so thoroughly unsatisfactory that they would have been unacceptable even if the drug were to remain on the market. The proposed letter minimized, qualified, and cast doubt upon the validity of the reactions and did not inform about the high incidence of fatality. The proposed labeling revisions were similarly inadequate to reflect any true disclosure of the danger.

After Dr. Wingard's review of these applications, including a consideration of all previous submissions in them, we asked on August 23, 1961, for all the pertinent information on injury from Flexin. The firm submitted this on October 3, 1961. The reason it took so long is that their records of evidence of injury were so voluminous that the physical task of reproducing them was substantial.

Although this consideration has been principally from the standpoint of danger of hepatitis, I should mention that many other untoward reactions have accumulated over the years and consisted of some serious ones of which we knew nothing. All the information in this latter regard has not been fully reviewed; our greatest concern was with the hepatitis.

The sequence of events described above does not include all submissions in which the firm could have furnished pertinent information had they chosen to do so. Instead, the summary is limited just to the more outstanding occurrences in which failure to submit the information seems extraordinarily inappropriate.

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October 20, 1961.

To: Bureau of Enforcement. Attention: Dr. Milstead, Deputy Director.

From: Bureau of Medicine.

Subject: Flexin.

Attached are a number of summaries covering our recent concern and action on zoxazolamine (Flexin and related products).

As a result of the development of an increasing incidence of injury including serious, fatal liver damage due to the drug, the decision was reached to remove the drug in all its forms from the market. The firm is doing this and will voluntarily request suspension of the NDA's for these products.

The main point of this note and Dr. Archer's memorandum of October 17 is to point out that it appears very strongly that the firm had certain information concerning the hepatitis hazard available to them, and the fact that a number of deaths occurred associated with hepatitis in patients receiving zoxazolamine, which was not submitted at the time of submission of various supplemental NDA's or with the submissions of the various mixtures of zoxazolamine and other agents.

The question arises whether we should pursue this failure to submit information (which we feel may well have altered our handling of the previous submissions and consider possibly prosecution for withholding information) in view of the fact that these drugs are now off the market.

This is a rather complicated sequence of events and we would like to be consulted again if the decision is made to investigate this matter further.

WILLIAM H. KESSENICH, M.D.,  
Medical Director.

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October 1961.

MCNEIL LABORATORIES, INC.

IMPORTANT: NOTICE OF DRUG RECALL

DEAR DOCTOR: This letter is to inform you that McNeil Laboratories is withdrawing from the market Flexin® zoxazolamine and all Flexin-containing products; namely, Flexilon-HC and Triurate.

This action is being taken because of reports in medical literature, and observations submitted to McNeil Laboratories by physicians, which suggest that Flexin may be associated with the development of hepatitis in an occasional patient.

The incidence of hepatitis associated with the use of Flexin and Flexin-containing products is low, but because it is extremely difficult to determine whether the hepatitis associated with the use of these drugs is of viral origin or drug-induced, it is considered in the best interests of all concerned to recommend that



you discontinue the use of these drugs. If you have any samples of Flexin or the other drugs listed above, we request that they be destroyed.

It is unfortunate that this problem has arisen in regard to a useful and effective therapeutic agent and we hope that this action on our part will not cause you undue inconvenience.

Your cooperation and continued confidence in McNeil Laboratories is greatly appreciated.

Cordially yours,

McNEIL LABORATORIES, INC.  
JAMES M. SHAFFER, M.D.,  
*Medical Director.*

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(Note by editor: pt. 2, exhibit 80, p. 516, contains a chronology furnished by the Food and Drug Administration with respect to actions on the New Drug Application for Flexin. Numerous adverse reactions to the drug were noted therein. On August 12, 1963, in response to a subcommittee inquiry, Commissioner George P. Larrick, supplemented the previous tabulation of reactions by reporting as follows: "Since the Flexin New Drug Application was suspended on October 13, 1961, we have received reports of 30 additional reactions by patients who have received Flexin Zoxazolamine or Flexin-containing products (12 cases of liver damage, 8 cases of nausea, 5 cases of gastrointestinal irritation, 3 cases of dermatologic reactions, 1 case of leukopenia and 1 case of agranulocytosis). These injuries are in addition to the cases already reported to you."

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*(Internal Agency Document on Another Specific Case)*

October 20, 1961.

MEMO OF TELEPHONE INTERVIEW

NDA: 11-973 and 12-869.

Product: Dornwal and Amphenidone.

M.D.: Frances O. Kelsey.

SUMMARY OF SUBSTANCE OF CONTACT

At a meeting between clinical investigators of psychotherapeutic agents held at NIH on October 16, and 17, Dr. Douglas Goldman of Columbus, Ohio, mentioned that he had observed a case of agranulocytosis with Dornwal, that he had reported the incidents to the company about 1 month ago and that it was too soon to be published.

Dr. Goldman remarked that he assumed the company had appraised us of this case. Despite the fact that company representatives visited me on September 27, 1961, and that I have subsequently talked by phone with Dr. Connor, no mention was made of this case. Furthermore, on October 12, 1961, I made their new brochure effective conditionally to two further changes in the text. This brochure states all side effects noted were "minor and transitory" and that "extensive testing of the drug in laboratory animals has failed to produce any evidence of bone marrow depression."

In talking to Dr. Connor of Strasenburg on October 18, 1961, he readily admitted they had the information on this case at the time their supplemental application was under consideration, and that there was no question that Dornwal was the offending agent. He further stated they had received five other reports of agranulocytosis in patients on Dornwal but in these cases, other drugs causing bone marrow depression had been used. Only one of these cases was drawn to our attention. In this case the patient was apparently also taking chloramphenicol.

FRANCES O. KELSEY, M.D.

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*(Illustrative Article in Trade Press)*

November 13, 1961.

F-D-C Reports—"The Pink Sheet":<sup>13</sup>

Adverse reactions withheld by manufacturers disturb FDA-ers who mumble about need for criminal prosecution to get full and prompt reporting. \* \* \*

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<sup>13</sup> Vol. 23, No. 46, p. 26.



February 9, 1962.

Earl L. Myers,<sup>14</sup> Chief Chemist, Division of New Drugs, Food and Drug Administration:

Drug manufacturers as well as the FDA know that occasionally adverse effects are found in the course of extensive distribution of a new drug under marketing conditions although they were not encountered during the more limited investigational use. Further, marketing experience may yield significant information with respect to the incidence of adverse effects found but not accurately assessed as to incidence during the investigational period.

Over the years responsible drug manufacturers have promptly submitted such information to this Administration on a wholly voluntary basis. In some cases this has led to labeling changes with respect to conditions of use. In other cases it has been necessary to remove the drug from the market.

#### FAILURE TO DISCLOSE ADVERSE REACTION CASES GROUNDS FOR SUSPENDING NDA

We think the prompt reporting of such adverse information with respect to a drug is essential. We are very much concerned with evidence that in some cases it is not being done. We have encountered from time to time information with respect to untoward reactions with new drugs in reports in the literature or through correspondence with physicians. We have followed up these leads only to learn in some cases that these reactions, and even additional cases, were known to the manufacturer but were never submitted as part of his NDA. We view the failure to submit such information as a serious violation of the intent and the purpose of the entire NDA procedure.

I stated earlier that an important point to remember is that a supplement is not an entity in itself, but is only a part of the NDA which is incorporated. The failure to disclose any vital information available to the applicant, such as an adverse reaction, an unstable lot, or difficulty with an assay, is indeed, in our opinion, sufficient grounds for an application to be suspended on the basis that it contains an untrue statement of a material fact.

Apart from the disclosure of all information, and especially adverse information, pertinent to the evaluation of safety of the drug with any supplemental application for a drug, we may recognize that there are circumstances when the failure to promptly report adverse information to this Administration may establish a basis for regulatory action. For example, the failure of current labeling to disclose known hazards of a drug may result in a misbranding under section 502(f) of the act and the current regulations under it. This concept of course applies to any newly found hazards pertinent to old as well as new drugs.

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April 25, 1962.<sup>15</sup>

George P. Larrick, Commissioner, Food and Drug Administration:

Almost 9 months ago a drug firm informed us that one of its products was implicated in 54 cases of hepatitis and jaundice, including 15 deaths, about which we had no prior knowledge. This drug, a skeletal muscle relaxant, had been on the market since early 1956. We later learned the firm had accumulated reports of jaundice and deaths associated with the drug's use for a period of over 5 years before it reported them to us. After studying the case reports and consulting a number of medical authorities, we decided the product should be removed from the market. The firm was asked to recall the drug, which it did, and we suspended the product's New Drug Application.

Last October we learned of blood disorders associated with the use of a mild tranquilizer which had been on the market since April 1960. Upon investigation we found that the firm had information about 11 cases of injury attributed to the drug, including 3 deaths, that had not been reported to us. After evaluation of the evidence, this drug was recalled from the market and the New Drug Application was suspended.

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<sup>14</sup> Address before Parenteral Drug Association, New York, N.Y.

<sup>15</sup> "Our Common Goals," address before Annual Pharmacy Congress, St. John's University, Jamaica, Long Island, p. 2.



When a drug goes into commercial use the number of people who are exposed to its effects jumps from hundreds or a few thousands involved in investigational studies to many thousands or millions. Thus if the product causes bad effects in a very small percentage of people, these effects may not be discovered until the drug is marketed and used widely. So to safeguard consumers we must learn of adverse side-effects when they are first recognized. The present system is faulty because it does not guarantee this.

We believe the public has the right to the protection that would be given by requiring the distributor of a new drug to advise us of reports of adverse reactions to the drug as soon as they are received. Then we would be able to require corrective action promptly when it is needed.

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*(Testimony Before House Subcommittee)*

May 17, 1962.

STATEMENT OF DR. M. HAROLD BOOK, DIRECTOR OF LABORATORIES AT THE NORRISTOWN STATE HOSPITAL, NORRISTOWN, PA., AND ASSISTANT PROFESSOR OF NEUROPATHOLOGY IN THE GRADUATE SCHOOL OF MEDICINE AT THE UNIVERSITY OF PENNSYLVANIA<sup>16</sup>

As was pointed out on a number of occasions in the Senate hearings, the drug houses are noticeably coy in publicizing the exact number and seriousness of side effects attending the use of their new products. In their advertisements, their brochures, their detailmen's pitch, and so forth, they speak rather diffidently in terms like "side effects are minimal," "with few significant side effects," "no serious side effects noticed," and so forth.

However, they are careful to refrain from giving the number of the side effects, both slight and serious, per hundred treated cases.

It is only by careful reading of a large number of reports in the medical literature that one can obtain even a rough idea of the incidence of such side effects. The fact is that side effects are very common with many of these new drugs. One can hardly enter into a conversation with physicians in a hospital staff room without hearing of all sorts of unexpected ill effects from the use of these preparations. It would be impossible to determine the total number of such cases which occur the country over, even in the case of one drug. There are a number of reasons for this gap in our knowledge.

The average physician who encounters a serious side effect, such as a death, in the use of any therapeutic procedure, whether it involved drugs, operation, or other modality, is understandably loathe to publicize the event. In the vast majority of cases he has followed standard practice and instructions and is surprised to find that, in spite of having done so, he has encountered a bad result. In these days, and especially in this country, he is always faced with the possibility that a resentful relative will sue for malpractice, even though there is absolutely nothing in the physician's conduct of the case which would suggest that he was indeed at fault.

A straw in the wind in this respect may be the award of \$334,000 damages to a housewife who charged that she contracted aplastic anemia, a serious bone marrow condition, after treatment with Chloromycetin. The jury assessed the damages jointly against the drug manufacturer, Parke, Davis & Co., and the physician. This was reported in the AMA News, April 30, 1962.

Secondly, the reporting of these cases requires time, which is always a short commodity in the life of the practitioner. Any reward for the time and trouble he would take is rather nebulous. There is absolutely no legal requirement that he report such a catastrophe, although most physicians are probably aware of the fact that the pharmaceutical houses would like to know of these untoward events. Only recently have some organized attempts been made to collect information from the medical profession on these complications by agencies outside of the pharmaceutical industry.

The adverse reaction reporting program instituted by the Division of Research and Reference in the Bureau of Medicine of the Department of Health, Education, and Welfare has been encouraging a small group of hospitals to make a concerted effort to report all of their side effects, mild as well as severe.

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<sup>16</sup> House of Representatives, Committee on the Judiciary, Antitrust Subcommittee, on H.R. 6245, 87th Cong., pp. 101-102, 105-106.



In my long experience as a pathologist, I have performed some 2,000 autopsies in several hospitals. In the last 8 or 9 years I, and many other pathologists, have noticed a distinct increase in the number of serious adverse effects, even deaths, resulting from the widespread use of many of the newer, so-called wonder drugs.

For example, in a report issued from the Norristown State Hospital, 11 cases of serious depression of the bone marrow—this agranulocytosis mentioned earlier—during treatment with Thorazine were listed. Four of these resulted in death of the patients and I performed the autopsies.

I also examined the bone marrows.

It should be noted that this occurred in a series of several thousand patients, most of whom were very sick.

However, there is far more to be considered in this regard than such dramatic deaths. As a result of many autopsies I have done in the last decade, I am firmly convinced that the ill effects of some of these drugs go unrecognized by the clinicians and are frequently buried with the patient when he dies, so to speak.

In doing an autopsy on a patient who has had a serious illness and has been treated by a number of different drugs, as is usually the case when the doctor is striving desperately to save the patient, I have the distinct impression that the patient has suffered from the treatment as well as from the disease. The proportion varies from case to case. In some instances there is no doubt that the patient has died from the disease. In cases of incurable cancer it is obvious that no treatment would have been of real avail. Sometimes it is apparent that the treatment has shortened the life of the patient. This might be considered a sort of involuntary euthanasia.

At times it is apparent that the treatment, even if there have been no side reactions, has done the patient more harm than good. In many cases this is due to an erroneous diagnosis by the clinician.

In a large mental hospital such as the Norristown State Hospital, the diagnosis of physical disease in seriously affected mental patients is often quite difficult. Such patients frequently give absolutely no history and offer no complaints. Even in this day of widespread use of laboratory tests and X-rays for the diagnosis of disease, the history supplied by the patient or elicited by questioning on the part of the physician is still very important. If the clinician is not able to obtain this history he is at a considerable disadvantage. In addition, State hospitals are notoriously short of personnel and money so that the care of the patient does not quite come up to that provided in the average teaching or community hospital.

If you reflect that our hospital operates on a budget of about \$4 per patient a day, whereas in the average general hospital the cost is something like \$26 per patient per day, you realize how difficult our problem is there.

Even in the general hospitals mistakes in diagnosis occur and the patient is given the right treatment for the wrong disease. This is particularly true of internal diseases of the abdominal organs, organs of the chest and the central nervous system. \* \* \*

For example, a few months ago I did an autopsy on an elderly gentleman who was thought to have cancer of the stomach, based on the history, the physical findings by the physician and the X-ray picture. Since it was judged that the tumor was beyond surgical treatment, he was given one of the new experimental cell-destroying agents in a desperate effort to prolong his life. This particular drug has as one of its effects severe depression of the bone marrow which produces the white cells in the blood to fight infection. He died in short order and at the autopsy I found that he did not have a cancer at all but was suffering from an infectious condition involving the wall of the stomach. In this case he should have been treated by one or more antibiotics to combat the infection. Instead, he was given a drug which seriously hindered the body's own defenses against the infection. This incident, one of many, emphasizes the fact that exact diagnosis is obviously important in the use of any drug, old or new.

And it is important in the testing of new drugs. I want to emphasize that.

Many of these unusual effects of drugs and mistakes in diagnosis are only uncovered at autopsy. Unfortunately, postmortems are done in only a small percentage of deaths in this country so that much of this badly needed information goes to the grave with the patient.

Another phase of the use of the "wonder drugs" which has received comparatively little attention is the possible deleterious effect of these substances when used in combinations of two or more.



*(Illustrative Letter of Commendation of Program)*

June 20, 1962.

Frederick Meyers, M.D., Chief Medical Resident, George Washington University Medical Division:

JOHN W. NESBITT, M.D.,  
U.S. Department Of Health, Education, And Welfare,  
Food And Drug Administration,  
Bureau of Medicine,  
Washington, D.C.

DEAR DR. NESBITT: For the past 2 years I have been a participant in your Adverse Drug Reaction Reporting Program. During that time I have seen and reported many interesting observations, as you well know. As a direct result of the program, both at the District of Columbia General Hospital and The George Washington University Hospital, we have learned a great deal about the incidence and variety of adverse effects of drugs. This was to be expected from the nature of the program. Gradually, however, our knowledge has, in many instances, enabled us to anticipate these adverse effects. In time our interns and residents have learned to avoid drug reactions by adjusting dosages, using countermeasures or substituting more benign agents in the treatment and **diagnosis of illness**. Furthermore, early and more subtle signs and symptoms of reactions have been recognized and the more serious adverse reactions avoided.

I am certain that at present we are seeing a much lower incidence of all types of adverse drug reactions because of the knowledge gained from participation in the program. My purpose in writing this letter is to bring this trend to your attention. I'm sure that in the past certain other trends have become apparent to you. For instance, when we first began the program we reported more and more reactions as we became adept at recognizing them. Then we reported more of the less striking reactions. Well, now we are seeing less of both major and minor reactions.

So you see our association with you has been beneficial from several aspects. You might say this is a good side effect of the program. I'm sure the coming year will be as rewarding and perhaps new trends will develop. In any event we will do our best to continue observing and reporting any and all adverse drug reactions.

Very sincerely yours,

FREDERICK MEYERS, M.D.,  
Chief Medical Resident.

*(Illustrative Article in Hospital Bulletin)*

July 1962.

"Drug Letter,"<sup>17</sup> Committee on Pharmacy and Therapeutics, Johns Hopkins Hospital:

## SURVEILLANCE OF DRUG REACTIONS

For the past 12 months the Committee on Pharmacy and Therapeutics has attempted to assemble data on drug reactions in The Johns Hopkins Hospital. The Report of Infection card attached to the record of every hospitalized patient was modified to allow reporting of drug reactions as well.

<sup>17</sup> Pp. 1-2.



The reporting of drug reactions during the past 12 months has been variable and it is estimated that no more than 10 percent, at the most, of all drug reactions have, in fact, been reported. In a random sample of 100 charts selected from the wards, 7 case histories were found which involved clear instances of drug reactions—described as such—which had not been reported. These 7 drug reactions included a case of persistent fusion of the labia in a newborn (which in the record itself was considered to be associated with high doses of ethinyl estradiol for the first 5 months of pregnancy and a very high dose of Diethyl Stilbestrol, 600 milligrams per day, during the last 3 months of pregnancy, prescribed by an outside physician.)

Three deaths due to drug side effects were reported to this committee during the past year, including one due to penicillin anaphylaxis, one following intrathecal administration of Xylocaine leading to cardiac arrest and death, and a third of death after the administration of intravenous histamine during a workup for hypertension.

From the EKG records available to the Heart Station, some 12 cases of digitalis toxicity have been noted monthly during the past year. On following up the records of these patients, it appears that nausea, vomiting, and visual difficulties were the most common symptoms associated with this, while the most common EKG finding was the appearance of multifocal premature ventricular contractions.

Three cases of aplastic anemia following chloramphenicol have come to our attention since Christmas 1961. In one of these patients the drug was given postoperatively as a prophylactic and was, in error, continued for 6 weeks, leading to a severe anemia. None of these three patients succumbed to their reaction. Another interesting reaction has been the appearance of thrombocytopenic purpura following quinine.

In addition to failure to report, there is little doubt that occasionally the fact that one is dealing with a drug reaction may be entirely missed and thus appear neither in the record nor on the Report of Drug Reaction card.

An intensive effort will be made during the next year to obtain a better picture of the importance of drug reactions in the hospital, but success can only be achieved with the full cooperation of all members of the medical staff and by instilling an awareness in all M.D.'s of the possibility that they are dealing with a case of drug reaction.

It has been suggested that during the daily rounds by the resident or assistant resident, particular emphasis be put on inquiring into any possible drug reactions and that these be noted and reported on a daily basis.

The Report of Infection card is perforated down the middle, dividing the card in half. One-half of the card provides for reporting infections acquired in the hospital and the other provides for reporting drug reactions. If the patient develops infection in the hospital, the Report of Infection card should be promptly filled out and placed in the hospital mail. If no infection occurs in the hospital, the Report of Infection card should be filled out at the patient's discharge and placed in the hospital mail. The Report of Drug Reaction should be handled similarly. If both cards are completed at discharge, they need not be separated at the perforation.

Any and all drug reactions should be reported, regardless of severity or type. Such reactions include toxic responses, those attributed to overdose, and those thought to be due to idiosyncrasy. Whether these reactions are local or systemic, allergic or a novel type, and all symptomatology and physical signs which might be in any way considered an untoward reaction to a drug should be reported.



DATE OF DISCHARGE \_\_\_\_\_

DATE OF DISCHARGE \_\_\_\_\_

DOCTOR \_\_\_\_\_ M.D.

DOCTOR \_\_\_\_\_ M.D.

### THE JOHNS HOPKINS HOSPITAL REPORT OF INFECTION

THIS CARD IS TO BE COMPLETED ON EVERY PATIENT HOSPITALIZED AND PLACED IN INTERDEPARTMENTAL MAIL:

1. WHEN THE INFECTION OCCURS, OR 2. IF NO INFECTION, AT THE TIME OF DISCHARGE. INFECTION DEVELOPED DURING HOSPITALIZATION?

YES \_\_\_\_\_ NO \_\_\_\_\_

TYPE OF INFECTION (I.E., POSTOP WOUND, URI, BOIL, ETC.) \_\_\_\_\_

DUE TO STAPHYLOCOCCUS. YES \_\_\_\_\_ NO \_\_\_\_\_

IF OTHER ORGANISM, SPECIFY: \_\_\_\_\_

WAS THE INFECTION CULTURED: YES \_\_\_\_\_ NO \_\_\_\_\_

JHH FORM 8127 REV. 5/61

### THE JOHNS HOPKINS HOSPITAL REPORT OF DRUG REACTION

THIS CARD IS TO BE COMPLETED AT DISCHARGE ON EVERY PATIENT HOSPITALIZED AND PLACED IN INTER-DEPARTMENTAL MAIL.

DID THE PATIENT DEVELOP A DRUG REACTION?

YES \_\_\_\_\_ NO \_\_\_\_\_

DUE TO WHAT DRUG OR DRUGS? \_\_\_\_\_

TYPE OF DRUG REACTION (RASH, FEVER, HEMATURIA, AGRANULOCYTOSIS, ETC.) \_\_\_\_\_



July 14, 1962.

Dale G. Friend, M.D., Senior Associate in Medicine, Peter Bent Brigham Hospital and Assistant Professor in Medicine, Harvard Medical School:<sup>18</sup>

The tremendous developments in medicinal and industrial chemistry in the past two decades have made available an ever-increasing number of new drug entities and have greatly increased the use of chemicals in daily life. As a consequence, the human organism is being exposed to a host of new substances with chemical and pharmacological properties that are different from any known or experienced previously. Exposure of segments of the population to certain widely used agents has resulted in the appearance of many diverse and previously unrecognized types of reactions. This fact has resulted in the discovery that apparently normal individuals may have an impaired ability to detoxify or metabolize certain chemical agents because of inherent defects in their cellular metabolism. The result of this impairment is the appearance of many more, and far less easily recognized or understood drug reactions.

At the turn of the century, nearly all drug reactions were thought to be allergic in character. The rare reactions were labeled idiosyncratic, and little effort was made to understand them. When aminopyrine and the sulfonamides, among the first groups of the widely used synthetic agents, were found to have the ability to cause reactions, great interest was aroused in the problem. It soon became apparent that drug toxicity encompassed many factors besides allergy.

Since reactions vary in degree from minor inconvenience to serious toxic effects capable of causing severe damage or death of the patient, their occurrence is increasingly important in medicine. There is an urgent need to secure much more information about drug toxicity and to make it available promptly to all physicians.

In the past, there have been several excellent surveys of the subject. Alexander performed a notable service when he compiled, in useful reference form, a list of a large number of reactions. Carr has written helpful reviews on this subject and has done much to classify types of reactions. However, it is apparent to those interested in the subject that only a small fraction of the total number of reactions which occur is being recorded. It is apparent also that this information is not being made sufficiently available for general use. The situation is in urgent need of improvement; before a general program can be developed, however, it is necessary to clarify the goal and establish the mechanism whereby this can be accomplished.

At the present time, there exist two national efforts to obtain information on drug reactions. In 1954, the Council on Drugs of the American Medical Association established a Registry of Blood Dyscrasias. Information is tabulated semi-annually, and reports are sent to all those who are interested in the results of this program. Even though limited in scope, it has proved useful. Several informative reports have been prepared by the council from the data thus obtained. The Food and Drug Administration has initiated a program to obtain reports of drug reactions from interested physicians, hospital pharmacists, medical record librarians, and hospitals. Unfortunately, however, only a small number of institutions and physicians are assisting in these programs. Both efforts are laudatory and deserve our full support.

#### METHOD OF OPERATION

Most hospitals do not have a system or mechanism to encourage members of the staff to recognize, record, and report drug reactions. The results of a recent survey by the Council on Drugs revealed that nearly two-thirds of the hospitals queried had no committee for review or evaluation of adverse drug effects. Consequently, it is my belief that only a small percentage of all drug reactions is ever recorded. Although every physician should be concerned with, and report immediately, every adverse drug effect, the hospital is unquestionably the keystone in the development of an effective adverse drug reaction program. The information and personnel, as well as the means for securing and recording data, are available, and a smoothly functioning program can be established with little effort. Hospitals with an interest in the problem can accumulate much important and highly useful information which may contribute significantly to improvement in care of the patient.

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<sup>18</sup> "Drug Reaction Committees in Hospitals," *Journal of the American Medical Association*, p. 22.



August 9, 1962. At the second of the Reorganization Subcommittee's drug hearings, Senator Humphrey discusses the Adverse Reaction Reporting Program of the Food and Drug Administration. He states that, after 8 years of effort, the program has grown only to the point of including 44 of the Nation's 7,000 hospitals. Only around 27,000 of the million and one-quarter beds in the Nation's hospitals are reporting under the program. As of that time, only 8 of the 15 U.S. Public Health Service hospitals are included. No Veterans' Administration hospital, and no Defense Department hospital reports to F.D.A.

(Articles in the Open Literature)

August 11, 1962.

G. I. Watson, M.D.:<sup>19</sup>

REGISTRY OF TOXIC REACTIONS

SIR,—I would like to support those who favour the regular reporting of unexpected drug reactions, whether favourable or adverse, but hope that the registration of such reports will be centralized (Dr. F. Wilson, July 28, p. 255), not dispersed over a number of specialized study groups (Professor L. J. Witts, July 28, p. 254).

Linked with its wider programme of research into congenital abnormalities, the College of General Practitioners through its Epidemic Observation Unit has already opened a register of toxicity and side effects of new or established drugs.<sup>1</sup> All family doctors—and others, whether in the College or not—are invited to report clinical and therapeutic details about any instance where they suspect that a therapeutic agent has affected a patient (or offspring) adversely. Surmises and suspicions should not be withheld merely because there is no proof; sufficient of these from different doctors would provide a priori grounds for most searching inquiries.

If at some future date the collection of such reports is organized on an inter-professional basis between doctors and pharmacists, the information in our college register will be passed on to the national body concerned. Meanwhile all reports, addressed to the Director, Epidemic Observation Unit, Corran, Peaslake, Guildford, Surrey, will be welcome.—I am, etc.,

G. I. WATSON,  
Epidemic Observation Unit,  
Peaslake, Surrey.

REFERENCE

<sup>1</sup> J. Coll. gen. Practit., 1962, 5, 450.

October 1962.

Don E. Francke:<sup>20</sup>

During recent years the incidence of drug reactions has increased at a staggering rate until today they are one of the most prevalent "Diseases of Medical Progress," to quote the title of a book by Moser.

(Statement in Senate)

October 3, 1962.

Senator Hubert H. Humphrey:<sup>21</sup>

\* \* \* shocking reports of injuries and deaths to test patients, as received by drug companies, have often gone unreported to FDA, or have been downgraded by skillfully contrived half-truths, or have been reported accurately to FDA, but virtually ignored by FDA.

NEWSPAPERS MIGHT HAVE BEEN FILLED WITH SHOCKING STORIES

They are strong words, but they are true. In fact, as I said to my staff, had I wanted to claim headlines, I could have filled newspapers for weeks with scandal-pointing statements on shockingly inadequate standards and on a huge volume of adverse effects on the public health, because of the inexcusable marketing of dangerous new drugs without adequate prior testing.

\* \* \* \* \*

<sup>19</sup> Correspondence, British Medical Journal, p. 408.

<sup>20</sup> Editorial, Investigational Drugs and Drug Investigations, American Journal of Hospital Pharmacy, vol. 19, No. 16, Oct. 1962, p. 511.

<sup>21</sup> Congressional Record, pp. 20885-20886.



(Memorandum by Senator Humphrey)

POOR OVERALL REPORTING OF DRUG REACTIONS

5. Next, I should like to state that the whole program of collecting drug reactions throughout this country and the world is hopelessly obsolete.

It is a miracle that we learn as much as we do about drug reactions in view of the pitifully haphazard way in which clinical reactions are compiled.

All sorts of sources do attempt to compile reactions—pharmaceutical companies, the FDA, hospitals, the VA, NIH, and other sources.

None particularly talks with the other; none cooperates to any real extent with the other. One might just as well try to scoop out the Atlantic Ocean with a leaky "Dixie cup" as to collect drug reactions in the hit-or-miss manner which has been going on for so long.

The key to reporting is the individual clinician. But he tends to be so busy that often his reports are a fraction of what they might be. Negative results often go largely unreported. This is a crucial point; it explains in part a tendency to overvalue fragmentary favorable reports.

FDA itself has had a microscopic adverse reaction reporting program; we have yet to find anyone who has substantially used this program or anyone at the reporting end who has received useful "feedback" from it.

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(Canadian Report)

October 23, 1962.

D. L. McNeil,<sup>22</sup> M.D., F.R.C.P.(C), Chairman, Committee on Pharmacy, Canadian Medical Association:

The layman may properly ask why he should be the guinea pig; how it is that dangerous drugs ever get out of the laboratory and on the chemists' shelves in the first place. The reason is apparently neither scientific nor medical, but purely statistical. The obvious killers are identifiable at the laboratory. Really serious side effects show up if not in the laboratory, then when the drug is first tried out in hospitals. The long-odd chances, the disastrous reaction that appears in perhaps one case in a thousand, will not necessarily be obliging enough to crop up during these controlled trials. No drug may ever be considered 100 percent safe. It is as safe as modern science can make it—that is all that may be stated. To many people it seems an anachronism that it should be left to the good faith of manufacturers to decide whether the drug seems safe or even how extensively it should be tested before it goes on the market. The public's only protection is the industry's sense of responsibility and the knowledge that each company can stay in business only as long as it has the respect of the medical profession. On a statistical basis the Food and Drugs Division or any other authority could not necessarily prevent another tragedy such as thalidomide.

It is believed by some that if such dangers cannot be picked up in the laboratory, could they not be identified during hospital trials before doctors start prescribing a new drug in quantities. This is not what clinical trials in hospitals are for. They are to see whether the drug has any medical value and if so for what condition and with what dosage. They may indicate the price that the patient might have to pay for a cure in terms of side effects. The manufacturers cannot ask hospitals to use their patients like laboratory animals. There are not enough patients to provide the statistical sample that would be needed to save the public 100 percent guarantee that sentiment naively demands.

It would appear that physicians should urgently consider their methods of reporting drug reactions. Methods should be studied by pharmacy committees of the medical associations. A "central drug reaction reporting centre" has been recommended. In some hospitals drug reaction regulations have been instituted, making the reporting of unusual occurrences compulsory.

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<sup>22</sup> "A Submission to the Royal College Committee, Appointed at the Request of the Minister of National Health and Welfare, To 'Examine Critically and Objectively' the Present Procedures of the National Department of Health and Welfare for Dealing With New Drugs, the Requirements of the Regulations and Other Relative Matters."



October 25, 1962.

Second Citizens Advisory Committee on the Food and Drug Administration:<sup>23</sup>

A SOUND METHOD SHOULD BE DEVELOPED FOR OBTAINING INFORMATION ON ALL  
ADVERSE DRUG REACTIONS

There now is no systematic method for bringing adverse drug reactions to the attention of FDA, on either approved drugs or new drugs on trial. Many drug manufacturers make it a point to pass along to FDA information they receive concerning adverse reactions, and drug manufacturers generally act promptly in withdrawing drugs when dangerous side effects are reported. Thus, FDA reports that, of 35 defective or misbranded drugs recalled by manufacturers during 1960, only 11 were recalled at the request of FDA. FDA also receives periodic reports from a number of the leading hospitals in the country on adverse reactions experienced from drugs used in those hospitals.

However, neither of these programs for reporting adverse drug reactions is sufficient to protect the consumer. It is accordingly suggested that FDA, in cooperation with pharmaceutical manufacturers, establish a sound formal means of communication on all adverse drug reactions (both approved drugs and drugs on trial), from the manufacturers to FDA and from FDA to the manufacturers, where FDA may receive this information from other sources such as hospitals.

This committee believes that the interests of the consumer would be better protected if all drug manufacturers and all qualified physicians were required to report to FDA at once any information concerning significant adverse reactions or occurrences of such reactions, and that FDA should have the responsibility for seeing that prompt action is taken to protect the public.

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November 10, 1962.—Meeting is held at Drake Hotel, Chicago, Ill., by American Medical Association, Council on Drugs, Subcommittee on Adverse Drug Reactions. Among those present are AMA officials, representatives of drug companies, leading clinical pharmacologists, and representatives of FDA.

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(Internal Agency Documents on Overall FDA Adverse Reaction Reporting Program)

November 30, 1962.

LETTER OF TRANSMITTAL

To: Mr. Leo L. Miller, Assistant Commissioner for Administration, FDA.  
Thru: Mr. J. B. Cardwell, Acting Director, Division of Management Systems.  
From: A. D. Davis, Acting Chief, Management Surveys Branch.  
Subject: Factfinding Survey of the FDA Adverse Reaction Reporting Program.

In compliance with your letter of November 9, 1962, the writer has performed a factfinding survey of the FDA Adverse Reaction Reporting Program, and prepared the attached report for use by the FDA Committee on Scientific Information in re-evaluating the current program.

Generally speaking, this has been a pure factfinding endeavor, and we have attempted to confine our report to the many broad considerations which have direct bearing on the program. Your attention is invited, however, to the appendix which has been attached to this report. This appendix contains:

1. Schedule of Suggestions based on our appraisal of the survey data, and
2. Recommendation for the granting of an FDA Award of Merit to an associate of the Food and Drug Administration for his high quality of performance in serving as reported for the Adverse Reaction Reporting Program at the University of Michigan Hospital.

We realize that this appendix may well be in violation of the Survey charter, however, due to the nature of our findings, we feel compelled to include the material for whatever value it may have to the Committee on Scientific Information.

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<sup>23</sup> Ch. III-17.



Throughout this survey we enjoyed full cooperation from the many people interviewed. We are prepared to discuss the findings, in depth, and will make our back-up material available at the pleasure of the committee.

# FACTFINDING SURVEY OF THE FDA ADVERSE REACTION REPORTING PROGRAM

Prepared for the FDA Committee on Scientific Information, November 1962—  
Management Surveys Branch, Division of Management Systems, Office of the  
Assistant Commissioner for Administration

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- Example of Successful Application.<sup>20</sup>
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## APPENDIX

- Schedule of Suggestions.<sup>20</sup>
- Recommendation for the FDA Award of Merit.

## SECTION I. GENERAL

### 1. Purpose of the Study

Inherent in every FDA program is the responsibility for continual reevaluation of the activities involved. New laws, workload changes, improved procedures, and many other causes frequently make it necessary to adjust assignments, reappraise objectives, review performance, or determine new balanced approaches to program accomplishment.

<sup>20</sup> For reasons of brevity, only the items designated above are reprinted within the subcommittee's volume.



The purpose of this study has been to develop background information concerning the operation of the Adverse Reaction Reporting Program. The report is hereby submitted to the FDA Committee on Scientific Information for the committee's use in reevaluating the current program.

## *2. Statement of the Problem*

a. For many years FDA has recognized the need for evaluating drugs from the standpoint of safety. Recent developments strengthen the contention that FDA cannot rely on published literature and sporadic voluntary reports from the medical profession as its only sources of information concerning severe and unusual reactions to drugs.

b. The problem is primarily one of gaining the cooperation of a sufficiently large enough cross-section of hospitals and clinics in reporting promptly adverse reactions to drugs. This information, if received in sufficient detail, can serve as a basis for significant action on the part of the Food and Drug Administration in a systematic followup of untoward effects of new and old drugs, as well as certifiable antibiotics.

## *3. Need for Adverse Reaction Information*

It is important to note that FDA is not the only organization that has recognized the need for acquiring and appraising new knowledge on the adverse reactions of drugs.

In a recent Chicago meeting, the American Medical Association's Council on Drugs devoted their entire program to a discussion on the establishment of a Register of Adverse Reactions. It is reported that AMA plans to push this objective and will undoubtedly rely heavily on the cooperation of member physicians for comprehensive reporting.

Displayed as tab A is a copy of "Proposal No. 9; Drug Information Management System," which was a topic of discussion at the Public Health Service Conference on Health Communications, held at Warrenton, Va., on November 5-8, 1962. This, too, is an ambitious plan, and apparently envisions Public Health as a central repository of drug information.

FDA's need for information on adverse reactions to drugs is especially acute in connection with the agency's responsibilities for surveillance of new drugs. As an illustration of how such information is used, we have described in tab B, an interesting case involving severe reactions to Chloroquine Phosphate (ARALEN).

In summary, a September 1962 manuscript concerning Chloroquine Retinopathy was received from the National Institute of Neurological Diseases and Blindness indicating that there have been 26 cases of this condition reported. Dr. Esch, of the ARRP Medical Group referred the report to the Division of New Drugs, noting that the product brochure for Chloroquine Phosphate ("ARALEN") did not establish the possibility of resultant retinopathy and suggesting further evaluation of the labeling.

It should be noted that only three cases of Chloroquine Macular Degeneration had been previously reported in the literature. The NINDB manuscript made a significant new situation out of what appeared to be only 3 cases, and with 26 cases as a basis, the Division of New Drugs is moving forward with a reevaluation of the labeling.

## SECTION II. BACKGROUND OF ARRP

### *4. Early Developments*

ARRP had its inception in 1955 when the FDA Bureau of Medicine took the initiative in arranging for a pilot study to test the feasibility of such a reporting system. In cooperation with other Federal agencies and national organizations concerned basic reporting procedures were developed. The success of this pilot study led to the broader program under which FDA now accumulates information on unusual or adverse reactions to drugs. Copies of the Pilot Study reports are available in the Survey backup material.

### *5. New Emphasis*

The Drug Amendments of 1962 places new emphasis on ARRP. The amendments require (effective May 1, 1963) "In the case of any drug for which an approval of an application filed pursuant to the section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or informa-



tion, received or otherwise obtained by such applicant with respect to such drug."

Although the Division of New Drugs will continue to be the biggest user of ARRP information, the needs of the Division of Antibiotics for rapidly acquired and appraised knowledge on adverse reactions will also become greater as DA's responsibility for antibiotic certification broadens to include *all* antibiotics in March 1963.

#### SECTION III. PROFILE OF THE FDA PROGRAM

##### 6. Personnel

Dr. John W. Nesbitt, Acting Director of the Division of Research and Reference, provides overall supervision of the ARRP personnel. This personnel consists of:

- Albert F. Esch, Medical Officer—GS-14.
- Margaret A. Millikin, Medical Officer—GS-14.
- Ola H. Bain, Food and Drug Officer—GS-13.
- 1-2 clerical assistants.

##### 7. Budget

The program was initiated in 1960 at a cost of \$30,000, and was carried at this level through 1961. In 1962, \$17,000 was added to the program, resulting in a budget of \$47,000 each year for fiscal year 1962 and 1963. Failure to expand the program by negotiating contracts with a sufficient number of additional reporting sources has resulted in sizeable unobligated balances each year.

##### 8. The Information Collection Process

Information on adverse reactions to drugs is collected in two ways, (1) through literature search, and (2) through submission of report forms by hospitals and clinics on a periodic basis. We feel it is important to stress that these two plans are not in conflict. If the hospital reporting plan is developed properly it will not continue to be looked on as a weak supplement to literature search, but rather serve as a major complement to the older technique.

a. Literature search. This activity apparently works effectively under the guidance of Miss Elizabeth Kelly. This section maintains 3 by 5 cards with references to information gathered from many written sources. Reactions to drugs from these sources have been compiled by RRB since 1949, and we would estimate the file has over 65,000 cards on untoward effects of drugs and chemicals.

b. Hospital Reporting Program. In November 1962, we have 24 hospitals under contract or purchase order. This has grown from four in 1960. The program has a total of 78 reporting sources as of November 1, 1962; however, this total is deceiving as the number of actual monthly reports received averages only about 20 plus 5 reports of no incidents. From July 1, 1961, to July 1, 1962, there were 2,746 adverse reactions reported. Of these, 762 were reported in detail, or 27.6 percent of the total; 37 or 4.6 percent of the detailed reports were referred to other operating divisions, particularly DND, DMR, and DA (see tab C).

##### 9. Publication of Information Collected

a. Literature search: Reports of adverse effects which are derived from the literature are published weekly (sample of report displayed as tab D). Although this report does not contain information on reports received from the hospital reporting program, Miss Kelly plans to expand the system to include such information (sample card also displayed). Reports are for FDA internal use only.

b. Hospital Reporting Program: Feed back of information to the reporting hospitals has been poor. Only 1 report has been furnished back to the participants and this is of questionable value as it is of a statistical nature and does not describe reactions in detail (copy displayed as tab E). Starting in July 1962, a tabulation of reactions has been prepared monthly. These reports, however, are circulated only within the FDA.

##### 10. Participating Hospitals

The hospitals currently listed as participants in the program are displayed as tab F. As previously discussed, the size of the list is deceiving. The list credits 15 Public Health Service Hospitals and 2 PHS OPT Clinics to the program but our fact finding data shows their participation to be practically nil. There is only one Veterans' Administration Hospital in the program, and this hospital has not reported for the past 3 months.



### *11. Example of Successful Application*

It would appear that in general, the quantity and quality of information furnished by the reporting sources leaves much to be desired. We have noted, however, limited examples where significant reactions were reported which resulted in prompt and successful utilization by the ARRP personnel.

As an example of successful application we have selected the University of Michigan Hospital report on reactions experienced with the use of Phytonadione (vitamin K). The hospital reported these reactions by telephone on July 27, 1962, and at the end of the month forwarded the appropriate forms as part of the regular monthly report.

Copies of the pertinent reports and correspondence describing two anaphylactoid reactions to the drug, one causing death, are displayed as tab G. The material has been arranged chronologically and is self-explanatory.

Particular attention is invited to the final three pieces of correspondence (Oct. 1962) wherein ARRP's Dr. Esch suggested that the manufacturer (Hoffman-La Roche, Inc.) be required to provide revised labeling. Note also that the proposed revised labeling as submitted by the manufacturer in letter of October 18, 1962, contains actual reference to the fatality. Approval is currently pending in DND.

## SECTION IV. PRINCIPAL PROCEDURES OF THE PROGRAM

### *12. Program Expansion Procedure*

The original concept of the program called for a high degree of selectivity in assembling the participating group (representing a good cross section of medical experience). Recruitment for the program has concentrated principally on teaching hospitals. Packets of program information for distribution to prospective participants have been prepared (see tab H). Where necessary, the institutions (or individual physicians designated by them) have been reimbursed by contract or purchase order arrangements. Fifteen Public Health Hospitals and two PHS OPT Clinics are enrolled in the program.

On October 5, 1962, Dr. John W. Nesbitt of DRR met with officials of the Division of Hospitals, PHS, to discuss ways of improving their hospitals' cooperation in the program. During the period July 1-Dec. 31, 1961, the 17 PHS installations reported a total of only 27 reactions, 4 of which were reported as significant reactions on Form FD-BM-1. The PHS officials stated that they did not realize how poor the performance had been and promised to contact all stations in this regard. On November 7, 1962, PHS issued Division of Hospitals Bulletin No. 63-60 calling for all stations to review the program, and requiring submission of a quarterly report to PHS headquarters indicating what had been reported to FDA for the period involved. Copy of a Memorandum of Meeting for the October 5 visit, as well as a copy of Bulletin No. 63-60 are displayed as tab I.

We have been unable to find record of a meeting alleged to have been held on May 2, 1962 between Dr. Kessenich and "high level" Veterans' Administration officials for the purpose of obtaining cooperation of the VA in this reporting program. Apparently this meeting was not productive, since as of November 1, 1962, only one VA hospital is enrolled in the program, and this hospital has not reported in the past 3 months. No recent serious effort to enlist VA participation has been noted.

### *13. Reporting Procedure*

Displayed as tab J is a flow chart of the reporting procedure for adverse reactions. Participating hospitals are required to submit a monthly listing of all reactions to drugs encountered in the hospital. Possibly significant cases are reported in detail on individual forms. This survey has been unable to attach real value to the monthly listings of all reactions. These are the "drowsiness produced by phenobarbital" type of reactions, and are already well known by our medical officials. The significant reactions, which are reported in detail on individual forms, are our chief interest. It appears that in this category we have a pressing need to expand our coverage.

### *14. Fee Payment Procedure*

Currently the program has 24 hospitals under contract or purchase order. Fees for the reporting services of these hospitals vary from \$50 to \$200 per month. In general, the hospitals receiving payment are better reporters than the voluntary participants, however, the size of the payment does not necessarily guarantee good reporting results. George Washington University Hospital and



the D.C. General Hospital are fairly good reporters and both receive fees of \$83.33 per month. Washington University Hospital (\$108.33/mo) and Mount Sinai Hospital (\$150/mo) are poor reporters.

#### SECTION V. APPRAISAL OF THE PROGRAM

##### 15. *Scope of the Program*

At the present time there are approximately 7,000 hospitals in the United States. Apparently, in order for ARRPs findings to be valid, it is essential that the scope of the program be large enough and include a sufficient number of reporting sources. It would appear to this survey that if expansion is planned, some of the considerations involved may include:

Full participation of the many "free" sources of information (Government-owned hospitals and clinics). Present participation by Public Health Service Hospitals has dwindled to practically nothing, and only one Veterans' Administration Hospital is enrolled (but has not reported in the past 3 months).

Improved indoctrination of new program participants. We note that a promising new service (23 Texas hospitals, reporting through Baylor University) is about to join the program. This participation generates from a speech of Commissioner Larrick. They wrote in voluntarily, and will be reporting without compensation. Our response has been to send information packets (see tab H), but it is our understanding that no one has visited the university to encourage the participation, or get the program off to a proper start. It would appear to this survey that if the present pattern of participation holds true to form, the enthusiasm of these hospitals could possibly slump and their reports dwindle after a modest start.

##### 16. *Reporting Procedures*

The FDA Adverse Reactions Reporting Program apparently suffers from the lack of an efficient administrative system to receive, utilize, and disseminate needed information on a volume basis.

It would appear that the internal processing requirement for ARRPs information lends itself to modern data processing systems capable of receiving, storing and distributing information quickly and efficiently.

The present requirement that participating hospitals submit a monthly listing of *all* reactions to drugs would seem of little real value.

The present report form for significant reactions (FD-BM-1) appears to be complicated and the subject of much objection by the participating hospitals.

##### 17. *Basis for Fee Payments*

In connection with fee payments for adverse reaction reporting contracts, two facts appear significant:

Some of the participating hospitals are receiving payments for simply informing FDA that they have had no significant adverse reaction incidents during the month.

Payments on a "per report" basis, with emphasis on the reporting of only significant reactions may be more attractive to the hospitals. Under this plan a hospital would be guaranteed a fair and reasonable fee for its efforts in working up information on a significant reaction and be eligible to receive the scheduled fee for each and every significant reaction reported during the month.

We would like to acknowledge the fact that adverse reaction reporting contract rates were the subject of much discussion in the recent DHEW internal audit of FDA. Questions were raised concerning the possibility of establishing guidelines which might be used in establishing these contract rates, and our factfinding reveals that a set of guidelines has been prepared and may be put into effect, possibly as early as December 1, 1962.

##### 18. *Impact of New Legislation*

Provisions of the Drug Amendments of 1962 which require drug manufacturers to accumulate and report information (including adverse reactions) to FDA should be considered in early planning actions:

It would seem that no preparation for handling this information has been made to date, and that the effort should be coordinated, with interested FDA personnel invited to explore the problem.



It would also seem that, irrespective of the point of eventual use (DND, DA, DMR), all of the new information should be routed through the present ARRP group so as to assure inclusion of the data in total considerations and objectives of the Adverse Reaction Reporting Program.

#### 19. Participation by FDA Operating Units

To date we have had practically no participation by the Field Districts in the program. It appears that this could amount to a serious failure, particularly when it seems that the program suffers from a lack of liaison with the reporting hospitals.

We note the infrequent referral of drug injury reports to the ARRP group from the Records Branch. We also note that responsibility has not been placed for summarizing chronologically filed letters and reports which trace the history of individual drug injury incidents in AF jackets. It would seem that, without this end product, ARRP does not get information which could facilitate the objective of the program.

#### 20. Need for Two-way Communication

It appears to be important that two-way communication be developed and maintained with participating hospitals.

This may be especially important to participants whose only compensation is by way of what we feed back to them.

Lack of communication may be responsible for the low quality of reporting complained of by the ARRP personnel interviewed during the survey.

It would seem to be essential that ARRP personnel periodically visit the participating hospitals and maintain the system. Dr. Esch has made only one field visit in 4 months; Dr. Millikin two trips in 7 months.

#### Exhibit C

##### Record of reactions reported

	Report form	Tab only	Total for month	Cumulative total
<i>1961</i>				
July.....	50	145	195	195
August.....	66	155	221	416
September.....	57	131	188	604
October.....	50	132	182	786
November.....	66	150	216	1,002
December.....	52	181	233	1,235
<i>1962</i>				
January.....	75	176	251	1,486
February.....	72	187	259	1,745
March.....	42	187	229	1,974
April.....	46	149	195	2,169
May.....	74	187	261	2,430
June.....	56	155	211	2,641

#### Exhibit G

##### Example of Successful Application

JULY 30, 1962.

To: John W. Nesbitt, M.D.

From: Albert F. Esch, M.D.

Subject: Referable to adverse reaction report received July 27, 1962 from the University of Michigan.

Subsequent to the receipt on July 27, 1962 of a telephone call from the University of Michigan Hospital pertaining to the recent drug reactions experienced with the use of Phytionadione ("Konakion Injectable"), the New Drug Application (#11-745) for this preparation was reviewed for possible references to similar occurrences.

Pharmacological studies included in a report dated December 3, 1958, from the manufacturer indicated that allergic responses were observed during toler-



ance studies using the drug in dogs. It was noted that similar allergic manifestations had been observed in dogs by previous workers following administration of Tween 20, but it was "demonstrated that the allergic response to Tween administration occurs only in the canine species." (This limitation was based upon data from a series of four hospitalized patients!) The manufacturer's report concluded that " \* \* \* results obtained in both animal and clinical studies indicate that a formulation containing 2 percent (and 4 percent) Tween 80 would be suitable for clinical use".

Supplemental reports of clinical investigators forwarded by the manufacturer on January 6, 1959, included a total series of 104 patients who had received the drug. One investigator within this total group noted side reactions in 2 of 20 patients. These reactions consisted of "dyspnea, severe backache" in one patient and "shortness of breath, visual disturbance" in the other.

ALBERT F. ESCH, M.D.

- COPY -

REPORT OF ADVERSE REACTION TO DRUG				BUDGET BUREAU NO. 57-R004.4 APPROVAL EXPIRES 12-31-63		Serial No. 13-81
1. Case No. 7-62-2	2. Name or initials S.S.	3. Address	4. Sex F	Color W	Age 22	
6. Admission Date 5 July 62	7. Discharge Date	8. Attending physician's name & address				
9. Particular ingredient(s) in drug preparation responsible for reaction (see generic or official name)  Vitamin K <i>Phytonadione</i>			20. Drug reaction Anaphylactoid Reaction (Air Hunger, back pain, cyanosis generalized petechial reaction)			Drug Group(s)
10. Trade name of drug preparation KONAKION			21. Laboratory findings relating to reaction, if pertinent			
11. Quantitative Composition (generic or official name of each ingredient) in drug preparation 2-methyl-3 phytyl 1, 4 naphthoquinone			22. Treatment of reaction 0.3 cc sq epinephrene SQ			Responsible Ingredient(s) (Generic or official) and Trade Name: PHYTONADIONE (VITAMIN K)  For FDA use only. Do Not write above this line.
12. Dosage form IV 15 mg			23. Outcome: Still under observation <input type="checkbox"/> No sequelae <input checked="" type="checkbox"/> Permanent injury <input type="checkbox"/>			
13. Manufacturer's name and address Roche Laboratories Nutley, N.J.			24. If reaction occurred prior to hospitalization, was drug taken under: Direction of physician? <input type="checkbox"/> self-medication? <input type="checkbox"/>			
14. Mr. Lot or Code No. 012-071713			15. Is remaining portion of drug available? Yes			
16. Condition for which suspected drug was administered Low prothrombin time			No follow-up <input type="checkbox"/> Date of death <input type="checkbox"/> Autopsy <input type="checkbox"/>			
17. Other pertinent medical conditions Systemic lymphoma			25. Factors contributing to reaction, e.g., drug adulterated, mislabeled, etc. (see Guide) Drug administered over 1 minute ie in excess of 5 mg/min.			
18. Dosage schedule: a. Amount, route and frequency of individual dose 15 mg IV  b. Total number of doses 1  c. Total amount given 15mg  d. Date of first dose 23 July 62  e. Date of onset of reaction 23 July 62  f. Interval between last dose and onset of reaction 30 - 60 seconds			26. History of previous exposure to suspected agent(s) None			
19. Concurrent drug therapy (including dosage schedule) Phenobarbital 30 mg qid (o)			27. Evaluation of case. Include mechanism of reaction (e.g., overdose, allergy, etc.) (see Guide) Probable idiosyncrasy			



- COPY -

REPORT OF ADVERSE REACTION TO DRUG					BUDGET BUREAU NO. 57-0004.4 APPROVAL EXPIRES 12-31-63		Serial No. 13-80
1. Case No. 7-62-1	2. Name or initials N.A.	3. Address	4. Sex F	Color W	Age 65	5. Occupation Housewife	Drug Group(s)  Responsible ingredient(s) (Generic or official name and Trade Name) PHYTONADIONE For FDA use only. Do Not write above this line.
6. Admission Date 28 June 62	7. Discharge Date 7 July 62	8. Attending physician's name & address					
9. Particular ingredient(s) in drug preparation responsible for reaction (use generic or official name) Vitamin K <i>Phytonadione</i>			20. Drug reaction Death, Shock, cardiac and Respiratory Arrest - (? Anaphylactic type reaction)				
10. Trade name of drug preparation KONAKION			21. Laboratory findings relating to reaction, if pertinent				
11. Quantitative Composition (generic or official name of each ingredient) in drug preparation 2-methyl-3 phytyl 1, 4-naphthoquinone			22. Treatment of reaction 1:1000 epinephrine Aramine revophed plus resuscitation measures				
12. Dosage form Parental			23. Outcome: Still under observation _____ No sequelae _____ Permanent injury _____				
13. Manufacturer's name and address Roche Laboratories Nutley, N.J.			24. If reaction occurred prior to hospitalization, was drug taken under: Direction of physician? <input type="checkbox"/> self-medication? <input type="checkbox"/>				
14. Mfr. Lot or Code No. 012-07171-B			15. Is remaining portion of drug available? Yes				
16. Condition for which suspected drug was administered Low prothrombin concentration ie under 109°			25. Factors contributing to reaction, e.g., drug adulterated, mislabeled, etc. (see Guide) Box labeled: For directions see circular. One circular for each box containing 25 individual boxed capsules, which was not sent to floor.				
17. Other pertinent medical conditions Possible recent and definite old myocardia infarction			26. History of previous exposure to suspected agent(s) Unknown				
18. Dosage schedule: a. Amount, route and frequency of individual dose 50 mg IV cr 5 cc directly and undiluted b. Total number of doses 1 c. Total amount given 50 mg d. Date of first dose 10:25p to 10:30p 7 July 62 e. Date of onset of reaction 10:32p 7 July 62 f. Interval between last dose and onset of reaction 2 minutes			27. Evaluation of case. Include mechanism of reaction (e.g., overdosage, allergy, etc.) (see Guide) Probable (idiosyncrasy to Vit. K)				
19. Concurrent drug therapy (including dosage schedule) Antazoline 10 mg q.d. Digitoxin 1 mg q.d. Caumadin 5 mg q.d. Phenobarbital 30 mg q. 8 h							

July 31, 1962.

To: DND.

From: DRR.

Subject: Two Anaphylactoid Reactions to Konakion.

Roche Laboratories, Nutley N.J.:

Copies of reports of two anaphylactoid reactions to the above drug, one causing death, are enclosed. These were submitted by a participant in the Adverse Reaction Program. We have received no other reports involving aqueous K<sub>1</sub> preparations.

Dr. Esch has reviewed the New Drug Application of the product and has outlined some pertinent data in the attached memorandum.

The labeling of this preparation does not mention the possibility of allergic reactions to I.V. use.

Please do not reveal the reporting source until we obtain permission.

JOHN W. NESBITT, M.D.



August 7, 1962.

NDA 11-745.

AF 14-324.

HOFFMANN-LAROCHE, INC.,  
324-424 Kingsland Rd.,  
Nutley 10, N.J.

GENTLEMEN: Reference to made to your NDA 11-745 for "Konakion Injectable, (Vitamin K<sub>1</sub>) (Phytonadione)."

We are requesting that you furnish us (as soon as possible) any and all information you may have received concerning toxicity and adverse effects of the drug since the New Drug Application became effective on January 10, 1959. We are particularly interested in severe acute reactions resulting in deaths or severe disabilities.

Sincerely yours,

JOHN O. NESTOR, M.D.,  
Medical Officer, Division of New Drugs, Bureau of Medicine.

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HOFFMANN-LAROCHE, INC.,  
Nutley, N.J.

August 15, 1962.

Re: NDA 11-745—Konakion Injectable (Vitamin K<sub>1</sub>) (Phytonadione U.S.P.).

DEPARTMENT OF HEALTH, EDUCATION AND WELFARE,  
Food and Drug Administration,  
Washington, D.C.

(Attention John O. Nestor, M.D.).

GENTLEMEN: In response to your letter of August 7, 1962, concerning the above product, we are attaching a review of all complaints since the application became effective. There have been no severe reactions reported, as you will note.

Sincerely yours,

ALBERT B. SCOTT, Ph. D.,  
Technical Coordinator, FDA Relations.

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August 24, 1962.

To: John D. Archer, M.D., Acting Director.

From: John O. Nestor, M.D., Medical Officer.

Subject: Adverse Reactions to Konakion.

Hoffman-LaRoche, Nutley, N.J., AF 14-324—NDA 11-745.

On July 27, 1962, a telephone report from the University of Michigan Hospital to our Adverse Reaction Program indicated two severe reactions to Konakion (Hoffmann-LaRoche) (NDA 11-745) one of which resulted in death. In each case the drug was administered intravenously as permitted under the labeling.

Dr. Albert F. Esch of the Adverse Reaction Program immediately reviewed the New Drug Application and noted that similar adverse reactions had occurred in both animals and man. This problem was referred to Division of New Drugs by Dr. John W. Nesbitt in a memo dated July 31, 1962. In a memo dated August 6, 1962, the problem was referred to me by Dr. Ralph Smith with the suggestion we inquire from the firm if they have received reports of any adverse reactions. This was done by a letter dated August 7, 1962. A reply dated August 15, 1962, arrived at Food and Drug Administration on August 16, 1962, and was returned to me on August 23, 1962.

This reply from Hoffmann-LaRoche indicated that they had received only three complaints. Two of these were local reactions following intramuscular injections and one was a severe reaction from intravenous use and similar to the ones reported from the University of Michigan Hospital.

The original New Drug Application was dated November 14, 1958, and stamped in on November 17, 1958. It consisted only of labeling, controls, and a letter from one medical investigator (Carl T. Javert, M.D.) stating that he had administered Konakion intravenously to 34 newborn infants without observing a reaction. Additional material submitted on December 4, 1958, included an additional statement from Dr. Carl T. Javert concerning 48 newborn infants who received two different vitamin K<sub>1</sub> products intramuscularly also supposedly without the occurrence of any adverse reactions. Also included were some animal studies. Dogs exhibited violent adverse reactions interpreted as allergic and associated with a



drop in blood pressure. It was concluded that this type of allergic response occurred only in canines and that it could be given safely to humans despite the fact that a monkey also had a similar reaction. There is no evidence that the New Drug Application was sent to pharmacology for review.

On December 12, 1958, the New Drug Application was declared conditionally effective despite the adverse reactions in animals and on the clinical basis that 82 infants received the drug without any adverse effects although not a single individual case history was included.

A supplemental application was then submitted on January 7, 1959, for Konakion injectable 10 mgm/cc a different dose form. This was supported by testimonial letter from 6 medical investigators and covering 104 cases none of which was supplied in the form of an adequate case history. It is significant that Dr. Javert administered the drug intravenously to 20 obstetrical patients and 2 of these had violent reactions similar to those reported from the University of Michigan Hospital.

This supplement was declared conditionally effective on February 9, 1959. Additional supplements primarily concerning labeling and controls were submitted. Finally on July 16, 1959, the New Drug Application was declared fully effective.

In view of the grossly inadequate and incomplete animal and human data in this New Drug Application and the seriousness and severity of the adverse reactions reported, immediate consideration should be given to action to take this drug off the market. This is particularly so in view of the article concerning the toxic effects of Tween 20 as reported in the *Journal of Pharmacology and Experimental Therapeutics*, vol. 93 No. 20, June 1948. This article points out that Tween 20 given intravenously produces transient depression responses of all species of laboratory animals (except the dog) in small doses. In dogs it produces a deep protracted fall in blood pressure. Larger doses produce coma and death in all animals. Since Konakion contains polysorbate 80 the serious implications are obvious.

It is recommended that the Bureau of Medicine review this problem and decide whether the drug should come off the market.

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*September 17, 1962.*

To: John O. Nestor, M.D.

From: John D. Archer, M.D.

Subject: Your memo of August 24, 1962, on Konakion.

Hoffmann-LaRoche, Nutley, N.J., AF 14-324—NDA 11-745.

I regret getting to this matter so late. I have looked into this subject somewhat, but far from completely. I do believe that further information will be necessary before we can make a well-founded decision on appropriate action. I know you are busy at present, but perhaps DRR could help in gathering some information.

In particular, I think we should know the risk inherent in treatment with drugs of this type in general in order to evaluate whether this particular dosage form is unduly hazardous. Also, do the recommendations made by the firm embrace only conditions that warrant some risk? Undoubtedly, the labeling should be required to give full and adequate disclosure of any risks involved.

Perhaps the Division of Pharmacology can offer comment on this particular dosage form, as opposed to other similar agents used for similar purposes.

Also pertinent would be whether the firm has issued any promotional material, either exaggerating the merits or minimizing the toxicity of Konakion.

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*September 27, 1962.*

To: Division of New Drugs. Attention: Dr. J. O. Nestor.

From: Dr. E. I. Goldenthal, Division of Pharmacology.

Subject: NDA 11-745—Konakion Injectable—Hoffmann-LaRoche Inc., Nutley, N.J. (AF 14 324).

We are somewhat at a loss to explain the observed reactions with this injectable vitamin K preparation. It seems a little surprising that both of these severe reactions to this preparation have been reported by the same physician, and that he is the only physician reporting these effects. It is possible that others may have observed this but have not reported these to the FDA or published their results. We should look into this and determine if any other



physicians have experienced these adverse reactions. In addition, it might be advisable to visit Dr. Saker to discuss this in more detail. Many injectable preparations contain Tween 80 in this same concentration and as far as I know there have been no reactions of this kind. It would be difficult to implicate any of the other components. It is possible that this particular batch of the preparation contained some unwanted ingredient which is responsible for these reactions. As this preparation is injected as a colloidal suspension in water, it is possible that on long standing or improper storage a change was produced in the suspension so that on injection an embolic rather than an anaphylactoid reaction was observed, at least in the first case. Would it be possible to obtain such samples? On reading over the adverse reports, it might be concluded that in the patient that died the injection was given quite rapidly, contrary to labeling direction. Dr. Saker makes no mention of this in his first report, but does specify the time in his second report. As it appears we are unable to determine the causative agent for these anaphylactoid reactions, it might be advisable to limit the administration of this preparation to the oral and intramuscular route.

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October 2, 1962.

To: Division of New Drugs—Dr. Nestor.

From: Division of Research and Reference.

Subject: Phytonadione ("Konakion")—NDA 11-745.

Roche Labs.,

Nutley, N.J.—AF 14-324.

Subsequent to reviewing the correspondence referable to the two recent anaphylactoid type reactions with the use of Konakion Injectable, a clarification of the reporting physician's participation appears to be necessary. Dr. Saker, who advised us of these reactions, is the representative for the Adverse Reaction Program at the University of Michigan Hospital and consequently forwards all reports from that hospital. He would not, therefore, necessarily have administered the medications in these instances.

With the addition of the case of "sensitivity type" reaction provided by Hoffmann-La Roche, Inc., to those from the University of Michigan and the two described by clinical investigators cited in the New Drug Application, we now know of five similar, significant reactions to this preparation.

In each case, the drug was given intravenously, but in most instances at an undetermined rate; suggesting the rate as a direct etiological factor. Since the type of surfactant included in this preparation has been shown to cause sensitivity reactions in animals and its safety in humans has been only questionably demonstrated, it would inherently appear to be a possible causative element in the above cases. The relatively minute proportion of material would not exclude its potential as an anaphylactic agent.

On the basis of the above facts and the product information in the New Drug Application (11-745), our suggested immediate remedial approach would be a modification of the existing brochure to emphatically state the jeopardous potentialities of intravenous administration of the preparation. A specific maximal rate of administration should be included as well as the warning that rare fatalities have occurred. The usual route of administration should be specified as intramuscular, with intravenous usage being limited to emergencies.

It was noted, however, that in the correspondence dated August 15, 1962, received by Dr. John O. Nestor from Hoffmann-La Roche, Inc., a new brochure issued January 1962 was enclosed, and some of the recommended changes had already been included. This more recent brochure does not appear to be included in the New Drug Application.

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ALBERT F. ESCH, M.D.

October 3, 1962.

NDA 11-745.

AF 14-324.

HOFFMANN-LA ROCHE, INC.,

Attention: Dr. Albert B. Scott,

324-424 Kingsland Road,

Nutley 10, N.J.

GENTLEMEN: Reference is made to your letter dated August 15, 1962, concerning Konakion Injectable (NDA 11-745) and our previous correspondence on this subject.



We are now aware of five severe and serious reactions to the administration of Konakion Injectable intravenously, one of which ended in death.

We suggest a revision of all your labeling pertaining to this product to emphasize more strongly the danger of intravenous administration and to include a warning that this type of reaction has occurred as a result of this method of administering the drug. The usual route of administration should be specified as intramuscular with intravenous use being limited to emergencies.

We also request that you notify us immediately of any similar adverse reactions that may come to your attention.

Sincerely yours,

JOHN O. NESTOR, M.D.,  
*Medical Officer, Division of New Drugs, Bureau of Medicine.*

HOFFMANN-LA ROCHE, INC.,  
*Nutley, N.J.*

October 18, 1962.

Re: NDA 11-745—Konakion Injectable.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,  
*Food and Drug Administration,*  
*Washington, D.C.*

Attention: John O. Nestor, M.D.

GENTLEMEN: This transmittal letter acknowledges receipt of your letter of October 4 regarding the above product.

We are suggesting changes in our literature, as indicated by Dr. Svenson in the enclosed letter.

Further adverse reactions will be reported without delay.

It would be helpful to us if we could be informed in more detail regarding the five serious reactions, as Dr. Svenson suggests in his enclosed letter.

Sincerely yours,

ALBERT B. SCOTT, Ph. D.,  
*Technical Coordinator, FDA Relations.*

HOFFMANN-LA ROCHE, INC.,  
*Nutley, N.J.*

October 18, 1962.

Re: NDA 11-745.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,  
*Food and Drug Administration,*  
*Washington, D.C.*

Attention: John O. Nestor, M.D.

GENTLEMEN: In response to your recent letter, we are glad to take steps to revise our labeling recommendations for Konakion Injectable.

We would like to offer the following suggested changes for your consideration and approval:

1. *Section—Dosage and Administration* currently reads:

"Konakion can be administered orally, intramuscularly or by *SLOW* intravenous injection (not more than 10 mg. per minute). Whenever rapid action is desirable, Konakion should be given by *SLOW* intravenous injection. The intramuscular route is recommended for patients in whom oral or intravenous administration is not feasible."

To be revised to:

"Konakion can be administered orally or intramuscularly. *Slow* intravenous injection (not more than 10 mg. per minute) should be reserved for emergency use where rapid action is desirable. The intramuscular route is recommended for patients in whom oral or intravenous administration is not feasible."

2. *Section—Caution* which reads as follows:

"Konakion is of value only when hemorrhagic tendencies are due to hypoprothrombinemia; it is not effective when heparin-like compounds have been used for anticoagulant therapy. Excessive doses of Konakion may cause temporary refractoriness to anticoagulants of the coumarin type; therefore, the minimum effective dose should be used in continuation of anticoagulant therapy is intended. When hypoprothrombinemia due to anti-



coagulant therapy results in severe hemorrhage, vitamin K<sub>1</sub> is not a substitute for the use of fresh whole-blood transfusions, but should be considered adjunctive therapy."

The opening sentence will be as follows:

"Serious reactions, including a fatality, have been reported to occasionally follow the intravenous administration of Konakion Injectable. The intravenous administration should, therefore, be reserved for emergency situations only."

The remainder of the Caution statement quoted above will remain unchanged.

We would very much appreciate the opportunity of reviewing the five cases of serious reactions that you mention since we apparently have not had them reported to us.

We hope that the suggested changes will meet with your approval, and we shall look forward to your advice.

Sincerely,

S. EVERT SVENSON, M.D.,  
Medical Director.

October 5, 1962.

MEMORANDUM OF MEETING

Between: Division of Hospitals, PHS:

Chief: Myron Miller, M.D.

Deputy: Linden Johnson, M.D.

Drs. Elliott and Dudley Miller.

Mr. George Archambault, Chief Pharmacist.

Miss Erickson, Medical Records.

And: John W. Nesbitt, M.D., DRR.

We met to discuss ways of improving their hospitals' cooperation in the Adverse Reaction Program. They did not realize how poor it has been. I showed them the figures for the last fiscal year.

Drs. Dudley Miller and Elliott had recently come in from the field and felt there were several reasons for the poor response. It has not been stressed enough that the names of patients and attending physicians are not required. They are concerned about possible medico-legal complications. Some think the form is "too complicated." They do not always realize that it is completed on only the possibly significant cases. The Pharmacy Committees may understand the program fairly well but the physicians on the wards actually know little about it.

They are in the process of getting up a new explanatory memo to all stations dealing with the program. They feel that if the ward nurses will complete the short alerting form or urge the physicians to do so, more reports will be obtained.

I explained the methods found useful at other hospitals and distributed new copies of the "Outline."

They will have their hospitals send a quarterly report to them on the number of reactions reported to us. We all felt that this would be a desirable feature.

I mentioned that we would try to visit their hospitals more often in behalf of the program now that we have some long sought help.

Appendix—Part 1

Schedule of Suggestions

Based on an appraisal of the factfinding data, the following suggestions are submitted for whatever value they may have to the Committee on Scientific Information.

(1) The FDA Adverse Reaction Reporting Program should be either improved or abandoned.

(2) Improvement of the program hinges primarily on a successful expansion of the level of participation so as to provide valid findings. We



believe such expansion can be best accomplished by enlisting full participation of Government-owned hospitals and clinics. This would not preclude participation by currently enrolled (or additional) teaching hospitals; however, it is our opinion that a well-organized Federal Hospital Chain should serve as the base for expansion to the needed level of participation.

(3) Procedures should be improved for the indoctrination of program participants.

(4) Drug reaction information should be received, stored, retrieved, and distributed through the utilization of modern data processing techniques.

(5) Present reporting procedures should be re-evaluated. Consideration should be given to—

(a) discontinuance of the monthly listings of *all* reactions to drugs. These listings seem of little real value.

(b) redesign of the present report form for significant reactions (FD-BM-1). Undoubtedly the form can be simplified, and questions which participating hospitals have found objectionable (such as names of patients and attending physicians) should be eliminated.

(6) Guidelines for determining adverse reaction reporting contracts fees should be adopted without delay. In this connection, consideration should be given to payment on a "per report" basis.

(7) Planning action should be initiated to provide for the handling of information which will generate from the requirements of the Drug Amendments of 1962.

(8) The role of the Field Districts in the Adverse Reactions Reporting Program should be appraised with the view of determining if the District Office can provide useful service to the program in a liaison and coordinating capacity.

(9) Responsibility should be placed to assure that all drug injury reports received at Headquarters for inclusion in AF jackets are referred to the appropriate personnel in the Division of Research and Reference for consideration.

(10) Two-way communication should be developed and maintained with participating hospitals.

(a) Information developed by the program should be promptly fed back to the participating hospitals.

(b) ARRP personnel should encourage and maintain the system through regularly scheduled visits to all participating hospitals.

(EDITOR'S NOTE.—The above is the final item in the reprint of the internal FDA report of November 30, 1962.)

February 15, 1963.

Arthur Ruskin, M.D.,<sup>24</sup> Acting Director, Division of New Drugs, Food and Drug Administration:

"Granted that we lead the world in medical and therapeutic advances, surely we must all take cognizance of the fact that iatrogenic diseases and therapeutic mishaps are making large inroads into our medical textbooks and into our hospital admissions."

*(Illustrative Letter Commending Program)*

March 8, 1963.

John P. Delaney, M.D., University of Minnesota Hospital:

DEAR SENATOR HUMPHREY: This is in reply to your letter regarding the Food and Drug Administration's Adverse Drug Reaction Reporting Program.

In my opinion the program is a well-conceived one. It provides a channel for reporting unusual reactions to the common pharmaceutical agents but, more important, a means for prompt collection of information on untoward effects of recently introduced drugs. Because the occurrence of serious reactions to new drugs is relatively uncommon, this program yields only sporadic concrete results. When serious reactions do occur, however, it seems very likely that they will be

<sup>24</sup> Transcript of Conference on the New Drug Law and Regulations, Drug Topics Publishing Co., p. 6.



reported in time to avert tragedies such as those caused by thalidomide in Europe.

The program might be improved with regard to disseminating information. Perhaps the American Medical Association would donate a space in its journal for periodic reports of significant drug reactions and for emergency reports when necessary. Information from sources other than the hospitals formally cooperating in the program could be obtained if the medical profession was made more aware of its existence and solicited to provide reports. Most doctors, I'm afraid, are unaware that a central office exists to collect and disseminate information on drug reactions.

Yours truly,

JOHN P. DELANEY, M.D.

March 12, 1963.

Forrest E. Linder,<sup>25</sup> Director, National Center for Health Statistics, U.S. Public Health Service:

PRESENT AND FUTURE SOURCES OF DATA ON THERAPEUTIC MISADVENTURES FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

The National Center for Health Statistics of the Public Health Service recognizes and appreciates the importance of reliable statistics on therapeutic misadventures in the administration of drugs and biologicals as well as in therapeutic misadventures from blood infusion and transfusion, in the administration of anesthesia and during surgical treatment.

Until the recent publication of "Persons Injured by Detailed Type and Class of Accident," Series B, No. 37, of Health Statistics from the U.S. National Health Survey, the only available figures on an annual basis came from mortality statistics. However, because of the method of disease classification employed (World Health Organization procedures), deaths are attributed to therapeutic misadventures only when no other morbid condition is reported. Consequently, the mortality statistics relating to this problem have been seriously deficient. Also, the International Classification of Diseases currently in use does not classify as therapeutic misadventure such occurrences as allergic reactions to drugs, accidental overdoses, or wrong drug given in error.

There are certain fundamental difficulties in collecting and compiling precise statistical information on the subject of therapeutic misadventures. One is the problem of defining events of this type in such a way that all untoward effects will be included. This is a special problem when dealing with lay respondents as in a health survey of the general population based on interviews. Another problem is that of securing complete reports of therapeutic misadventures on death certificates or on hospital records. The reluctance of medical practitioners to put on record all cases of therapeutic misadventures is understandable, especially if such action is regarded as a potential basis for litigation.

It is unlikely that satisfactory data on therapeutic misadventures can be obtained routinely without special effort. Even with intensive efforts, it would be difficult to determine the precision with which an estimate of the true problem of therapeutic misadventures can be made. However, the National Center for Health Statistics is seeking to improve the quality of both morbidity and mortality data in this area.

In the National Health Survey Division of the Center there is at present only one activity producing information bearing on the problem of therapeutic misadventures. This is the Health Interview Survey, a nationwide sampling and interviewing in about 40,000 different households each year. Among other things, this general-purpose health survey collects data on episodes of illness reported by the families which are of sufficient severity to have caused the sick person to seek medical care or restrict his usual activities for one or more days.

This survey is the source of the recent estimate of 1,368,000 cases of therapeutic misadventure per year in the 2-year period July 1959-June 1961. This estimate appeared in "Persons Injured by Detailed Type and Class of Accident," Series B, No. 37 of Health Statistics from the U.S. National Health Survey. (Therapeutic misadventures are classified as injuries in the International Statistical Classification of Diseases, Injuries, and Causes of Death.<sup>1</sup>)

<sup>25</sup> Letter to subcommittee in response to inquiry.

<sup>1</sup> Actually, this category includes both therapeutic misadventures and adverse reactions to preventive procedures, such as immunizations. (Footnote by Public Health Service.)



The report gave no details regarding the nature or circumstances of the therapeutic misadventures, and the text explained part of the reason for this.

Actually, the limitations of the Health Interview Survey as a source of reliable and detailed information on therapeutic misadventures are the following:

1. The relative rarity of these events (about 8 per 1,000 persons per year for all types combined) makes detailed classification unreliable, strictly from the standpoint of the size of the sample. The relative standard error of the estimate of 1,368,000 is approximately plus or minus 18 percent. For subcategories, the standard error would be higher.

2. The families can pass on to the interviewer only such information as has been given them by the physician who treated the case. To the extent that the physician does not know that the illness was the result of the preventive measure or treatment (or of an idiosyncrasy of the patient, as in the case of an allergy or drug) or, knowing of it, the physician does not pass on this information to the patient (or parent, in the case of a child)—to this extent, the cases will not be reported in the interview.

3. The reliability of the information reported in the interview is also limited by the education and medical knowledge of the members of the family. The Health Interview Survey is generally strong on the social effects of illness upon the family, such as disability, and can give a moderate amount of information on the nature of the illnesses reported, but it cannot be relied upon for detailed medical information. For such information, one must go to the medical sources themselves. (See below.)

4. The interviewer is not an expert on medical classification. Consequently, she cannot be expected to identify cases of therapeutic misadventure from the illness circumstances that have been reported by the family. Thus, the kinds of details one might wish to get about the circumstances of the event will not be obtained at the time of the interview. Once the results are in the office, however, it is possible for trained medical coding clerks to pick out the cases from the descriptions given by the family and assign them to the general group—"therapeutic misadventure."

For all these reasons, the National Health Survey has not attempted to exploit the data on this type of illness in any detail. It is believed that overdependence on the results of such analysis would detract rather than add to our knowledge of this important subject. On the other hand, the figure published, plus a certain amount of demographic detail, does serve to give an estimate of the general dimensions of the problem in the noninstitutional population of the United States. We believe this figure of 1,368,000 is probably an underestimate, for reasons covered in the numbered list above.

Recognizing that for many badly needed types of health statistical information it is necessary to go directly to the sources of medical, hospital, and nursing care, the National Health Survey is beginning to set underway some new projects under the general heading of the "Health Records Survey." At least one of these activities shows promise of adding to the current fund of quantitative knowledge on adverse reactions and therapeutic misadventures.

This activity will be known as the Hospital Discharge Survey. It is currently in a developmental stage. Funds have been requested in the fiscal year 1964 budget to undertake pilot data collection and will be requested in the fiscal year 1965 budget to establish a moderately sized national sample on a continuing basis. The sample, at least initially, will probably not be large enough to provide much detail on this kind of hospital admission.

In the Hospital Discharge Survey, a national sample of short-term hospitals will be selected, and the hospitals will be paid to make copies of records for a representative sample of discharged patients, including persons discharged dead as well as living. Such discharges number roughly 23 million per year, and from these it is hoped to draw a sample of about 50,000 discharges in the first full year of operation (fiscal year 1965) with a possible increase in the year following.

A considerable amount of diagnostic detail should be available on these hospital records, including, it appears reasonable to expect, such information on adverse reactions and therapeutic misadventures as the records contain.

It must be pointed out that even this added source for statistics has limitations:

- a. Only cases occurring in or treated by short-term hospitals will be included.
- b. It is not known at the present time how fully therapeutic misadventures are reported in hospital records. Again, the case must be recognized as a condition resulting from a preventive measure or treatment before it can be reported as such.



Nevertheless, this new source should provide more detail on the circumstances for the hospital cases in the form of national estimates on a year-by-year basis.

The general purpose of official mortality statistics is to present data on mortality from illness in the population. Therefore, if death results from treatment for a particular disease, the death is classified to the disease rather than to the therapeutic misadventure. Because of this procedure, mortality data on therapeutic misadventures is limited to deaths where only the adverse effects of treatment are mentioned.

There are two possible methods of obtaining figures on the number of times a drug reaction or drug use is mentioned on the death certificate by the certifying physicians as having some connection with the cause of death. The first is by examination of each record. Since this is a laborious process, plans are now being developed with the Bureau of Medicine of the Food and Drug Administration to scan a 10-percent sample of deaths reported for 1961 and 1962 in order to record statistical information for every death on which a drug or chemical is mentioned, but is not part of the underlying cause to which the death has already been assigned. A pilot study in which 3-month records were examined found about 200 such deaths in a sample of about 47,000.

The second method is to classify all information reported in the medical certification rather than the only underlying cause alone. Such a procedure was carried out for a sample of deaths occurring in 1955, after the initial coding of the underlying cause of death. As an example of the kind of data produced by this study, 115 deaths were assigned to "therapeutic misadventure in administration of drugs or biologicals" in 1955 as the underlying cause. When all conditions on the certificate were coded, there were an additional 798 deaths in which there was mention of therapeutic misadventure.

Provided additional funds are made available, the National Vital Statistics Division of the Center is now making plans to code all data on the medical certification beginning with the data year 1965. It is hoped to make this activity part of the regular annual mortality program.

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May 27, 1963.

American Medical Association: <sup>26</sup>

#### AMA COLLECTS DRUG REACTIONS

A Central Registry of Adverse Reactions to Drugs and Chemicals has been established by the American Medical Association to guide American physicians in prescribing drugs for patients.

The new Central Registry will be an important part of AMA's continuing program of service to the public by providing fast, up-to-date information about reactions to drugs, said Maxwell M. Wintrobe, M.D., chairman of the section on adverse drug reactions of AMA's Council on Drugs.

*Planned by Experts:* Thirty-five experts in all phases of adverse drug reaction studies completed plans for the three-point program:

To acquire information on possible reactions to drugs which had not been previously suspected and on serious reactions to any drug, even if these are already known.

To evaluate the reports of adverse reactions to drugs with the help of impartial experts.

To inform the profession promptly of the nature and significance of reactions to potentially toxic drugs and other agents.

The Central Registry is an outgrowth of AMA's Registry on Blood Dyscrasias, which has for several years collected, tabulated, and disseminated information on blood disorders caused by drugs.

"There is need for a Central Registry of Adverse Reactions to Drugs and Chemicals which is national in scope, since only a small percentage of significant drug reactions reach the professional journals. The vast number of medical journals in which early reports appear makes it difficult for the physician to be well informed in this area," said Dr. Wintrobe, who is head of the Dept. of Medicine at the U. of Utah.

*AMA Qualified:* "At present," Dr. Wintrobe explained, "unpublished reports of suspected untoward drug reactions are collected by many separate organizations. The AMA is uniquely suited to maintain a Central Registry. Impartial

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<sup>26</sup> AMA News, vol. 6, No. 11, pp. 1, 5.



expert evaluation of the data received is readily available to the AMA. The wide distribution of the Journal of the AMA and its other publications facilitates publicizing the program to encourage reporting, and disseminating information derived from the data collected."

The drug warning project will be directed by AMA's Council on Drugs. At the outset, seven small "study groups" of three to five experts each will guide the council. Medical specialists covered will be dermatology, gastroenterology, hematology, neurology and psychiatry, nephrology, and allergy.

*MD's Help Asked:* Physicians are asked to send reports of adverse reactions to the Central Registry at AMA headquarters where they will be screened and filed. If an important trend is noted, copies will be sent to members of the appropriate study group.

"All case reports will be tabulated periodically, together with those culled from professional journals. Tabulations, special reports and articles will be reviewed and approved by the Council on Drugs before publication," Dr. Wintrobe said.

The Central Registry is interested in reports of possible reactions to drugs which had not been previously suspected, serious reactions to any drug, and unusual reactions to drugs.

"It is not necessary that the patient be identified by name if other adequate identification is supplied," Dr. Wintrobe said. "We consider this information confidential and the name of the patient or reporting physician will not be revealed without consent."

June 5, 1963.

Pat Barnes,<sup>20a</sup> Drug News Weekly :

#### FDA TO INFORM MD'S DIRECTLY OF SIDE EFFECTS, WARNINGS

(By Pat Barnes)

WASHINGTON.—The Food and Drug Administration will approach the Nation's physicians directly with drug warnings, instead of relying solely on manufacturers' "dear doctor" letters.

The new policy went into effect last week with the dispatching of 243,000 letters warning of side effects and contraindications for topical corticosteroid preparations for ophthalmic use. The information was assembled by FDA's Bureau of Medicine. New and clarified points of information will be required in labeling and advertising of the products, FDA said.

By using the direct approach, FDA hopes to "help close the communication gap" on drug information, according to Assistant Commissioner Winton B. Rankin.

Asked if the agency plans to dispatch future drug warnings in permanent record form, Mr. Rankin said this has not been decided.

With such a reference source, physicians would not have to refer to the package insert.

Under the law, manufacturers must include in each package of drugs for retail sale the package insert, containing all pertinent information on the product. Theoretically, the pharmacist assembles these in a file to which he refers when consulted by the physician. This setup has been widely criticized as impractical and unrealistic. Senator Hubert Humphrey (Democrat, Minnesota) recently commented during FDA hearings that such pharmacist-physician consultation may be feasible in very small towns, but it is impossible in large urban areas.

Mr. Rankin said the package insert "has been of more value than people think," however. He referred specifically to the inclusion of the insert with drug samples distributed to physicians by detailmen.

In addition to getting drug information to physicians faster, the direct approach by FDA will preclude the duplication of warnings to physicians, Mr. Rankin said.

He noted that ophthalmic corticosteroid preparations are a good case in point since some 25 firms produce these products.

If physicians were to have received warning letters from all these manufacturers, the warning would have lost impact, he said.

FDA will leave warnings to the manufacturer in some cases, such as when a drug is manufactured by a single firm.

In a cover letter to the corticosteroid warning, FDA Commissioner George P. Larrick stated that "From time to time, the Food and Drug Administration,



individually or in cooperation with professional or industry groups, will issue statements of important drug developments from the standpoint of new and serious adverse reactions, warnings, and contraindications."

Mr. Larrick urged physicians to reciprocate by reporting any adverse drug reactions they observe to FDA.

The letter warned of possible increased intraocular pressure in patients using ophthalmic corticosteroid preparations and stated that these drugs have been known to cause perforation of the cornea when used in connection with cornea-thinning diseases.

FDA said the drugs are contraindicated in cases of fungal diseases or tuberculosis of the eye; acute herpes simplex, vaccinia, varicella "and most other viral diseases of the cornea and conjunctiva."

Also listed under contraindications was this carefully worded statement:

"Acute purulent untreated infections of the eye, which, like other diseases caused by microorganisms, may be masked or enhanced by the presence of the steroid. Purulent conjunctivitis and purulent blepharitis are not indications, but contraindications for topical steroid or steroid-antibiotic combinations.

"If conjunctivitis and blepharitis are listed as indications, they should be qualified as nonpurulent, not purulent."

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*(FDA Report Furnished to Subcommittee)*

June 11, 1963.

George P. Larrick, Commissioner of Food and Drugs:

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,  
FOOD AND DRUG ADMINISTRATION,  
Washington, D.C.

DEAR SENATOR HUMPHREY: As requested in your letter of May 24, 1963, we are transmitting a copy of the November 1962 report to the FDA Committee on Scientific Information on the Adverse Reaction Reporting Program, together with the committee's report of June 10, 1963, which supplements its December 1962 report.<sup>20b</sup>

As indicated in the committee report of June 10, we do need improvement in the Adverse Drug Reaction Reporting Program. We are also enclosing, because of its interest to your committee, a copy of our memorandum of June 11, 1963, instructing that steps be taken looking to improvement.

Sincerely yours,

GEO. P. LARRICK,  
Commissioner of Food and Drugs.

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June 10, 1963.

To: Mr. Geo. P. Larrick, Commissioner of Food and Drugs.

From: FDA Committee on Scientific Information; Chairman: O. L. Kline.

Subject: Adverse Drug Reaction Reporting Program.

In the report of the FDA Committee on Scientific Information of December 1962,<sup>20b</sup> it was stated that the committee was still studying the Adverse Drug Reaction Reporting Program currently operated by the Bureau of Medicine and that recommendations concerning this program would be submitted at a later date. The committee is now in position to offer specific suggestions and recommendations.

To develop basic information about the program, the committee requested that a survey be made. At its meeting late in November last year, it had for review a report prepared by Mr. Arthur Davis which contained information with respect to the hospitals taking part in the program, the kinds of reports received, and the manner in which the data were utilized. At that time it was apparent from statements to the committee from the director of the program that progress was being made, and that some improvement, not noted in the Davis report, was in evidence and more was to be anticipated in the coming months. In view of this anticipation, the committee thought it desirable to consider the new developments in its evaluation. In April of this year, after a period of nearly 5 months, the committee asked that a second survey be conducted. This has been accomplished and has now been considered by the committee.

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<sup>20b</sup> EDITOR'S NOTE.—For text of FDA report of December 1962 on Scientific Information, see exhibit 171, p. 1230.



The program began as an experiment to determine whether or not a hospital reporting system would provide useful and timely information with respect to adverse reactions of drugs. It was recognized that there were difficulties in establishing such program, that there were anticipated inhibitions in the process of reporting, and that there were problems in developing an interest and enthusiasm on the part of hospital staffs to provide this kind of information. The FDA staff to conduct this program has been small. Some indication of the feasibility of the program was needed to determine whether or not this or some alternative procedure would be most useful in the acquisition of drug information. We believe that the period of experimentation is past and that feasibility has been demonstrated. It is apparent that more effort needs to be directed to this program.

The more recent survey provided data with respect to the program up to April 30, 1963. In the 5 months' interim since the prior survey report there has been an important increase in the number of reporting sites that have been brought into the program. The increase from 78 to 189 sites derives principally from Government hospitals and a large proportion of these are the relatively small Indian Health hospitals maintained by the Public Health Service. Also, recently included in the program are a number of the large service hospitals which are in the class of "teaching" hospitals in which there is emphasis upon the use of new drugs and new medical treatments. With the anticipated inclusion of the veterans' hospital system the cross section of drug experience in Federal hospitals will be such as to provide data on drug reactions that will be of significant value to the FDA.

The budget provided for this program allows for contracting of private hospitals and payment for services in providing adverse reaction reports. The private hospitals in the program under contract number 22, and include some of the largest of the private hospital systems. The committee notes that the large proportion of reports received in this program have been developed in the hospitals under contract. It is further noted that a considerable proportion of the total reports received come from one such hospital—The Charity Hospital of New Orleans. For the present fiscal year, the budget for contract purposes has amounted to \$47,000, of which approximately \$25,000 has been used to date.

The committee expressed concern over the relatively small number of contracting hospitals in view of the pattern of reports that has been developed thus far. It is difficult to explain the lack of reporting from Federal hospitals in contrast to the nonfederal group reporting. The committee is aware that the approach to hospitals has been mainly by correspondence and it is quite possible that those responsible for the reporting program in the Federal hospitals are not fully aware of the need for or the significance of the information desired.

The committee is also concerned that the proportion of university associated hospitals recruited in the reporting program is not a better representation of the total. Of the approximately 200 academically associated hospitals, only a few are now under contract. It is apparent that a significant proportion of these teaching hospitals would provide an expansion that would give a much greater cross section and increased significance.

The committee recognizes the many difficulties in recruitment of hospitals. Reliance upon correspondence for this purpose may be insufficient. The development of personal relationships by visits of the program medical officers with hospital staffs may be needed in the recruitment effort. Careful attention to encourage and stimulate interest on the part of the hospital officials to whom the program is assigned will be profitable. With an explanation that emphasis should be placed upon the reporting of significant adverse reactions rather than all reactions, the amount of reporting may be kept within bounds and yet provide information about those incidents or accidents that will make for a successful program. It is urged that contact be made by personal visit, wherever possible, to develop interest among key persons.

#### *Recommendations*

The committee recommends that attention be given to the FDA staff needs of the program. In view of similar kinds of information to be received in the investigational drug program, it may be well to consider consolidating these two activities. The committee urges that attention be given to the recruitment of the university hospitals by whatever means that may be successful. This effort should contemplate and include personal visits at intervals that will encourage continued attention to the program. Sufficient budget should be provided to allow for expansion of the contracting group.



June 11, 1963.

To: Bureau of Medicine.

From: Geo. P. Larrick, Commissioner of Food and Drugs.

Subject: Adverse Drug Reaction Reporting Program.

We have reviewed the report dated June 10, 1963, from the chairman of the FDA Committee on Scientific Information with regard to the adverse drug reaction reporting program. It is apparent that we need to take steps to strengthen this reporting program.

Won't you undertake the following measures and let us have a progress report on their implementation within 30 days:

1. Have individuals responsible for the adverse reaction reporting program make personal contacts with those responsible for supplying reports from Federal hospitals to be sure that the other Federal agencies are fully aware of the need for and the significance of the information desired.

2. Have those responsible for our program intensify their recruitment efforts through personal contacts to arrange to have more academically associated hospitals come into the program.

3. Make a study of the staffing needs of the adverse reaction reporting program and the relationship between this program and the reporting of adverse reactions now required of prescription drug manufacturers by the Kefauver-Harris amendments to determine:

- a. Whether the staffing is adequate;

- b. Whether the two programs should be combined;

- c. And (whether or not they are combined) if planning for future handling of both programs is adequate.

4. Also, let us have your evaluation of the adequacy of present staff in the adverse reaction reporting program to accomplish the goals set forth for it. This should give attention particularly to the adequacy of the supervision now being exercised.

We are making provision in the fiscal year 1965 budget request to the Department for expansion of the number of contracting hospitals participating in this program.

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*(Another U.S. Agency's Program)*

June 14, 1963.

Joseph H. McNinch, M.D., Chief Medical Director, Veterans' Administration:

DEAR SENATOR HUMPHREY: A member of your subcommittee staff telephoned Mr. Trygstad recently to request information on any directive material regarding adverse drug reaction reporting which we may have sent to our hospitals since our last communication with you.

We are pleased to advise you that we now have developed procedures for reporting of adverse drug reactions by all Veterans' Administration hospitals and clinics, with provisions for exchanging summaries of such information with our field stations. The required procedure is now in the process of publication and is expected to be implemented by July 1, 1963.

We are enclosing a final draft of the material, along with a copy of the present section of our manual relating to committees on therapeutic agents, to which it will be added. You will note that references in the manual have been made previously to reporting and reviewing of adverse drug reactions by committees on therapeutic agents. We have marked these in red for your convenience in relating the new material to the existing requirements. We also are enclosing a copy of paragraph 201.02 of our manual on Investigation Policy which includes a requirement for immediate reporting of severe drug reactions. This, as Doctor Middleton mentioned to you previously, has been in effect for a number of years.

In addition to serving our own immediate purposes, we believe the new reporting procedure, when fully implemented, will lend itself to a more effective exchange of information with other organizations and agencies which you have been advocating.

Sincerely,

JOSEPH H. MCNINCH, M.D.  
Chief Medical Director.



(Warning Letter Issued on Drug Mentioned in FDA's Report of November 30, 1962 on Adverse Action Reporting<sup>20c</sup>)  
July 3, 1963.

Roche Laboratories:

NUTLEY, N.J.

DRUG WARNING LETTER

Re: Intravenous use of Konakion® (phytonadione) vitamin K<sub>1</sub> activity

DEAR DOCTOR: Konakion Injectable has been in general use in the United States since early 1959. It has recently come to our attention that five patients receiving Konakion (phytonadione) by intravenous administration experienced serious reactions including one fatality.

We are therefore advocating the elimination of the intravenous use of the product. In an emergency situation, such as actual hemorrhage, the treatment of first choice is the administration of whole blood or plasma. Konakion (phytonadione) may then be administered intramuscularly.

You are requested to submit to the company or the Food and Drug Administration reports of all side effects and all adverse reactions that you have encountered in your patients during or subsequent to the administration of Konakion (phytonadione) Injectable.

Sincerely,

ROBERT E. DIXON, M.D.,  
Director, Professional Services.

(Revised Package Insert)

See pages which follow.

<sup>20c</sup> See subsequent comment by Senator Humphrey, p. 1256.



# KONAKION<sup>®</sup> (phytonadione) Roche<sup>®</sup> INJECTABLE

## Vitamin K<sub>1</sub> Activity FOR INTRAMUSCULAR USE ONLY

**DESCRIPTION:** Konakion (phytonadione) contains as active substance synthetic vitamin K<sub>1</sub>, for intramuscular injection only.

**PROPERTIES:** Konakion (phytonadione) has the physiological activity of natural vitamin K. As a component of an enzyme system, vitamin K is intimately associated with the blood-clotting mechanism of the body through its essential role in the formation of prothrombin.

**ADVANTAGES:** In counteracting excessive hypoprothrombinemia during anticoagulant therapy, the superiority of phytonadione (vitamin K<sub>1</sub> activity) over the water-soluble vitamin-K preparations has been repeatedly demonstrated.

Konakion (phytonadione) is available in convenient low-dosage forms, designed to conform to the present trend toward lower doses in vitamin-K therapy. Parenteral Konakion



(phytonadione) is an exceptionally fine aqueous dispersion which can be administered intramuscularly. Its margin of safety is greater than that of vitamin-K analogs—especially in the prevention and treatment of neonatal hemorrhage.

**INDICATIONS:** Prevention and treatment of hypoprothrombinemia—hemorrhagic disorders of newborn infants, low prothrombin values incident to anticoagulant therapy of the coumarin type, obstructive jaundice, biliary surgery, hypoprothrombinemia due to inadequate absorption of vitamin K associated with prolonged diarrhea, inadequate intestinal synthesis of vitamin K incident to intensive antibiotic therapy or to large doses of salicylates, barbiturates or other prothrombin-depressing drugs.

Injection of Konakion (phytonadione) should be in the upper outer quadrant of the buttocks.

**DOSAGE:** *To prevent or control neonatal hemorrhage*—To the infant immediately after birth: 1 to 2 mg intramuscularly. Repeat dose if necessary.

*Anticoagulant antagonism*—To control excessively low prothrombin levels caused by coumarin-type therapy: 5 to 10 mg intramuscularly, initially; or up to 20 mg, if necessary.

*Prevention of excessive bleeding due to hypoprothrombinemia in surgical procedures* (biliary tract surgery, tonsillectomy and other operations in highly vascular areas, surgery on jaundiced patients or those receiving anticoagulant therapy): intramuscularly, 25 to 50 mg daily preopera-



tively (but not more than 25 mg in any one injection site).

*In hypoprothrombinemia due to other causes* (obstructive jaundice, impaired synthesis or absorption of vitamin K because of drug therapy or prolonged diarrhea, prothrombin depression by salicylates, barbiturates, etc.): 2 to 20 mg, the amount depending upon the severity of the situation.

**PRECAUTIONS:** It must be borne in mind that when hypoprothrombinemia due to anticoagulant therapy results in severe hemorrhage, no vitamin K<sub>1</sub> preparation is a substitute for the use of whole-blood transfusions, but should be considered adjunctive therapy. Konakion (phytonadione) is of value only when hemorrhagic tendencies are due to hypoprothrombinemia; it is not effective when heparin-like compounds have been used for anticoagulant therapy. Excessive doses of Konakion (phytonadione) may cause temporary refractoriness to anticoagulants of the coumarin type; therefore, the minimum effective dose should be used if continuation of anticoagulant therapy is intended.

In severe liver disease, Konakion (phytonadione) should be discontinued if no significant change in prothrombin time is observed in one or two days following the initial dose, since the vitamin may not be utilized.

**Note:** While Konakion (phytonadione) Injectable is an essentially clear aqueous dispersion, slight opalescence may occur in the 10-mg and 25-mg ampuls. However, this does not affect the potency, safety or usefulness of the preparation.



**HOW SUPPLIED:** Konakion (phytonadione) Injectable, 0.5-cc Ampuls, 1 mg/0.5 cc (boxes of 100). Each 0.5 cc of solution contains 1 mg phytonadione (vitamin K<sub>1</sub> activity) compounded with 10 mg polysorbate 80, 0.45% phenol as preservative, 10.4 mg propylene glycol, 0.17 mg sodium acetate and 0.00002 cc glacial acetic acid.

Konakion (phytonadione) Injectable, 1-cc Ampuls, 10 mg/cc (boxes of 12 and 100). Each 1 cc of solution contains 10 mg phytonadione (vitamin K<sub>1</sub> activity) compounded with 40 mg polysorbate 80, 20.7 mg propylene glycol, 0.8 mg sodium acetate and 0.00006 cc glacial acetic acid.

Konakion (phytonadione) Injectable, 2.5-cc Ampuls, 25 mg/2.5 cc (boxes of 6 and 25). Each 2.5 cc of solution contains 25 mg phytonadione (vitamin K<sub>1</sub> activity) compounded with 100 mg polysorbate 80, 51.8 mg propylene glycol, 2 mg sodium acetate and 0.0001 cc glacial acetic acid.

Licensed under U.S. Patent No. 2,417,299



*(Response to Subcommittee Inquiry)*

July 17, 1963.

T. J. Kirby, M.D.:

MAYO CLINIC,  
SECTION OF OPHTHALMOLOGY,  
Rochester, Minn.

DEAR SENATOR HUMPHREY:

\* \* \* \* \*

Your efforts to help make drug reactions and their evaluation readily available to the busy practitioner are greatly needed.

The idea of collecting and disseminating information regarding drug reactions encountered by the various medical departments of governmental services is good. The basic structure of organization and communication already is present but does need effective implementation. The vast amount of research being done within the governmental services today puts them in the forefront to see, record and report unusual reactions to drugs.

For the private or institutional investigator, several things would help:

1. Each clinical investigator who is to use a drug should have available all the pertinent animal experimentation data which has been accumulated by the drug manufacturer.

2. The investigator should know which man or men in the FDA are responsible for the decision concerning the drug and its eventual approval or disapproval for marketing. In this way the investigator could report his impressions, good or bad, simultaneously to the drug company and to a specific individual of the FDA. To be effective, this reporting should be as simple as possible, preferably in narrative form as a letter. The implementation of a specific governmental form immediately becomes a psychological block to most physicians.

3. The FDA officer or officers responsible for a specific drug should also know the name of each clinical investigator to whom the drug is released for study. It would be preferable that at least a correspondence acquaintance be established between the FDA officer and each clinical investigator.

4. The responsibility for tabulation and evaluation of the results of the investigations should still be the prerogative of the manufacturer. However, the FDA would automatically have all the same information for review if necessary before making a decision for marketing.

Adverse reactions occurring after the drug is on the market do need reporting in a manner that would reach all physicians. The usual "drug warning" letter is good but does not fit the entire need. Reports of difficulties with drugs often are buried in specialty journals, and the general physician may be unaware of a drug's potential danger under certain circumstances. The Journal of the American Medical Association reaches most physicians. Possibly this should be the main medium for reporting drug reactions. The various specialty journals would reach the remainder of the physicians.

What must be guarded against is the indiscriminate or hodge-podge reporting of drug reactions. We all are aware that a certain number of susceptible individuals will react unfavorably to drugs of proven worth and value. Also, for the sake of fairness and intellectual and scientific honesty, reporting of all drug reactions would be impractical and unwise. All that a patient complains of, or all that happens to him is not necessarily due to the drug he is taking. In many instances, a physician needs more than coincidental occurrence or an impression before he feels honestly capable of blaming a drug. In most instances he needs statistical proof to implicate a drug. Therefore, the delay in establishing reasonable proof is desirable. What might be improved, however, is the delay between the time a paper is ready to be presented and the time it can actually appear in a qualified journal. The mechanics of solving this problem fall into agreement between the FDA, the proper committee of the American Medical Association, and the various reputable medical journals.

I feel that a report of adverse drug reactions should fit the usual requirements of any other paper to be accepted by a reputable journal and that we should avoid the undesirable effects of undocumented reports being released to the press or to nonscientific journals. On the other hand, if the previous requirements have been met, the warning signal will have been flying within the FDA for some weeks or months, and appropriate action could be taken at as early a date as seems advisable.

These suggestions are some that have occurred to me. Your subcommittee and the FDA probably are far ahead of me with thinking along these lines. I



offer them as thoughts for discussion or consideration. Please feel free to call on me for any help that I can offer. You may use this letter in any way you wish.

Sincerely yours,

T. J. KIRBY, M.D.

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EXHIBIT 158

EXCERPTS FROM ADDITIONAL VIEWS AS REGARDS THE RELATIVE VALUE OR LACK OF VALUE OF THE "FLOOD" OF NEW DRUGS

On p. 1060 of his testimony, Dr. May referred to differences of opinion to the significance of a diminution in the number of new drugs. There follow excerpts of additional views on the subject.

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*January—February 1961.*<sup>27</sup>

Walter Modell, M.D.:

If the pharmaceutical chemists took the time to look at the net result of their prolificacy, would they be shocked to discover that the point of no return may have been passed? Do they suspect that now, instead of helping mankind with new drugs, they may be making matters worse? Will they realize that there is such a thing as too many drugs, that as matters stand there are too many drugs for the patient, for the physician, and, surprisingly enough, for the pharmaceutical industry? Although no one would suggest that they cease or even slow the pace of their search for useful drugs, if they are at all interested, I suggest that they do take the time to follow the effect of their creativity to its ultimate conclusion.

Five years ago, in an article entitled "Hazards of Modern Diagnosis and Therapy—The Price We Pay," Dr. David P. Barr pointed out that to the already staggering total of about 140,000 medicaments in current use, of which an estimated 90 percent did not exist 25 years previously and 75 percent had been introduced within 10 years, some 14,000 new ones had been added during the current year. Untoward reactions to medication have also increased at a staggering rate. This comes about primarily because of lack of experience with many different and entirely new active drugs and because of inability to master the full implications of these agents as rapidly as they are marketed and much less because of the unpredictable and unavoidable cases of hypersensitivity, which are relatively rare. Dr. Barr notes that on the medical service of one great hospital, 5 percent of the patients—one of every 20—were admitted as the result of "sanctioned and well-intentioned" use of drugs. One needs only to read Moser's *Diseases of Medical Progress* (what an ironic title!) to realize the dimensions of this danger; Friend and Hoskins point out that there are now 40 new diseases of this kind and that more are probably on the way.

As the number of new and active drugs increases and both knowledge and experience with each therefore become smaller and proportionately more difficult to obtain, not only is it a mathematic inevitability that drug reactions will also mount, but since more than a single factor is involved, it is also a certainty that the incidence of reactions will increase at an even faster rate than the rate at which new drugs emerge. Even now the situation is alarming; but the future looks dismal indeed.

If this was all a hazard inherent in medical progress, in the well-intentioned search for better treatment for mankind, there would be some justification for it, but too often this is not the case. Too often new drugs are not introduced for the only proper reasons: because there is a real or presumed need for them, because they are genuinely superior to those in current use. Too often they are turned loose on the public to horn in on a market which has been created by someone else's discovery, to compete with drugs which have recently been established as good and useful. Too often they are hurried into use to get in on a market before it vanishes. I know of a pharmaceutical company in possession of a series of congeners which kept what it deemed to be the best for its own use and licensed the inferior ones to other distributors, to be sold by them to the medical profession for use on patients. Thus, drugs are being marketed and promoted and advertised by precisely the same techniques used for soaps and detergents.

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<sup>27</sup> Editorial, "The Drug Explosion," *Clinical Pharmacology and Therapeutics*, vol. 2, No. 1, pp. 1-6.



A large proportion of claims for superiority for new drugs are patently invalid. But in addition, it is impossible that of the huge number of new drugs available, each one is the "best" for a separate medical indication. Thus for the approximately 45 different tranquilizers, the 30 different sedatives, the 18 different psychic energizers, the 25 different antihistamines, the 32 different antispasmodics, the 30 different diuretics on the market at this writing (and this census accounts only for different chemical entities and not different brands), each manufacturer claims his to be the best. Is each of the 150,000 preparations on the market the "best"? The best for what? The best for whom? There is a manufacturer who sells one drug entity in this country and a congener in another country, making precisely the same claims in each case: namely that each is the best for the same purpose. We are accustomed to this in soap advertisements, but drugs are not soaps. Since more than one drug cannot be the best, for the same indication, we simply don't have enough diseases to go around. At the moment the most helpful contribution is the new drug to counteract the untoward effects of other new drugs; we now have several of these.

It is too bad that the American Medical Association gave up the publication of that small and masterful book, *Useful Drugs*. It provided a good, unbiased formulary for everyone. This, or its equivalent, is one way of ensuring both safe and effective use of drugs as well as limiting their number through authoritative suggestion. Is it the only way? Perhaps not, but how else clarify the confusion created by excessive numbers of unproved new drugs promiscuously and prematurely introduced into the drug market? Of course there would be no confusion if the pharmaceutical industry saw the immorality in claiming a drug to be the best when a better drug was in fact available, if the sole criterion for the introduction of a drug was the good of the patient.

The situation is more serious now than it was 5 years ago when Dr. Barr pointed out that untoward reactions to drugs "could be regarded as one of the commonest conditions encountered." This is understandable. There are now more drugs; some are extremely potent and exert diffuse effects, others interfere with basic physiologic function; many are most unusual pharmacologically, hence poorly understood; many suffer from limited clinical trial; all are vigorously advertised. And, it seems, too many are used with little discrimination. In commenting on this situation in a lecture, "The Rational Era of Therapeutics," Dr. K. J. R. Wightman stated that if ever we were in danger of irrational and irresponsible behavior as therapeutists, it is now.

Are physicians characteristically irrational and irresponsible? No! But they may sometimes appear to be because of the sheer impossibility of dealing rationally and responsibly with so many new drugs about which so little is known but for which extravagant claims are made and for the use of which pressure is exerted by the drug industry and by patients who have heard of new cures through newspapers, magazines, and other patients. Vigorous drug promotion even before the drugs are available helps build up pressure to use them. It is beginning to look as if the success of a new drug will depend less on how well it works and more on how well it is promoted. This is why physicians are led to use drugs when the indications are lacking, to use drugs that are not the best available or even those which do not apply. It is because of this that the rate of serious drug reaction is mounting. And it is because physicians are not irresponsible that they may be expected to react with some violence to this ever mounting hazard.

That the situation gives every indication of worsening is suggested by the title of a paper on steroids, "How to Win at Structural Roulette." The pharmaceutical industry has had a prolonged winning streak at this game, but every winning streak ends sometime. Already it is abundantly clear that the medical profession is one of the losers. It is gradually giving over its initiative in choosing drugs for its patients to the detail man because it cannot deal with the plethora of new drugs expertly, safely, effectively. Obviously, the public is an even heavier loser.

What will happen when, as it eventually must, physicians refuse to gamble with their patients' lives and health or an enraged public demands that such gambling stop? Certainly the winning streak of the pharmaceutical industry will come to an abrupt end, but the rebound may well be excessive and may lead to unhealthy cynicism on the part of physicians and a state of therapeutic nihilism.

If the pendulum then swings as far in the other direction, as pendulums do, the medical profession will tend to lean more and more on the handful of proved, established drugs such as morphine, penicillin, and digitalis, about which it can



read substantial unbiased statements in textbooks, about which it will hear nothing from the detail man, and about which it will see nothing illustrated beautifully in drug house brochures, but on which it knows it can depend because of the accumulation of an enormous body of useful experience. And in this counterplay, surely important discoveries of our time will be overlooked and lost. How long before the public, medicine, and the drug industry are the losers to this type of general reaction?

What does the future hold if present practices continue? Twenty years ago the industry had already synthesized over 6,000 different sulfonamides; about a score or so were introduced and only about 15 are in current use. There is no census on barbiturate synthesis, but although only about 30 were marketed in this country and about 2 dozen remain with us, the total number the chemists created certainly ran into many thousands. Several years ago one pharmaceutical company revealed that in its own laboratories it had synthesized and screened 1,000 nonphenothiazine tranquilizers. Thus there is a formidable stockpile of new and untried drugs which could be unloaded with very little notice. The present legal restraints could not effectively stop it; yet if all the active drugs available were introduced at one time, the result would be chaos.

In the past, the pharmaceutical industry has shown admirable restraint, but such restraint no longer exists. That drugs could be introduced still more rapidly is only a relative concession; it may be slow in relation to the rate which is possible, but otherwise it is far too rapid for the medical profession to acquire the knowledge essential for safe, effective use. Excessive numbers of drugs are now being introduced—excessive in view of the working capacities of those competent to test their safety and utility in man, excessive in view of the subjects available for the testing of their effects, dangers and uses in man, and excessive in view of the ability of those who must assimilate the essential knowledge and learn how to prescribe them effectively and safely, rationally rather than routinely. This together with drug promotion and advertising, far more forceful than the comparative ignorance about them warrants, will lead just as inevitably to chaos, more insidiously perhaps than if all available new drugs were thrown on the market at one time, but the same chaos nonetheless.

If the therapeutic morbidity continues to rise, as it must under present conditions, it is clear that something will have to be done about it and this will be necessary if, as it gives every indication of doing, the pharmaceutical industry continues along its present lines. There is every reason to believe that the Government will step in in the interests of public health unless some better and effective program is established first.

Is governmental control the only answer? Is it naive to hope that, as a few industries have in the past, the pharmaceutical industry would undertake to control its own practices? It seems to me that such an unusual procedure is justified because the pharmaceutical industry is a unique industry and it cannot operate in the same way or with the same attitude to its consumer public as other industries do. It must be concerned with the welfare of its public, of the public in general. It must have a high moral standard.

It makes little difference if, under the impression that it is the best, a housewife buys the next best detergent. *But you may not fool any of the people any of the time about drugs!* For even the slightest deviation from fact may be vital; if, under the misapprehension that it is the best, a doctor prescribes something less than the best, it may be the difference between life and death. Unlike the housewife and her detergent, it is clearly immoral if the physician is even *slightly misled* by claims made for the drugs he is importuned to use on the sick. It matters to him, it certainly matters to the patient, and it should matter to the pharmaceutical industry. There is the very real ethical question of whether the pharmaceutical industry has the right to sell all the drugs it creates and whether it does not have the moral obligation to select only the elite of its creations for use in man. There is no room for presumption or supposition. The catalog of the drug industry must be a "blue ribbon" list. If industry takes the view that as a purveyor of chemicals it can put all of its products on the open market, it should act as proper chemical manufacturers do and should remove itself from the field of drug promotion, certainly from a biased program of medical education.

I do not believe that the pharmaceutical industry is Public Enemy Number One or that its collective attitude is *après moi le déluge*. The industry has done many wonderful things for medicine and for mankind. It is to be hoped that it will continue to do so. But insofar as its operations are intimately connected with



the life and health of the community, it has a moral obligation to the community which is in no wise lessened by its contributions of the past; perhaps the responsibility is even increased because of the precedents it has set. Unless it recognizes and acts on this aspect of its established function, does it not now stand in serious danger of having to give over its initiative as well as its controls to the Government?

What can the pharmaceutical industry do? It seems to me that it can do a great deal. And it seems to me that it can do it more efficiently through its own devices than through any other agency, academic or governmental. Industry should undertake to control its practices. This would not be quixotic but, in my opinion, genuinely practical, really realistic. It should plan broadly for the effective screening of the drugs it synthesizes and terminate the current practice of the hurried introduction of new drugs in order to establish a foothold on the market while leaving the real testing of drugs in the hands of practicing physicians with patients as unwitting subjects. Industry should undertake to limit the number of congeners of a single drug on the drug market to some practical number, to the two or three or four shown to be the best in industry's own grand clinical trials. Such a system would insure a uniform high standard of preliminary investigation of new drugs.

While today most companies conduct careful and thorough explorations of new drug actions and toxicity in the laboratory as well as careful preliminary trials in the hands of experts before the drugs are marketed or even distributed for trial in the hands of clinicians, there are a few who, at a considerable savings in dollars and, often more important to them, a saving in time, put new drugs into circulation with the flimsiest minimum of preparatory work in order to inch in quickly on markets established by others. This inequity and immorality would be ended. To do this fairly as well as effectively, industry must arrange for cross-licensing so that companies which are not the patent holders of the drugs selected for general use can also distribute them and, therefore, will not lose all if their congeners are not chosen.

If clinical trials were carried out on a grand scale with an entire group of drugs examined in a coordinated program at one time instead of the present shortsighted system in which closely related drugs are examined separately and are not adequately compared, the truth about the group as a whole as well as the relative merits of its members would emerge much more promptly. Not only would the therapeutic morbidity rate fall but, perhaps even more important, since only the best drugs in each group would be available, patients would not be deprived of the best drug for their illnesses. A half dozen well chosen antihistamines would serve everyone's needs far better than the present 25. The market would not be cluttered with near duplications for which the most conflicting claims are made. There would be more knowledge and more knowledgeable medical discussion and far less hucksterish mumbo jumbo about drugs. The Tower of Babel of drug names would collapse.

Can there be any doubt that under such a system the public and the medical profession would benefit? What about the pharmaceutical industry and its stockholders? If the medical profession merely continues to use drugs when they are needed, it will obviously not prescribe less after the inauguration of such a system than it does now. It is possible that it might prescribe even more because it would feel more secure; physicians might exploit drugs more fully, using more effective dosage. There might well be fewer token prescriptions given because of patient demands for the latest in drug development. If the industry manufactures larger amounts of smaller numbers of stable drugs, production costs should fall. Furthermore, if there are fewer drugs, more brands of the same drugs rather than more different drug entities, the very costly system of detail men and the enormously expensive and elaborate brochures which routinely stuff our mail boxes and monotonously extol the virtues of their principals should take no more of the pharmaceutical manufacturer's dollar than they are really worth.

Would not the discovery of new drugs pay off even better than now, since new drugs would be more firmly established by this system? Since their effective lives would be longer, their use through cross-licensing would be more extensive and the income to the discoverer through royalties should be greater. Would not the savings in drug production and distribution be enormous in such a system? Would there not be greater profits to industry as well as lower cost to the consumer? In this connection, it is suggestive that even now, of all the leaders in the field of pharmaceutical manufacture, one of the most successful (if not the



most successful) of all American pharmaceutical companies from the point of view of gross profits introduces the smallest number of new drugs for a company of its magnitude and indulges in virtually no molecule manipulation as the means of encroaching on markets established through the original research of other manufacturers. Those who follow such a system may therefore have larger profits as well as clearer corporate consciences. In addition, "the most ethical of the ethical companies" will not be forced by competition, as the *New England Journal of Medicine* points out they now are, to "meet the tactics of the least ethical."

It seems to me that the only segment of industry which may not wish to participate in an arrangement along the lines proposed because it cannot possibly profit by it is that small marginal portion which (1) has nothing to contribute to a cross-licensing system and (2) is interested only in seeing that its own product, rather than the best medication for the patient, is used in each instance. Since the organized industry will have gained such a high order of confidence of the medical profession and the public at large, should any firms refuse to participate, would they be able to compete with those who do? This system would serve to separate and distinguish in the ethical drug industry the ethical and the really ethical.

Because of coordination and increase in efficiency, the trials on humans could be more carefully and safely conducted. Because there would be far less waste of that invaluable commodity, the human subject, the clinical investigator would have much less trouble getting adequate clinical material for his needs and would be able to conduct more satisfactory clinical trials. Because this arrangement would eliminate much duplication and overlapping, that even rarer commodity, the expert clinical investigator, would be better able to deal with the heavy load provided for him by the new drugs. Finally, because clinical trials would be planned on a broad base, far less time and money should be wasted in preliminary trials before new drugs could be safely and properly marketed, and as a result there should be less delay in the safe use of new drugs.

It seems to me that advertising would continue at its present pace but would have to change from product promotion to institution promotion. Brand names would take on much more meaning because drugs would at once be identified with their distributor. The type of competition this would engender should lead to the highest standards in drug manufacture. It would no longer be essential for industry to educate (sic) the physician about drugs. Postgraduate medical education would return where it properly belongs, to the aegis of academic institutions, accredited medical journals, and medical societies.

Research in industry would continue at its present pace; new drugs will always be needed. But under such a system, those drugs which reach the market would be used without reluctance and cynicism because faith in industry's claims for drugs would be reestablished. Since structural roulette would be restricted to the search for better drugs and not used to circumvent patent rights, research in industry would become far more meaningful than it presently is.

There can be no question: The medical profession's gain would be enormous. Because there would be fewer drugs in use, there would be a much larger overall experience with each and more information about the unusual as well as the more common drug actions, about hypersensitivity, toxicity, synergism, incompatibility, and treatment of poisoning, of tolerance and addiction, and of use in refractory cases. Because the drug companies would be selling the same drugs, there would be few conflicting claims about their actions and effects, thus far less confusion. As the result of more knowledge and greater confidence, the physician would use his medicaments with greater assurance and exploit drugs to the greater good of his patients.

Will the patient benefit? How can the patient fail to benefit? Only the best drugs would be available. This is, of course, the most important consideration, but there are ancillary benefits as well. \* \* \*



*(Canadian Comment)**October 11, 1962.*

J. G. Aldous,<sup>27a</sup> Professor of Pharmacology, Dalhousie University, Halifax, N.S. and approved by the Faculty of Medicine, for Special Committee of the Association of Canadian Medical Colleges:

Pp. 3-4

We are ultimately concerned with the safety of drugs used in human subjects; and here the problem is the number of drugs of a given type which are available. It would seem to follow that if the clinical evaluation of the efficacy of a drug were properly carried out, fewer drugs of any one type would be available to the physician for use on his patients. What the medical profession needs is better drugs—not more drugs. Thus, if clinical screening for efficacy were more rigidly controlled, there would be fewer poor drugs on the market; and fewer drugs on the market would lessen the potentialities for therapeutic poisoning.

Walter Modell has emphasized this point in an article entitled "The Drug Explosion" (*Clin. Pharmacol. and Therap.*, vol. 2, p. 1, 1961).

*April 11, 1963.*

New England Journal of Medicine: <sup>28</sup>

## FEWER NEW DRUGS IN 1962

A year ago the signs of leanness evident in the introduction of new therapeutic agents was discussed in these columns with passing reference to the situation anticipated by Joseph when he cannily interpreted Pharaoh's dream. Now, according to Paul de Haen, who stands in somewhat similar relation to the pharmaceutical industry, another and still leaner year for the introduction of new products can be chalked up. No predictions for the next 5 years are yet available, although it is said that history often repeats itself.

Total new products introduced nationally have fallen to 255 for the year, from 265 in 1961 and from a high point of 403 in 1955; new single products have dropped to a significant low of 28, from 41 in 1961, 45 in 1960, and a high of 63 in 1959. Perhaps 3 of the 7 lean years have already passed, and barring any drastic moves by Congress in the next 4 years, the industry will survive, possibly in better condition for a wholesome loss of fat.

To bear out such an assumption, Mr. de Haen suggests that the trend toward fewer product failures and the absence of high introductory costs has offset an increase in research expenses and a necessary reduction in the price of some products. He further suggests that "new knowledge and the development of significant therapeutic advances cannot be kept from fruition." There is comfort in the thought that truth, like murder, will out. Like the Persian messengers mentioned by Herodotus, unstayed by adverse weather, the addition of truly valuable items to the physician's armamentarium will not be prevented even by the passage of overreaching legislation. It is interesting, nevertheless, that 48 percent of the new drugs introduced in 1962 were developed abroad. Any loss of aggressiveness in the development of new products in this country may, on this segment of the New Frontier, represent fear of the unknown; it may also be considered as not unwholesome.

It is regrettable that reliable published data are not always available when a new drug is put on the market, so that the prescribing physician may have really accurate information about it. This situation is difficult but should not be impossible to remedy. Moreover, in Mr. de Haen's opinion, the trial to which modern therapeutics and the pharmaceutical industry have been subjected in the past 2 years cannot be successfully concluded until a closer understanding between manufacturer and consumer or prescriber of drugs comes into existence. "Manufacturers," he writes, "must endeavor to provide more comprehensive and useful information for the use of drugs based on adequate clinical research, and physicians must learn to realize that the use of potent modern drugs requires great care and circumspection."

<sup>27a</sup> A Submission to the Royal College Committee, op. cit., C. B. Stewart, M.D., President, The Association of Canadian Medical Colleges, Office of the Dean of Medicine, Dalhousie University, Halifax, N.S., app. 21.

<sup>28</sup> Editorial, vol. 268, No. 15, p. 846.



Moreover, adverse reports on the action of drugs must be presented with the same objectivity that should be employed when the tests are apparently favorable.

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(Interview)

August 16, 1963.

George Larrick, Commissioner, Food and Drug Administration.<sup>28a</sup>

Mr. Larrick enters a vigorous defense of FDA actions in its recent relations with industry, including the hotly controversial regulations governing clinical testing of drugs.

"Our critics should remember that, despite our growing research capability, we remain essentially an enforcement agency, and what we must enforce is the law.

"If people are unhappy with the law, they should direct their protests to Congress and not the FDA."

Against charges by the Pharmaceutical Manufacturers Association and others that the regulations go beyond the intent of the law, Mr. Larrick holds that the regulations were put into effect only after the most extensive consultation with industry and researchers and after careful review of comments and petitions.

"But if we are wrong, we can change the regulations at any time by democratic processes," he said. "Besides, any action we take is subject to review by the courts."

Question. Do you believe medical research will be hampered by the new regulations?

Answer. No. The present decade will see even greater expansion of medical and pharmaceutical research. It will see the application of new, more efficient techniques to deal with chronic as well as infectious processes. Any slowdown in research will not be because of the new regulations but may be because of voluntary actions by industry.

Question. How about the 1,000 or so drugs that have been withdrawn from investigational use by manufacturers rather than go through the red tape required by the regulations?

Answer. There is no evidence that the health of the American people will be harmed by such withdrawals. Numbers mean little. The important thing is the quality, safety and efficacy of the drugs, not quantity. Many of the drugs that were withdrawn were in an early stage of development.

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EXHIBIT 159

1955 AND 1956 EDITORIALS IN JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION  
ON CHANGES IN POLICIES OF THE AMA COUNCIL ON DRUGS

There follow the texts of two editorials which appeared in the Journal of the American Medical Association as regards policy changes involving the Council on Drugs. The initial editorial appeared in the February 19, 1955, issue (vol. 157, No. 8, pp. 664-665). The second editorial appeared in the June 2, 1956, issue (vol. 161, No. 5, p. 460).

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AMA COUNCILS EXPAND THEIR PROGRAMS

For many years, the evaluating councils of the American Medical Association have provided leadership in the evaluation of products used by physicians and to some extent by the public. The Council on Pharmacy and Chemistry since 1905 has evaluated drugs and reported to the medical profession on these and related therapeutic procedures. The Council on Physical Medicine and Rehabilitation, formerly the Council on Physical Therapy, has been developing information on therapeutic and diagnostic devices since 1925. The Council on Foods and Nutrition since 1929 has evaluated nutritional claims and food products. The newer Committee on Cosmetics has been in existence since 1948.

The AMA's product evaluating councils have awarded seals to manufacturers and distributors of drugs, foods, devices, and cosmetics that have complied with

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<sup>28a</sup> "FDA: A Time of Crisis—Growth Patterns Cause Problems, Larrick Believes," Medical Tribune, vol. 4, No. 65, p. 16.



the rules for such acceptance. Over the years the councils have become well known for this phase of their activities, in fact, probably better known for this work than for their other never-ceasing efforts in the broader educational aspects of collecting, digesting, and disseminating medical information. Their work has been diversified, but the seal or acceptance program has appeared to dominate because of the dramatic effect of and the prominence given to such a program. Also, it has been so time consuming that there has been too little time left for attention to other important work. In addition to the seals of the councils, there has been made available an advertising emblem for products that have not fallen within the scope of a council. Thus, the public has become familiar with the statements "Accepted for advertising in the publications of the American Medical Association" and "Accepted for advertising in *Today's Health*." Often these statements have been displayed in the form of an emblem. This too has been part of the "acceptance" program of the American Medical Association.

For months the councils of the American Medical Association and the board of trustees have been studying ways and means by which the association can increase its service to the public and the medical profession. While many avenues for pursuit were explored, there were always the limiting factors of time, personnel, and money to be considered. One of the programs seemingly in greatest demand by the profession is one that calls for more information on the more recent advances in health problems. Various devices introduced in recent years have posed questions for true usefulness; new drugs have raised problems concerning their proper use and possible toxicity; cosmetic-type preparations have become complicated by the introduction of synthetically prepared ingredients; and nutrition, although long studied, has many phases in need of study and report. To meet the demand caused by the tremendously and broadly expanding horizon in diagnostic, curative, and preventive medicine is a problem of no small dimensions. Therefore, the board of trustees and the councils have decided to spend more time on this important phase of their work and to increase this work to match the need. The so-called acceptance program has been useful and helpful, but the need for it has become much less as laws have been enacted and as manufacturers have assumed more and more their share of responsibility in marketing worth-while products.

As of now, the issuance of seals or emblems by any part of the American Medical Association is discontinued. Obviously the seals may be seen for some time, as advertising material already printed is used. But it is only a matter of time before an "AMA seal" is a thing of the past.

What will the programs of the councils provide to be of more service to the public and the profession? It is impossible to describe in a few words all of the ways in which the councils will conduct their expanded programs. Briefly, however, they can be summed up by stating that these bodies will issue reports promptly and frequently on what is new in diagnostic, curative, and preventive medicine in the respective fields of the councils; they will periodically review the status of agents and techniques; they will develop basic standards for classes of goods as, for example, the Council on Physical Medicine and Rehabilitation long has done for resuscitators and inhalators; and they will undertake educational efforts to insure as much as possible the utilization of the information they gather, digest, and evaluate. This information will be made available regularly in the *Journal*. It will be gathered from various sources, including manufacturers, researchers, and published medical literature. In addition, the councils will continue to issue books or booklets in which such information can be brought together handily and usefully.

There may be some who wonder if the advertising standards for the publications of the American Medical Association will be lowered by the change in emphasis in the council's programs. All readers of the *Journal* can be assured that careful scrutiny will be continued for items for the advertising pages. While the long-familiar seal will not be seen, basic principles will continue in effect. Advertisements that by either intent or inference would result in deceiving, defrauding, or misleading the reader are not suited to AMA publications; nor are sweeping superlatives and unfair comparisons. Any claims for superiority of a product will have to be supported by acceptable evidence. Disparagement of competitor's goods will be discouraged. Quotations or excerpts from published papers will not be accepted if by themselves they distort the true meaning intended by the authors. These and other desirable principles will guide those who are responsible for the acceptance of advertising for the publications of the American Medical Association, so that the best interests of the



members of the association can be served. All of the publications are published under the direction of the board of trustees, and its members are responsible to the house of delegates of the association. In due time the councils are expected to issue statements on their programs, and at the same time details on the principles of advertising for AMA publications will be available.

An exciting challenge today faces all of medicine because of the swiftly moving pace of medical knowledge and the eagerness with which physicians and the public too, await it. With their long years of experience the councils of the American Medical Association are in a unique position to provide the leadership required. They are to be commended for their prompt response to the challenge. Both doctors and patients will benefit from it.

#### THE NEW N.N.R.

The 1956 edition of *New and Nonofficial Remedies*, just off the press of the J. B. Lippincott Co., reflects an important change in the scope of information that is to be included in this well-known annual publication of the AMA Council on Pharmacy and Chemistry. The new edition implements for the first time in book form the revised program for evaluation of drugs that the council instituted during 1955 to render a better service to the medical profession.<sup>1</sup> Under its revised method of operation, the Council issues monograph statements on all individually available new drugs on the basis of currently available evidence, whether or not such information is adequate at the time to determine their ultimate importance or usefulness in medicine. Wherever possible, attempts also are made to compare or show the relationship of new drugs to older and well-established drugs. Accordingly the N.N.R. section of the council's column of the *Journal* and the book, both of which formerly were restricted to descriptions of relatively well-established drugs, now provide more complete coverage of current information on drug therapy. The N.N.R. section of the council's column of the *Journal* also has been made more newsworthy to physicians by publication of supplemental statements concerning evaluated new uses, routes of administration, or significant changes in the therapeutic status of previously evaluated drugs. This added feature of the N.N.R. section of the *Journal* replaces the former procedure of listing commercial dosage forms and sizes. *New and Nonofficial Remedies*, in both column and book form, thus has become a more complete source of clinical information on individual drugs and excludes technical information respecting pharmaceutical dosage forms or sizes. The time saved by the elimination of product information amply provided by pharmaceutical concerns has made it possible for the council to evaluate the evidence for many more drugs than was possible under its former procedure. The 1956 edition of N.N.R. contains 58 new monographs on drugs not described in the previous edition.

*New and Nonofficial Remedies* continues to describe drugs under suitable nonproprietary terminology and to include both proprietary and nonproprietary names for the various commercial preparations of individual drugs concerning which the council is informed.<sup>2</sup> Names of commercial preparations (exclusive of dosage form terminology) are listed as a matter of information in conjunction with monographs and in the index of the book without the name of the manufacturer or distributor. The listing of such names no longer is restricted to those complying with the principles used in selecting nonproprietary (generic) names, so that physicians who may be unfamiliar with this terminology can more readily identify preparations by one or more of the names under which they are marketed. Future editions of N.N.R. will include additional names as the council is informed of their applicability to preparations for use of individual drugs as described in the publication.

Evaluation of ready-prepared mixtures of drugs for monograph description in N.N.R. has been discontinued to enable the council to concentrate its primary effort on the evaluation of available evidence pertaining to the actions, uses, dosage, hazards, and other pertinent properties of individual drugs. Publication of timely information on each new compound should make it easier for the

<sup>1</sup> New Program of Operation for Evaluation of Drugs, statement of the Council on Pharmacy and Chemistry, *JAMA* 158: 1170-1171 July 30, 1955.

<sup>2</sup> Listing of Trade Names, statement of the Council on Pharmacy and Chemistry, *JAMA* 160: 50 Jan. 7, 1956. (JAMA footnotes.)



physician to judge which combinations are best suited for the individual patient on the basis of the council's evaluation of separately available component drugs.

Physicians and other users of New and Nonofficial Remedies should realize that this publication has ceased to function as a book that describes only selected or well-established drugs. By publishing monograph statements for inclusion in N.N.R. concerning any and all new drugs (exclusive of mixtures) at the earliest opportunity, the council seeks to provide more comprehensive and up-to-date information on the basis of which physicians may exercise their own clinical judgment in the selection of therapy for patients. The council believes that this approach to the dissemination of unbiased information on new drugs will better enable both physicians and medical students to keep abreast of developments in the rapidly expanding field of therapeutics.

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#### EXHIBIT 160

#### MEDICAL AND OTHER KEY SCIENTIFIC POSTS IN THE FOOD AND DRUG ADMINISTRATION: OFFICIAL AGENCY COMMENTS AND EXCERPTS OF COMMENTS FROM OTHER SOURCES

On p. 1035 of his testimony, Dr. Charles D. May referred to issues of scientific personnel in the Food and Drug Administration. The present exhibit is devoted to this subject. It consists of (a) a letter from the director of personnel of the Department of Health, Education, and Welfare, and (b) a reply from the Food and Drug Administration to an inquiry as to employee turnover in 4 key posts, including comments as to the problem of levels of compensation in recruitment of medical personnel. Thereafter, in chronological order appear several articles from the trade and general press on the same general subject. The articles are submitted for illustrative purposes as to news and views which have appeared from time to time. In addition, there are reprinted pertinent excerpts from reports by the first and second Citizens Advisory Committees on the Food and Drug Administration.

The first article consists of a trade press article on comments submitted before a joint meeting of the Senate and House Government Operations Committees 10 years ago.

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#### *(Agency Comments in Response to Subcommittee Inquiries)*

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,  
November 30, 1962.

MRS. EMMA ABBOTT,  
Office of Senator Hubert H. Humphrey,  
U.S. Senate, Washington, D.C.

DEAR MRS. ABBOTT: This is in response to your telephone call asking about the distribution of supergrade spaces in this Department, especially with respect to scientific positions. I think the following will give you the picture.

The Civil Service Commission has allotted the Department approximately 80 supergrade spaces. These spaces are more or less evenly distributed according to size and mission among our five principal operating agencies: the Social Security Administration, the Food and Drug Administration, the Office of Education, the Public Health Service, and the Office of Vocational Rehabilitation. St. Elizabeths Hospital has also been allotted a few of these spaces. A very small percentage of positions, perhaps half a dozen, have been warranting supergrades in the scientific fields. This has not been too much of a handicap, however, for the following reasons.

First, in the majority of situations where scientific work is done, the supergrade spaces have been assigned to the officials having responsibility for program management, and these people, by and large, are not practicing scientists, but administrators.

Secondly, and more importantly, we have had other methods of recognizing the need to pay top scientific skills salaries commensurate with their contributions and to offer attractive salaries to scientists whom we wish to recruit. The first of these is section 208(g), of the Public Health Service Act, in which Congress has authorized the Department to establish up to 150 positions paying salaries equivalent to those paid in the supergrade salary range for scientists engaged



in research or the furtherance of research activities. In addition, Congress has also authorized the establishment of 13 scientific positions under 5 U.S.C. 1161 (Public Law 313 type) with the same salary range as supergrade positions. One of these positions has been allotted to the Office of Vocational Rehabilitation, and the other 12 to the Food and Drug Administration. Another means whereby a different pay level can be established for scientists is in our system of commissioned officer personnel in the Public Health Service. A number of scientists at the National Institutes of Health are in the commissioned corps and, although the pay rates for these positions are not necessarily higher than the highest supergrade rates, they have in the past provided some flexibility in the pay picture.

The above, therefore, represents our general situation with respect to pay rates for scientists. Of course, you know, the recent pay legislation removed the quota restrictions on supergrade positions for personnel in the medical, physical, and natural sciences. This action should assist us materially in relation to our needs for establishing these types of scientific jobs in the future. However, in other scientific fields we may well have to ask the Congress to allot additional Public Law 313-type positions as our responsibilities in these scientific fields increase. If you or Senator Humphrey would like to have more specific information or detailed tables, we should, of course, be glad to furnish them to you.

Sincerely yours,

JAMES C. O'BRIEN, *Director of Personnel.*

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,  
FOOD AND DRUG ADMINISTRATION,  
Washington, D.C., July 5, 1963.

DEAR SENATOR HUMPHREY: Below is the information requested by Mr. Cahn in a telephone conversation with Mr. Goldhammer on May 29, 1963.

1. A chronology of significant dates with respect to the following positions in FDA and the filling of such positions:

(a) *Scientific Director*.—This position was established on August 1, 1958. Dr. Paul L. Day was appointed to the position on January 5, 1959. He transferred to the Public Health Service on February 11, 1962.

(b) *Assistant Commissioner for Science*.—The duties and responsibilities of the position of Scientific Director were reviewed and the position was replaced by that of Assistant Commissioner for Science on September 12, 1962. Dr. O. L. Kline was appointed to that position on the same day.

(c) *Director of the Bureau of Medicine*.—Mr. Cahn requested that we begin with Dr. A. H. Holland and follow through to the present in setting forth significant dates for this position.

Dr. Holland was appointed as a member of the Commissioned Corps of the Public Health Service to serve as Acting Director of the Bureau of Medicine. He served in that capacity from March 31, 1954, to October 20, 1958, when he was appointed Director. He resigned on January 16, 1959.

Dr. William Kessenich was appointed as Director of the Bureau of Medicine on May 31, 1959. In September of 1961 he expressed his intention to resign and he resigned on August 18, 1962.

Since the resignation of Dr. Kessenich, Dr. Ralph G. Smith has been serving as Acting Director of the Bureau.

(d) *Deputy Director of the Bureau of Medicine*.—Dr. Peter J. Farago served as Deputy Director from September 10, 1956, to August 21, 1957. Dr. William Kessenich served as Deputy Director from March 9, 1958, to May 30, 1959. Dr. I. Siegel was appointed Deputy Director on March 19, 1961. Dr. Siegel transferred to the Public Health Service on May 4, 1963.

2. Significant dates in the consideration of Dr. Charles May as a candidate for the position of Director of the Bureau of Medicine.

(a) In April 1962 the Food and Drug Administration Commissioner and Deputy Commissioner discussed with Mr. Boisfeuillet Jones, the Special Assistant to the Secretary for Health and Medical Affairs, the offering of the position to Dr. Charles May. Mr. Jones agreed that the offer could be made subject to routine security investigation and approval by the Secretary.

(b) On April 20, 1962, the Commissioner wrote to Dr. May offering him the position.



(c) On April 29, the Commissioner received a letter from Dr. May accepting the offer on certain conditions.

(d) On May 29, 1962, FDA submitted a request for full field investigation of Dr. May to the Office of Internal Security, and Office of the Secretary.

(e) On June 5, 1962, the request was sent from Office of the Secretary to the Civil Service Commission.

(f) On August 17, 1962, Dr. May telephoned Deputy Commissioner John L. Harvey to request assurance as to his appointment by the end of the day. Mr. Harvey advised him by the end of the day that the Secretary would make no decision before the pending field investigation was completed.

(g) On August 21, 1962, Dr. May wrote Mr. Harvey indicating that he would wait for a final decision on the appointment.

(h) On September 6, 1962, the final report of investigation was sent by the Civil Service Commission, to the Department of Health, Education, and Welfare.

(i) On September 21, 1962, a memorandum was sent by the Commissioner to Mr. Jones reconfirming his recommendation to appoint Dr. May.

(j) On December 17, 1962, Dr. May wrote FDA withdrawing his candidacy.

3. Key scientific and medical positions in the Food and Drug Administration and salaries.

Organization	Title	Salary
Office of the Commissioner.....	Asst. Commissioner for Science.....	\$20,000
	Asst. to the Asst. Commissioner for Science.....	16,500
Bureau of Biological and Physical Sciences:		
Office of the Director.....	Director.....	19,000
	Deputy Director.....	16,000
Division of Antibiotics.....	Director.....	18,500
Division of Color and Cosmetics.....	Director.....	18,500
Division of Food.....	Director.....	18,500
Division of Microbiology.....	Director.....	18,500
Division of Nutrition.....	Director.....	20,000
Division of Pharmaceutical Chemistry.....	Director.....	18,500
Division of Pharmacology.....	Director.....	20,000
Bureau of Medicine:		
Office of Director.....	Medical Director.....	20,000
	Deputy Medical Director.....	18,000
Division of Antibiotic Drugs.....	Director.....	18,000
Division of Medical Review.....	Director.....	18,000
Division of New Drugs.....	Director.....	18,500
Division of Veterinary Medicine.....	Director.....	18,000
Division of Research and Reference.....	Director.....	16,965

The above list shows the salary levels we have been able to obtain for these key posts after years of effort. FDA now has 12 Public Law 313 positions, 29 scientific super-grades, and 8 administrative super-grade positions. The scientific super-grade positions were just recently obtained in May 1963 as a result of the removal of the ceiling of the scientific super-grade positions by the passage of the Salary Reform Act of 1962. Until May 1963 FDA had only the 12 Public Law 313 positions obtained gradually over a period of 4 years.

While the Salary Reform Act of 1962 has been helpful in alleviating the difficulties of recruiting scientists and physicians, it has not solved the problem of obtaining and holding top grade medical specialists and scientists. The Director of the Bureau of Medicine carries a salary of only \$20,000 a year. While current figures are not available, based on the most recently published data, the average American medical specialist has a net income before taxes of at least \$30,000 a year. A current executive employment agency brochure lists a pharmaceutical company which is offering \$35,000 a year for a Medical Director. FDA must have unusually well-qualified medical specialists, but qualified people would almost invariably have to accept a severe financial loss by coming to work for the agency.

The situation with respect to top scientific positions is no better. For example, the scientist who is taking over the position as Director of Division of Nutrition, a distinguished biochemist, will receive a salary of about \$5,000 a year less than that which he received as head of an industrial laboratory. Our top cosmetic specialist who is one of the world's leading cosmetic chemists receives \$18,500 a year. A similar position in an industrial laboratory pays an estimated \$25,000 a year.

Sincerely yours,

GEORGE P. LARRICK,  
Commissioner of Food and Drugs.



*(Articles in the Trade Press)**March 21, 1953.***F-D-C Reports—"The Pink Sheet."**<sup>1</sup>

APhA's Fischelis hit FDA's topside personnel and policies in testimony given March 16 before the joint House-Senate committee hearing on Eisenhower's FSA reorganization plan. Fischelis vigorously criticized FDA for failure to: (1) Have a professional pharmaceutical man in its topside; and (2) utilize a professional approach to regulatory problems. Fischelis approved the reorganization plan in general—as did all other witnesses, including spokesmen for AMA—and the plan was swept through the House by the end of the week. Senate approval is also certain, although Senator McCarthy may call for further hearings by his committee.

FDA will not be affected by the reorganization plan in any way, it was pointed out at the March 16 hearings. Budget Director Dodge and FSA Administrator Hobby were questioned on whether the new medical adviser to the department, as provided for in the reorganization plan, would have any supervision or veto power over FDA. Dodge and Mrs. Hobby denied that the medical adviser would have any supervision over FDA and repeatedly pointed out that, under the reorganization plan, this position was merely advisory to the Secretary.

Budget Director Dodge also was questioned by Senator Humphrey (D-Minn.) on whether there was any intention of removing FDA's topside from its traditional civil service status. Dodge replied: "No, not that I know of." Mrs. Hobby told Senator Humphrey she had sent a list of jobs to civil service which she wanted exempted. However, "F-D-C" has been officially informed that there are no FDA topside jobs on this exempt list ("F-D-C" March 14).

Fischelis' attack on FDA's topside came shortly after a deluge of industry telephone calls and telegrams apparently had changed Mrs. Hobby's mind about removing FDA topside jobs from civil service. Two weeks ago, Mrs. Hobby's top assistant, Jack Beardwood, had indicated to a reporter that the FDA jobs would be on the list of requested exemptions, and civil service sources say they were on one list submitted by FSA, but this one had to be returned for more information. However, following the telephone deluge late last week, Beardwood told "F-D-C" that the top FDA jobs would not be on the list. He told the same thing to another reporter on March 16.

Fischelis told the House and Senate committees that it is not necessary for the new department to be headed by an M.D., an educator, or a sociologist because the job can be done by "a public-spirited citizen of great capacity, who has an adequate appreciation of all of the factors that make up a program of health, education and welfare, in the public interest." He said "We are favorably impressed" with the provision of the reorganization plan calling for a Special Assistant for Health and Medical Affairs whose office "should be so set up as to assure continuous contact with leaders in the auxiliary professions dealing with health and medical care."

Pointing to the diversified functions involved in medical care, requiring teamwork on the part of all members of the healing arts and auxiliary professions, Fischelis offered the services of APhA to speak for the pharmaceutical field. He said: "The development of drugs and medicines and their proper production and distribution is a matter of primary concern in providing adequate medical care. Competent pharmaceutically trained persons, who have had broad experience in this field, will be required to advise and consult with those who guide health and medical affairs within the new department.

"We believe that the profession of pharmacy and the drug industry should be represented in the development of policies in the department. To this end, the APhA, which is the national professional society of pharmacists in the United States and which, in its House of Delegates, brings together representatives of every phase of pharmacy and pharmaceutical practice, pledges its wholehearted cooperation."

Launching his attack on FDA, Fischelis said: "However, at this time we wish to reiterate our concern over the trend of administrative supervision within the FDA which is one of the units of the proposed department. We have pointed out in the past that neither the Commissioner of Food and Drugs nor any of the Associate Commissioners, nor any of the personnel of the FDA, at the policy-making level, include a pharmaceutically-trained executive. So much of the

<sup>1</sup> Vol. 15, No. 6, pp. W11-12.



administrative activity of the FDA deals with drugs that it is difficult to understand the deliberate omission of pharmaceutically-trained personnel in this agency at the policy-making level.

"While it is true that the agency has a medical department, it has not been able to retain top-ranking medical personnel in this section. The reason which has been assigned for this failure to retain highly qualified physicians is the relatively low salary schedule. We do not believe that this is a major consideration. On the contrary, we wish to point out that when this agency was headed by professional men like Dr. Harvey Wiley, Dr. Carl Alsberg and Mr. Walter Campbell, the first two having been physicians, and the last named a lawyer, they were able to attract scientific and professional personnel of a very high order and to keep them there continuously because the policies were then being made on a professional level with the outside consultation on the same level.

"In recent years the line of succession in the administration of the FDA has been on the basis of its policing activity and those who have headed it have been in a position to dominate and overrule the professional personnel within the administration. In our judgment, this is the real cause for failure of professional personnel to look upon this activity as a career. Recent rulings and legislation fostered by the administration have failed to take into consideration the professional character of American medicine and pharmacy, and have tended to run rough-shod over established professional custom with resulting unwarranted interference with professional prerogatives.

"It is our hope that these methods, which are completely unwarranted in dealing with the regulation of profession groups such as we represent, may be curbed when the Department of Health, Education, and Welfare is set up, and proper supervision is exercised through the Special assistant and his staff, who, presumably, will be professional persons in the medical and allied professions."

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August 29, 1953

F-D-C- Reports—"The Pink Sheet."<sup>2</sup>

Recent attacks on FDA by APhA Secretary Fischelis were echoed at the APhA convention in Salt Lake City last week. On recommendation of APhA President Richards, the House of Delegates approved resolutions to:

1. Urge HEW Secretary Hobby to name a pharmaceutically trained executive to one of the top administrative posts in FDA. (In addition to this, incoming President Franzoni urged that Hobby name a pharmacist as a USPHS Assistant Surgeon General.)

2. Call to Mrs. Hobby's attention, with a view to correction, the damaging publicity which FDA issues in its annual reports and via other means re the unrestricted sale of dangerous drugs.

In his presidential address recommending these resolutions, Richards said: "When a professional organization like ours, which has always been on the side of strong regulation of the quality and distribution of drugs, becomes publicly critical of a law enforcement agency like the FDA, it is important that interested people should know why we are critical and why we have to oppose some of the methods and procedures which we have covered in editorials in our journal and in bulletins to the membership.

"At the outset, let it be stated that this association believes strongly in the doctrine that the regulation of drugs at the Federal, State, and local level should be in the hands of persons who are familiar with the industry or the profession they are called upon to regulate. It is a well-known fact that in the FDA the top level personnel does not include a pharmaceutically trained executive or administrator. \* \* \*

"In making these statements, let it be understood that we are not recommending the displacement of any civil service officer or of the Commissioner of Food and Drugs. We recognize the good work the present Commissioner, Mr. Charles W. Crawford, has done in his long service in the FDA, and we honor him for his arduous labors with Senator Copeland and others who worked out the Federal Food, Drug and Cosmetic Act of 1938.

"However, as is usually the case in Federal bureaus, a group of bureau chiefs and administrative officers are apt to work out in their own minds a line of

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<sup>2</sup> Vol. 15, No. 25, pp. W-6, 7.



succession, and guide things to bring about what they have planned. We believe that this is the time to call attention to the fact that the apparent line of succession does not include professionally trained persons, but rather those whose chief activity has been in the inspection and prosecution services of the administration. There is too much at stake here to overlook the desirability of advancing professionally trained and professionally-minded individuals to the administrative and supervisory level where policies, rather than details, are developed.

"Having pointed out that we are not interested in personalities, or advocating any individual or group of individuals for promotion or for appointment to positions, let us now make it clear whoever administers this important agency should be health-minded rather than publicity-minded.

"In recent years, the annual reports of the FDA have been very uncomplimentary to pharmacy and especially to retail pharmacy. This has resulted from over-magnification of the relatively few violations of ethics and laws in the dispensing of drugs. If there are in the ranks of pharmacy, individuals who place the greed for dollars above health services to the public, they can be mentioned by name when the evidence has been submitted and the courts have found them guilty. This will exonerate the thousands who never even think of the kind of violations which have caused a few members in our ranks to be apprehended.

"Not only in these annual reports, but also in testimony before congressional committees, has the FDA relied on a few sensational derelictions on the part of pharmacists to attract attention to its work." \* \* \*

*December 4, 1954.*

F-D-C Reports—"The Pink Sheet."<sup>3</sup>

FDA Medical Division has been reorganized with 5 branches—Antibiotics, Drug and Device, New Drugs, Research and Reference, and Veterinary. The reorganization is part of the general overhauling of the Medical Division's activities, operations, and policies that has been underway since last April when Dr. A. H. (Jerry) Holland took over as the new FDA Medical Director. Holland came to FDA from industry with a fresh approach to the medical policy aspects of Government drug regulation. He has been willing to review with an open mind all outstanding determinations of FDA medical policy.

\* \* \* \* \*

Under the staff reorganization, the Antibiotics Branch will continue to operate much as it has in the past, except that it will be more closely tied in with the Medical Division proper. The Antibiotics Branch will continue to be located physically in the South Building of the Agriculture Department (12th and C Sts., SW.) alongside FDA's Antibiotic Division. Though responsible to Holland as FDA Medical Director, the branch will work closely with Dr. Henry Welch and his staffers in the Antibiotic Division. Dr. Charles N. Lewis continues as head of the Antibiotics Branch, assisted by Drs. Lawrence E. Putnam and Marian C. Mills.

The New Drug Branch will continue to be headed by Dr. Ralph G. Smith, assisted by Dr. Ernest Q. King. Other members of the branch are: Julius Hauser, who has developed into a key regulation drafter for FDA; Earl L. Meyers, Ph. D.; Claudia S. Prickett, Ph. D.; and Paul M. Sanders. With powers almost equivalent to licensing, the New Drug Branch has developed into one of the most important parts of the Medical Division. Its importance has been pointed up by the fact that well over 50 percent of all the Rx medication used today has been developed in the past 15 years and therefore is subject to New Drug Application control. The New Drug Branch serves as virtual czar of the pharmaceutical business—except for products made from certifiable antibiotics.

\* \* \* \* \*

<sup>3</sup> Vol. 16, No. 43, pp. 10-11.



*(Official Report)**June 1955*<sup>4</sup>

First Citizens Advisory Committee of the Food and Drug Administration reports:

The stature, prestige, and salaries of the professional personnel who must bear the burden of passing on new drugs must be increased.

*July 6, 1956.***F-D-C Reports—"The Pink Sheet."**<sup>5</sup>

FDA reorganization which went into effect July 3 decentralizes administrative authority into 5 new topside bureaus and marks the Food and Drug Administration's (FDA) transition from a "small" to a "large" Government agency prepared to handle increased responsibilities, appropriations, and future expansion. The reorganization will change FDA actual operations and procedures very little, but it relieves the Commissioner and his deputy of the need for keeping their fingers on all FDA activities. As a practical matter, one-man administrative control has been impossible for some time ("F-D-C" May 7).

Administrative responsibility under the reorganization will be shifted to directors of the 5 "bureaus." Most of the old FDA "divisions" are now grouped under the bureaus. Aside from changes of nomenclature, major readjustments were consolidation of the technical and laboratory divisions in a new Bureau of Biological and Physical Sciences. In another consolidation, the Divisions of Regulatory Management and Administrative Review were joined in a Bureau of Enforcement.

FDA's Medical Division was upgraded into one of the 5 major bureaus. Everything remains the same in the Bureau of Medicine. The antibiotic, cosmetic, food, nutrition (vitamin), pharmacology, and pharmaceutical chemistry divisions were grouped under the new scientific bureau. The Bureau of Medicine's status is in line with recent pharmaceutical industry suggestions that the importance of the Medical Division be recognized. There were no major changes in personnel or salaries. Two associate commissioners, M. R. Stephens and R. S. Roe, were named bureau chiefs.

New organization chart of FDA and listing of key FDA topsiders with their telephone extensions are reproduced on the next two pages of this issue of "F-D-C Reports." Reprints of this handy organization directory and telephone listing will be available—for free—on request by subscribers who wish to keep this information in their desks for ready reference.

Industry contacts with FDA will not be affected by the reorganization because the same staffers will continue to handle the same problems. FDA-ers familiar with special problems or areas should be contacted as they have been in the past. The reorganization was prepared by Deputy Commissioner Harvey. Net result will be that fewer people will report direct to the commissioners, who will have more time for topside contacts with the HEW Secretary, Congress, and industry.

Emphasis on scientific phases of FDA work is another reason for the reorganization. The divisions primarily engaged in lab work have been centralized under the Biological and Physical Sciences Bureau, headed by R. S. Roe, formerly associate commissioner for scientific work.

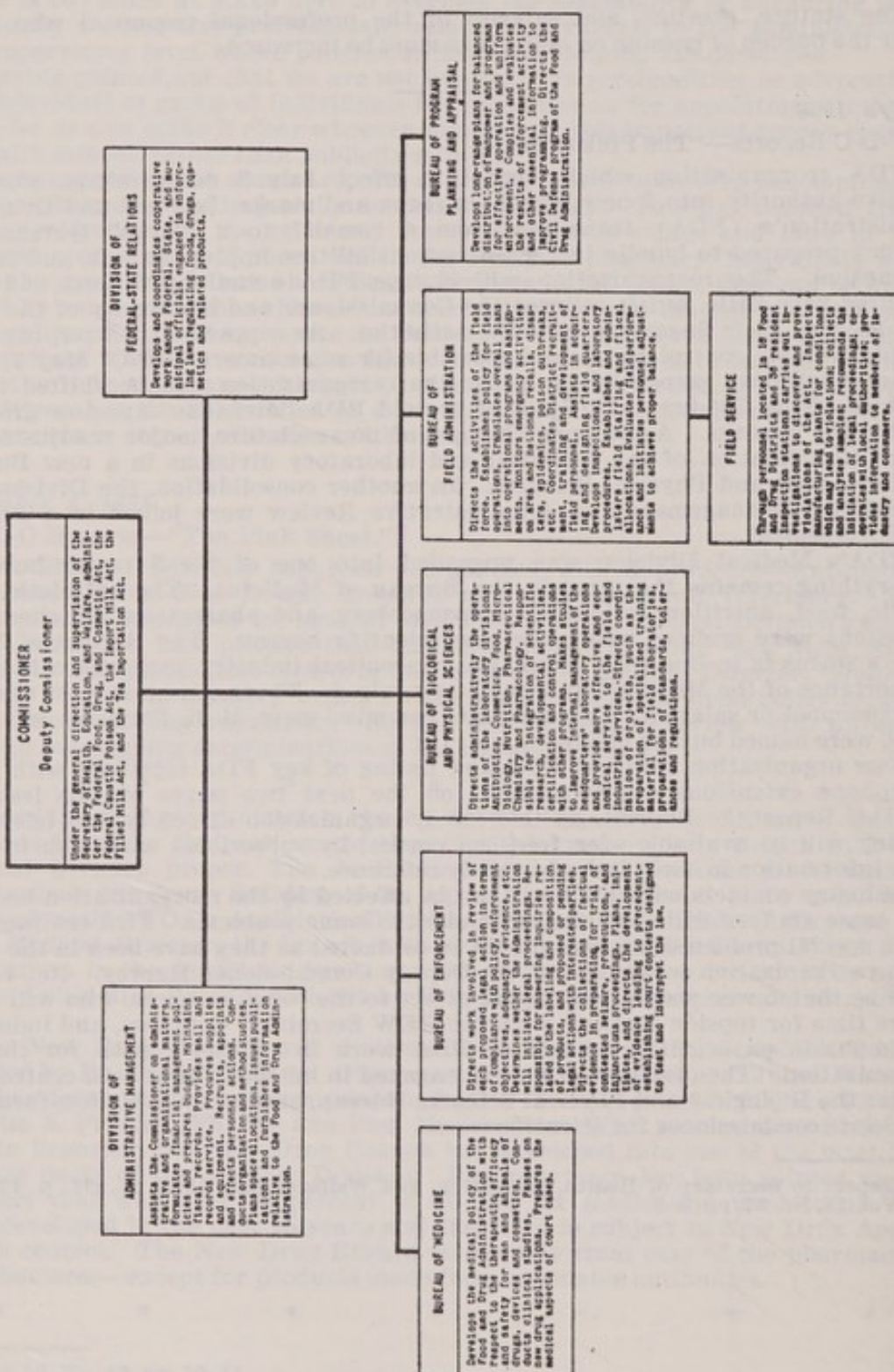
<sup>4</sup> Report to Secretary of Health, Education, and Welfare, June 1955, op. cit., p. 42.

<sup>5</sup> Vol. 18, No. 22, pp. 8-9.



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
Food and Drug Administration

FOOD & DRUG ADMINISTRATION





August 5, 1957.

F-D-C Reports—"The Pink Sheet."<sup>6</sup>

FDA Deputy Medical Director, Dr. Peter Farago, has resigned the Government position he has held for almost 1 year, to return to the Clinical Research Department at Abbott Laboratories. Widely popular and respected in both Food and Drug Administration (FDA) and industry quarters, Farago's decision to leave Government service and return to his home in Lake Forest, Ill., was based entirely on personal and family considerations. Hired by FDA after a 2-year search, Farago was quickly tabbed as "heir apparent" to FDA Medical Director Holland in the event the latter was ever lured away from Government service by one of the many choice industry offers that are periodically made for his services.

Farago's leaving means that FDA must again start the long search in industry and elsewhere for candidates to fill the very important No. 2 spot in the Medical Division. This points up the importance of the industry drive, sponsored by the American Drug Manufacturers Association (ADMA), to get congressional authorization for the payment of higher salaries for a limited number of professional and scientific positions. The HEW topside proposed legislation months ago raising the salary for the FDA Commissioner and providing for 14 FDA positions in the Government's so-called "super" grade—salary up to \$19,000 a year, but the proposal got hung up in the Budget Bureau, which has finally indicated it will send it to Congress with the number of FDA "super" positions cut back to three. An ADMA committee, headed by Merck President Connor, which has been working on the project for 2 years, met in Washington recently.

March 17, 1958.

F-D-C Reports—"The Pink Sheet."<sup>7</sup>

Deputy FDA Medical Director, Dr. William H. (Bill) Kessenich, named to the post last week, was promoted from the New Drug Branch where he had served for more than 2 years as a Medical Officer.

Kessenich came to the Food and Drug Administration (FDA) in 1955, and worked in the Drug and Device Branch for less than a year before he was switched to new drug work. He is a native of Washington, got his M.D. from Georgetown in 1946, was on the staff of Providence Hospital in Washington until 1950, practiced internal medicine in New York State 1950-1951, served in the Air Force for 2 years, and practiced medicine in Washington from 1953 to 1955, when he joined FDA. The FDA deputy medical directorship has been vacant since last August when Dr. Peter J. Farago returned to Abbott after spending 1 year in the job.

In another promotion within FDA's Medical Bureau, Dr. Eugene R. (Dick) Jolly was named Assistant Chief of FDA's New Drug Branch—a new position created to take some of the burden off of Branch Chief Dr. Ralph Smith. Jolly, who has been with FDA only since July, is an M.D., a pharmacist, and a pharmacologist. FDA Medical Director Holland's selection of two men identified with new drug work for promotion points up the growing importance of this phase of FDA's drug activities. The upping of Kessenich, however, accentuated the manpower shortage in the New Drug Branch which now has 3 M.D. vacancies. It operates with 3 full-time and 4 half-time M.D.'s.

November 3, 1958.

F-D-C Reports—"The Pink Sheet."<sup>8</sup>

FDA Research Director, Dr. Paul L. Day, 58-year-old University of Arkansas biochemist, whose appointment was announced last week, will function as a staff aid to Commissioner Larrick in planning scientific policy and coordinating the research activities of the 7 divisions under the Food and Drug Administration's (FDA) Bureau of Biological and Physical Sciences. These divisions are: Antibiotics, Pharmacology, Pharmaceutical Chemistry, Cosmetics, Food, Nutrition, and Microbiology. Larrick said the existing organization of the bureau will not be disturbed and Robt. S. Roe will continue to be its director.

<sup>6</sup> Vol. 19, No. 31, p. 16.

<sup>7</sup> Vol. 20, No. 11, pp. 18-19.

<sup>8</sup> Vol. 20, No. 44, p. 7.



Day's appointment is expected to focus Capitol Hill attention on the fact that FDA, usually regarded as a regulatory or "police" agency, also engages in research. This may help FDA find a place on the research appropriations bandwagon which Congress has been generously greasing in recent years.

Day will join FDA before the first of the year. He has been with the University of Arkansas' School of Medicine for 31 years and is now professor and head of the Department of Biochemistry, and assistant dean of the graduate school. His appointment was hailed by a press release quoting both Larrick and HEW Secretary Flemming.

December 15, 1958.

#### F-D-C Reports—"The Pink Sheet."<sup>9</sup>

#### HOLLAND'S RESIGNATION AS FDA MEDICAL DIRECTOR WILL TEST HEW SECRETARY'S ABILITY TO WITHSTAND POLITICAL PRESSURES

The resignation of Dr. A. H. (Jerry) Holland, Jr., as medical director of the Food and Drug Administration (FDA) formally handed to FDA Commissioner Larrick last Friday (December 12), faces HEW Secretary Flemming with a test on whether he can withstand pressure to fill the important \$19,000-a-year position with a political appointee. It is expected that the FDA post will be filled quickly.

Holland's letter of resignation, dated December 12, formally confirmed the wide-spread rumors that were the major topic of corridor and cocktail conversation during the Pharmaceutical Manufacturers Association (PMA) Eastern Section meeting at the Waldorf in New York City last week. Pharmaceutical industry speculation centered on two potential candidates for the post:

(1) Dr. Austin Smith, whose resignation as editor of the American Medical Association (AMA) Journal and other AMA scientific publications was announced several weeks ago ("F-D-C" Dec. 1 and 8). Pharmaceutical industry executives tagged him as the most outstanding possibility for the FDA medical directorship, provided he could afford to take the job at the \$19,000-a-year salary.

(2) Dr. William H. (Bill) Kessenich, named deputy FDA medical director last March after serving 2 years as medical officer in the FDA New Drug Branch. Kessenich's appointment would be in line with the FDA tradition of career service which always has been vigorously supported by the regulated industries who have been successful in fighting off all past efforts to infuse partisan politics into FDA.

#### Industry Has Chance To Give Flemming Its View This Week

Now that the news of Holland's resignation has been confirmed, the drug industry is expected to make its views on political appointments to FDA clear when its leaders meet with Flemming on Wednesday (December 17) in one of the series of conferences the HEW Secretary has arranged with groups interested in FDA's regulatory program.

Twice in the past 6 years the regulated industries have rallied in support of a "nonpolitical" FDA by making their views known via letters, telegrams, telephone calls, and personal visits.

The first time came in March 1953 when the regulated industries deluged former HEW Secretary Hobby with calls and telegrams within a 24-hour period on the basis of reports that the late Charles W. Crawford, then head of FDA, might be replaced by a political appointee. The second time was in June 1954 when Crawford's retirement became known and industry lined up solidly behind Larrick, a career man, for the top FDA post.

Because Crawford had delayed public news of his impending retirement, it took heroic efforts on the part of industry to maintain the FDA career tradition for the top spot. Brad Mintener, a long-time personal friend of President Eisenhower, went to the White House on the matter, and subsequently agreed to resign his post in private industry to become Assistant HEW Secretary, thus insuring Larrick's appointment as FDA commissioner.

In the past, the FDA medical directorship has not been a particularly attractive political plum, and in fact FDA has had difficulty even in finding competent men who would take the post on a merit basis. But the situation is different now for the following reasons:

<sup>9</sup> Vol. 20, No. 50, pp. 3-5.



*Among Defeated GOP'ers Is Representative Miller, an M.D.*

The woods are filled with lame duck GOP'ers, both State and national, who lost out last November and who are pressing the GOP National Committee and the White House to be cemented into civil service jobs. Like all Congressmen of whatever party, defeated GOP House members hate to leave Washington, and are combing the brush for Government posts. Among defeated GOP'ers is Representative Miller (R-Neb.), an M.D. who wrote FDA's pesticide act and has been active in other FDA legislation.

The FDA medical directorship now pays \$19,000, almost as much as a Congressman who gets \$22,500 but who has heavy political expenses. Largely as a result of the rapid advances being made in drug research, the post during Holland's 5 years with FDA has become the most important Government M.D. position insofar as drug therapy is concerned.

HEW Secretary Flemming, though he has a long background in Washington, is relatively new in the Cabinet post and has not yet had an opportunity to publicly demonstrate that he will adhere to a political "hands off" policy with regard to FDA. After Flemming's nomination to succeed Secretary Folsom was announced, Bertha Adkins, former assistant chairman for the GOP National Committee in charge of women's activities, was named HEW Undersecretary, the second highest post in the Department.

Even if Flemming wants to keep FDA "politically pure" he may need a strong expression of views from the regulated industries to help withstand the pressures from party job seekers. While industry may have little to fear from any topside FDA political appointment made by the Eisenhower administration, a break in the career and merit tradition at the agency could pave the way for potential difficulty after some future national election by breaking the precedent.

Except for the availability of an outstanding candidate like Austin Smith, industry probably would go down the line for the career tradition which would put Kessenich in line. As JAMA editor for almost 10 years and as head of AMA's Council on Pharmacy and Chemistry for 7 years before taking the editorship, Smith is thoroughly familiar with all the problems of drug research and regulation.

As the AMA's major contact with the drug industry for over 16 years, he is widely and favorably known in all segments of the drug field. He is a member of the Pharmaceutical Manufacturers Association (PMA) Award Committee, and last week (December 9) presented the 1958 PMA Award to FDA Commissioner Larrick at a banquet in New York City.

The award was made and the program was arranged long before Smith's resignation from AMA was announced. Since then, Smith has been deluged with fabulous offers from the pharmaceutical industry and other sources. In presenting the PMA award, Smith praised Commissioner Larrick for his fairness, his policy of discussing problems with industry, his skill as an administrator, and his willingness "to forthrightly admit when FDA has made an error."

Kessenich is not as well known as Austin Smith, but he has been favorably accepted by industry and the belief exists that he could easily grow into the job if given a chance. The \$19,000-a-year salary for the FDA medical director was obtained after a long campaign by leaders in the pharmaceutical industry. Two weeks ago, the FDA subcommittee of the PMA industry-Government relations committee had its introductory meeting with Flemming and could have made its views known if news of Holland's resignation had been public at the time ("F-D-C" Dec. 8).

*Holland acquiring interest in Enloe Medical Ad Agency*

In his letter to the FDA Commissioner, Holland said he has "arranged to purchase a substantial stock interest in the Cortez F. Enloe, Inc., medical advertising agency and will join that firm as executive vice president and chief operating officer." The FDA Medical Director told Larrick his resignation would be "effective at your pleasure during early 1959."

Holland, who has had a steady stream of attractive offers from the pharmaceutical industry during the past several years, explained to Larrick that he was resigning with "a sincere sense of regret" but added: "I feel constrained to do so for personal reasons and in order to enter business for myself." It is believed his agreement with the Enloe agency puts him in a position eventually to acquire majority control of the organization and it is anticipated that Holland's name will, in time, become part of the name of the agency.



The agency was founded by Dr. Cortez F. Enloe, Jr., an M.D., when he returned from service in the Air Force after World War II. Enloe is active in AMA affairs and has served on its councils and committees. Holland, formerly with AEC and Armour Laboratories, gave stature and visibility to the FDA medical directorship.

December 22, 1958

F-D-C Reports—"The Pink Sheet"<sup>10</sup>

NONPOLITICAL APPOINTEE TO SUCCEED FDA MEDICAL DIRECTOR HOLLAND URGED  
AT HEW DEPARTMENT'S DRUG-COSMETIC CONFERENCE

HEW Secretary Flemming indicated that he favors continuation of the Food and Drug Administration's (FDA) nonpolitical and career traditions at his December 17 conference with representatives of trade and professional groups in the drug and cosmetic fields.

Coming 2 days after the news broke on Dr. A. H. Holland, Jr.'s resignation as FDA Medical Director ("F-D-C" Dec. 15), the conference provided spokesmen for drug groups with an opportunity to urge continuation of FDA traditions. This and FDA's budget problems were the main themes of the conference.

Flemming's December 17 conference with drug-cosmetic groups and his December 18 meeting with representatives of consumer groups, unions, et al were part of a series the new HEW Secretary has been holding with "opinion leaders" interested in the work of agencies under his department. \* \* \*

Flemming was urged to keep key FDA appointments out of politics by Dr. Karl Bambach, executive vice president of the Pharmaceutical Manufacturers Association (PMA); Robert Brown (Bristol-Myers) president of the Proprietary Association (P-A); Dr. Robert P. Fischelis, secretary of the American Pharmaceutical Association (APhA); and Dal Bruner, executive secretary of the Animal Health Institute. None of these statements specifically asked Flemming to make a civil service appointment from within FDA in filling Holland's position, but they did ask that the successor be selected on the basis of "qualifications."

There is no official indication as to who is being considered for Holland's post, but pharmaceutical industry speculation has centered around Dr. Austin Smith, whose resignation as editor of the American Medical Association Journal was announced several weeks ago. If Smith could afford to take the job at FDA's \$19,000-a-year salary, his appointment would be welcomed by the drug industry as being solely on the basis of outstanding qualifications.

Smith, who has been deluged with very attractive offers from industry and others, was understood to be in Washington over the weekend. If Smith is not available and if the appointment is then made on a straight career basis, Holland's job would go to Dr. William Kessenich, Deputy FDA Medical Director.

*Larrick "Confident" of No Politics in FDA*

At the conclusion of the December 17 meeting, Flemming declared he is "proud" of FDA's record, and described the agency as "one of the finest examples we have of what a career civil service can mean." FDA Commissioner Larrick told the conference that "I have never known a time \* \* \* when I felt more confident" that politics would be kept out of FDA appointments. Flemming is a former member of the Civil Service Commission.

Larrick recalled that in 1953, when it was rumored that former HEW Secretary Hobby might name a political appointee to replace the late Charles W. Crawford as FDA Commissioner, industry flooded Mrs. Hobby with telephone calls and telegrams. Larrick said he was well satisfied with the results.

APhA's Fischelis urged the appointment of a medical director with a "pharmacy background as well as a medical background." He said he has long believed that FDA should have "someone who is trained in pharmacy" at the "top policy-making level."

PMA's Bambach called the medical director's post "one of the most important medical positions" in Government. He said, "We would not presume \* \* \* to support any individual to succeed Dr. Holland," but said that the successor should be "a medical scientist" who is "up to date on medical science \* \* \* research \* \* \* literature \* \* \* a man of stature well regarded by his \* \* \* professional colleagues." Bambach said that in and out of Government are men "who could fill this position well."

<sup>10</sup> Vol. 20, No. 51, pp. 3-5.



In officially confirming Holland's resignation in an HEW Department press release issued December 17, the day of the drug-cosmetic conference, Larrick declared:

"From the standpoint of the consumer, the position of the Medical Director of the FDA is one of the most important public health positions in the Nation." \* \* \*

#### *Industry Support Would Help Flemming Counter Pressure*

\* \* \* Even if Flemming was already committed to maintaining the no-politics tradition in FDA, the show of industry support for this position at the December 17 conference can help him ride out any pressure that may develop, now that the vacancy has been publicly announced. The industry statements will make it easier for Larrick and Flemming to say "no" if the need arises.

In the practical realities of the Washington scene, the FDA no-politics tradition will be safe only after the vacancy has been filled by an appointment based on professional qualifications or career service. If it is desirable to keep FDA out of politics, the battle must be fought on a continuing basis, regardless of which party is in power. \* \* \*

October 17, 1960.

F-D-C Reports—"The Pink Sheet."<sup>11</sup>

Dr. Paul L. Day, who was brought into the Food and Drug Administration (FDA) in 1958 to fill the new post of scientific director, last week aired his year-long "classified" controversy with FDA Com. Larrick in public for the first time. He charged that FDA's "research productiveness" has been "near an all-time low" in recent years despite a sharp upturn in total agency appropriations. \* \* \*

Day's speech indicates the frustration suffered by the \$19,000-a-year scientist. He pointedly changed the title of his paper last week from "Long Range Program of FDA" to "Long Range Program for FDA." His speech presumably caught Larrick and Deputy Com. Harvey by surprise since it was not cleared through FDA's normal public information procedures. \* \* \*

October 31, 1960

F-D-C Reports—"The Pink Sheet"<sup>12a</sup>

#### 44 PERCENT OF FDA TOP STAFF THOUGHT OF LEAVING IN PAST YEAR: SURVEY

The general atmosphere within the Food and Drug Administration (FDA) is one which "discourages and stultifies communication," according to a survey of employee attitudes toward the agency released last week.

Charles H. Goodman, American University psychology professor who conducted the survey and analyzed the results, reported that FDA-ers feel that "information is kept at the top and not passed down," and "professional employees feel they are not consulted in decisions which affect them or their work."

The 82-page report contains a number of plusses for FDA management, but generally reflects the need for overhauling the agency along newer, more streamlined lines to keep pace with its rapid expansion in recent years. \* \* \*

#### (Official Report)

October 25, 1962.

Second Citizens Advisory Committee on Food and Drug Administration:<sup>12</sup>

FDA should be made attractive to medical and scientific personnel of high caliber. The chronic problem of vacant positions and high turnover in the Bureau of Medicine should be overcome. While recent recruiting efforts by the bureau have produced some results, more comprehensive and aggressive actions are needed. The divisions in the Bureau of Biological and Physical Sciences have many of the same problems in recruiting and retaining qualified scientific personnel. The quality of work in both bureaus will suffer unless competent younger persons are brought in to build for the future and other steps are taken to upgrade the scientific and medical work done by FDA. These other steps should include closer professional relationships with university and other research centers, greater cooperation with the Public Health Service, provision for a continuous exchange of knowledge and ideas with the scientific and medical communities, and the development of sound research programs.

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<sup>11</sup> Vol. 22, No. 42, pp. 23-24. The text of Dr. Day's speech may be found in pt. 2, exhibit 60, p. 340.

<sup>12a</sup> Vol. 22, No. 44, p. 19. Excerpts of the response to the FDA questionnaire appear in pt. 2, exhibit 58, p. 337.

<sup>12</sup> Report, op. cit., pp. V-1, 2, V-4, 5.



*1. It is Proposed That A Food And Drug Institute Be Created To Strengthen And Give Greater Stature To The Scientific And Medical Work Of FDA*

The major objectives of the proposed Food and Drug Institute would include the following:

- To assist in formulating the overall policies and programs of FDA
- To be responsible for the scientific and medical work of FDA
- To develop a sound scientific base for regulatory programs
- To establish and execute research programs regarding methodology, testing and analysis; and to pass on the validity of tests and analyses in approving or withdrawing a New Drug Application
- To establish and execute research programs regarding pharmacology, toxicology, and other matters affecting the safety, quality, purity, and identity of food, drug and cosmetic products
- To serve as a focal point for close professional relationships of FDA with scientists in universities and research centers, industries, other Federal agencies, State agencies, and scientific professional organizations
- To administer research grants and contracts on scientific work within the foregoing limits
- To administer a program for the professional development of FDA scientific and medical personnel through leaves of absence, exchanges, study and research.

It is proposed that funds for the institute be appropriated as a separate item, in order to safeguard the integrity of the institute and promote the caliber of its work.

\* \* \* \* \*

(Pp. V-4, 5:)

However, the personnel problems which confront these bureaus arise not so much from a shortage of personnel as from the factors of quality, experience, maturity and judgment. In fact, some division heads have stated that personnel have been added too rapidly and have not been well assimilated. Other principal supervising officers in both bureaus report great difficulty in recruiting qualified persons and in filling vacancies. One division head reported that there is "almost no one" in his division who was there 5 years ago. In the Bureau of Medicine, there is recognition of the validity of industry complaints regarding the caliber of some of its personnel. \* \* \*

There are many outstanding, dedicated scientists and physicians in FDA. However, constructive plans should be made to meet present needs and to build for the future. Implementation of the provisions of Recommendation 1 should assist in creating conditions which would give greater stature to the scientific and medical staffs. \* \* \*

July 6, 1963.

Robert C. Toth, The New York Times:<sup>13</sup>

#### U.S. MEDICAL POST REMAINS VACANT

FIVE HAVE REFUSED JOB—DRUG CHIEF'S FUTURE INVOLVED

(By Robert C. Toth, special to the New York Times)

WEDNESDAY, July 5.—A key post in the Food and Drug Administration has been unfilled for 11 months. The vacancy sufficiently troubled Government officials to bring it to President Kennedy's attention.

The job is director of the agency's Bureau of Medicine, a critical role as the agency has taken on responsibilities for policing the Nation's medicine chests as well as its cupboards.

At least 4 prospects have refused the job. A fifth doctor accepted, but then withdrew after officials in the parent Department of Health, Education, and Welfare overrode the Commissioner of the Food and Drug Administration, George P. Larrick.

Reports have been circulating in Government and medical circles that "the word is now out" not to accept the job "until Larrick goes."

<sup>13</sup> P. 19.



Mr. Larrick, 61 years old, became head of the agency in 1954 after 30 years in enforcement, inspection, and administrative posts. He has been identified with the so-called policeman's philosophy that would add more inspectors, not more doctors, to the agency.

Critics say this approach is not conducive to creating the high level of scientific competence within the agency that its new duties demand.

#### CELEBREZZE BACKS LARRICK

"I have no intention of getting rid of Mr. Larrick," said Anthony J. Celebrezze, Secretary of Health, Education, and Welfare, in a recent interview. "He has 40 years of experience which we need. The FDA is primarily a regulatory agency."

"No one wants to fill the Bureau of Medicine job more than us," he said. "Perhaps we set our standards too high."

"The man we'd like to get," Mr. Celebrezze continued, "has an established reputation, and probably heads a medical school or a department in a school. He would understandably be reluctant to leave that job, especially when the most we can offer at present is \$20,000 a year."

Other officials say salary is only one difficulty impeding the recruiting attempts. The chief of the medical bureau, they point out, will be primarily concerned with regulation, not research, and he will be subject to many pressures because his decisions may involve millions of dollars in drug sales.

The bureau, they note, is responsible for licensing new drugs, controlling the distribution of test drugs, and judging effectiveness, safety, and standards of manufacture.

The organization of the agency, these officials say, is another major difficulty. The current thinking, they say, is to create within the agency a scientific institute, of which the Bureau of Medicine would be but a part.

At present, the post is filled by an acting director, Dr. Ralph G. Smith. Dr. Smith is head of a division within the bureau and, it is reported, does not want to be bureau chief.

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#### EXHIBIT 161

##### PACKAGE INSERTS: RESULTS OF 1960 SURVEY BY PHARMACEUTICAL MANUFACTURERS ASSOCIATION ON PHYSICIANS' INFORMATION PREFERENCES

On p. 1037, Dr. Charles May referred to the issue of capitalizing on information contained in package inserts. These inserts and related issues involving information preferences had been the subject in September and October 1960 of a survey commissioned by the Pharmaceutical Manufacturers Association. The attitudes of 1,552 physicians and surgeons as a "sample of medical profession leaders in the United States" were examined.

(It may be noted that there was pending at the time a new Food and Drug Administration regulation (later finalized) for including package inserts with prescription products.)

There follow excerpts from the text of a PMA release describing the 1960 poll.

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#### PHARMACEUTICAL MANUFACTURERS ASSOCIATION, *Washington, D.C., December 21, 1960.*

##### SURVEY OF PHYSICIANS: OPINION ON MEANS OF OBTAINING COMPREHENSIVE DRUG INFORMATION

A survey of physicians' opinions regarding possible alternative proposals for supplying the medical profession with comprehensive information about prescription drug efficacy was conducted under PMA auspices during September and October 1960. In conjunction with United Marketing Services, the PMA conducted a study of the attitudes of 1,552 physicians and surgeons, a sample of medical profession leaders in the United States. The sample contacted consisted of 2,736 active practicing physicians who have a common interest in clinical medicine as well as organizational activity. Mail questionnaires and personal interviews were both employed in obtaining responses.



In general, by major geographical divisions, the sample appears to be reasonably representative of medical practitioner attitudes in each region.

#### SUMMARY OF RESULTS

The following is a synopsis of the responses obtained for each of the questions, as numbered (see attached questionnaire \*). For further details, note the table references. Results are provided, wherever meaningful, by the four major census regions (East, South, North Central, and West), for the mail questionnaire responses; and by State in the inclusive region, for the States in which personal interviews were conducted (Pennsylvania, Kentucky, and Michigan).

(1) "Various methods are used to disseminate written information to the physician about the many new products introduced annually. Which three of the sources listed below are most important to you personally in obtaining complete information on indications, contraindications, and precautions for new drugs?"

The preferred source of information about new drugs, in all geographical regions of the United States, is literature detailed by manufacturers' technical representatives. Twenty-seven percent specifically cited this source first. Physicians' Desk Reference and "journal articles or papers" closely vied for second place of preference (see table No. 1\*).

(2) "Of the following sources, which do you commonly use to refresh or re-check your memory on usage, dosage, contraindications, side effects, and so on?"

As a means of refreshing his memory, on action of a drug, the medical practitioner prefers the Physicians' Desk Reference above all other sources combined. In fact, no other source was checked by more than 3 percent of the respondents (see table No. 2\*).

The replies to both questions Nos. 1 and 2 seem to indicate that the type of information on new drug usage, dosage, side effects, etc., is best supplied in the first instances by a combination of literature and verbal explanation and by broadly inclusive literature. An examination of the major sources cited in response to question No. 1 tends to point up the physician's desire for keeping current with respect to drug developments. The considerable dependence on the Physicians' Desk Reference, with its quarterly supplements, emphasizes the need for comprehensive material in ready reference form. It would seem that physicians like the way in which drug specifications are provided in a book or journal in a format such as employed by PDR.

(3) "Do you feel that you need better quality of informational material or service on new drug facts than is currently being provided?"

"(Check one) ☐ Yes; ☐ Qualified Yes; ☐ No; ☐ Qualified No; ☐ No opinion"

A majority of the respondents by region, and in total (58.9 percent), felt categorically that no change was needed in the present methods of supplying information on new drugs. An additional 10.9 percent qualified their "no" responses slightly (see table No. 3\*). Thus, at total of 70 percent indicated that no basic change was required. This was borne out in the comments in answer to question No. 4 which accompanied the "qualified no" replies to question No. 3. The responses to this question, analyzed in the light of answers to other parts of the questionnaire, indicate that relatively little dissatisfaction is felt with the current methods of supplying information on new drugs.

(4) "Please comment on good points or shortcomings, in your opinion, with regard to the question raised in No. 3."

Comments regarding needs for a better method for furnishing new drug information were quite varied. The statements were so extensive that they were not included here, in the interest of brevity.

(5) "Below are shown three possible alternatives for distributing new product information to the prescribing physician. Would you please check the one which would best serve your needs."

"(a) To have individual manufacturers regularly provide information directly to you for each new product in a comprehensive form, showing dosage, composition, action, clinical results, side effects, cautions, references, and other principal pertinent data.

\*Not included herein.



"(b) To have each manufacturer continue providing new product information to you using the present forms and methods.

"(c) To have an independent central office furnish to you monthly a standardized, looseleaf distribution of information on new products, showing the same facts as in (a), above.

"(d) None of the above. (Please comment)."

Half (49.2 percent) of the physicians responding to this question on new product information alternatives selected "to have an independent central office furnish \* \* \* monthly a standardized looseleaf distribution of information \* \* \*." A quarter (26.7 percent) chose "no change needed." Almost a fifth (18.4 percent) preferred that the manufacturer make more comprehensive his explanations. The filecard brochures currently being provided physicians by some of the leading manufacturers seem to fit this need. A small percentage (5.7 percent) indicated preference for some other method of supplying information than the three previously quoted (see table No. 4\*).

Perhaps it is apropos here to observe that the majority of doctors by type of present practice (question No. 7) show no significant difference in view on these alternatives. (For example; see tables No. 5 A, B.\*)

(6) "The Food and Drug Administration proposal is outlined in the accompanying letter. Essentially, this would require an official product brochure to accompany each individual bottle or container, regardless of size, which is sent to the physician and druggist. This brochure would provide a detailed statement of the manufacturers' new drug application.

"(a) Would these brochures distributed in this manner be helpful to you? Yes —. No —."

Among regions for the mail questionnaire, a range of 27 to 36 percent of the respondents felt the package insert would be helpful. The personal interview range was from 36 to 60 percent (see table No. 6\*).

The variation between mail and personal interview results may be accounted for, at least in part, by the different degrees of explanation provided the respondents in the two situations. Whereas a two-page letter giving full details accompanied the mailed survey form, the entire personal interview was confined to a 7- to 10-minute meeting, with only a brief uniform statement of the FDA proposal. This comment applies as well to parts (b), (c), and (d) summarized below.

"(b) Do you believe that this method would be worth a substantial addition to cost of the drugs affected?"

A vast majority of mail respondents replied that the FDA proposal would not be worth "a substantial addition to cost" (see table No. 7).\*

Although no indication of the additional cost was conveyed to the respondents, it has been estimated by knowledgeable industry leaders that if package inserts were required generally, it would add millions of dollars to production costs.

"(c) Would you prefer this method to any of the three first mentioned (in No. 5 above)?"

Less than 10 percent of the respondents completing the mail questionnaire showed a desire to have the FDA package insert proposal introduced in lieu of any of the three alternatives offered in question No. 5 (see table No. 8).\*

"(d) Would multiple brochures on each such drug in the hands of the druggist permit him to serve your needs better?"

This question provided more divergence of opinion than any of the above noted parts. Here, 19.3 percent of those responding replied that the druggist could serve the individual practitioner better by having a supply of brochures on each drug (see table No. 9).\* However, this is somewhat belied by the fact that a very small percentage of the respondents currently rely on the druggist either as an initial source of information or as a refresher source (see tables Nos. 2 and 3).\*

(7) "Please check the category in the list below which best describes your present practice." (Listed.)

No important differences in attitudes seem to be indicated among the various practitioner groups in the survey. The survey tends to give somewhat less weight to the general practitioners, surgeons, and internists than is properly representative of their numbers in the United States (see appendix table A and tables 5A-B).\*

\*Tables not included herein.



(8) "Approximately how many prescriptions do you write in an average or typical day?"

There was no evidence of great variation in opinion according to prescription volume.

(9) "What is the approximate population of your city of practice?"

No major differences of opinion were evidenced with respect to the key questions (Nos. 5 and 6) according to population of city of practice.

(10) "(a) From what medical college did you graduate?"

This part of the question (as well as part (b) below) was asked of each person (with the exception of those in the Kentucky personal interview). Because of the large number of colleges involved (93 including foreign institutions), no attempt was made in the tabulation to correlate responses according to the physician's medical school. This material was used primarily as an approximate check on the representativeness of the sample.

"(b) In what year?"

A date of graduation was used also in an endeavor to determine approximate age and time-orientation representativeness. The respondents were subsequently divided into approximate respondent quartiles: 1900-30, 1931-39, 1940-48, 1949-60.

There seem to be no important variations in attitudes by year of graduation and responses to Kentucky question Nos. 5 and 6. However, a breakdown on this material could be accomplished if desired. (For example, relating year of graduation, by quartile, to question No. 1 replies, by region, first place and second place ratings on the primary sources of information on new drugs was accorded as indicated in appendix table B \*—question No. 10.)

#### *Sample method:*

A dual technique was employed in obtaining the stratified partially random sample.

(1) 2,290 questionnaires and explanatory cover letters were mailed to AMA officers and delegates and other individual association officers including those at the county level, from whom 1,106 replies were received (a 44 percent return);

(2) 446 questionnaires, to which responses were obtained by random choice personal interview at State medical society meetings in 3 representative States (Pennsylvania, Kentucky, Michigan).

#### *Additional comments:*

Further detail can be furnished upon request.

\* \* \* \* \*

\*Tables not included herein.



## SUPPLEMENTARY EXHIBITS

### EXHIBIT 162

ADDRESS BY GEORGE F. ARCHAMBAULT, FORMER PRESIDENT, AMERICAN PHARMACEUTICAL ASSOCIATION, ON PHARMACY'S ROLE IN CONNECTION WITH INVESTIGATIONAL DRUGS

On November 15, 1962, George F. Archambault, Chief of the Pharmacy Branch, Division of Hospitals and Pharmacy, U.S. Public Health Service, delivered the following address before the Federal Services Pharmaceutical Seminar, sponsored by the American Pharmaceutical Association's Section on Military Pharmacy. Mr. Archambault was President of the American Pharmaceutical Association. The article appeared in the Journal of the American Pharmaceutical Association, March 1963, volume NS 3, No. 3, starting at page 124.

### A DRUG MOVES INTO HUMAN TRIALS

(By George F. Archambault)

New and startling headlines have appeared in the public press in recent months. "Sensational," "attraction-getting," "emotional pitched headlines," some say. Others call them "exaggerated." And others, the rank and file of the American people, read the headlines and wonder—and to themselves say, "If true, to whom do we turn? If our doctors, our pharmacists and our lawmakers do not protect us, to whom do we turn for protection?"

Public opinion moves "mountains" and—as a result of these headlines—it has done so once again, proving the power of the public press and public opinion.

But what are the real facts on drug testing on humans? What are the guidelines, the ethics and mores in this area of research of medicine and pharmacy? What have the national medical and pharmaceutical associations done about this? What are Federal and State legislators doing? The starting point must begin with the explanation of how a new drug reaches prescribing physicians in the United States. A drug manufacturer acquires a new drug in but one of two ways—by research and invention or by the purchase of patent rights or license of a foreign drug already being sold abroad. In either case, a new drug to be offered for use must be cleared by the Federal food and drug authorities.

Before applying for clearance, manufacturers must gather a large amount of evidence that the drug is safe. The drug is analyzed in laboratories and tested on animals. It then proceeds to human trials through experts on medications—usually physicians in private practice. On the basis of all these tests—chemical, animal and human—the new drug application is filed, in effect, requesting permission to make the medication available to all prescribers.

Until the thalidomide incident our Federal laws have said little relative to human trials concerning—

1. Who shall be the first humans to receive a new drug?
2. What information should the doctor be given by the manufacturer about previous tests?
3. Should the patient be told he is a "human guinea pig?"
4. Should the doctor obtain written consent from the patient?
5. Should FDA be notified before a drug goes into human trial?
6. Should the number of people on whom the drug is tested be limited?
7. Should FDA have authority to review animal testing results before authorizing human testing?
8. Should the "code" in double blind studies be capable of being broken at the locus of the patient?



We are fortunate in the United States that thalidomide was used only in an experimental stage and not, as in many other countries, as a fully approved drug. However, other potent dangerous drugs did move into interstate commerce and have had to be recalled—as MER/29, a cholesterol retardant, alleged to have caused cataracts, blindness and alopecia; Monase, one of the tranquilizers used in the treatment of depressed patients alleged to have caused blood disorders and Ostamer (MRD-535), a polyurethane polymer, the “bone glue.” John L. Keliher of Abbott Laboratories reported at a recent New Hampshire Pharmaceutical Association meeting that in the last 4 years 15 drug products were withdrawn from the market out of 784 because their safety was in doubt.

One thing is certain—there is a need for certain additional safeguards in the testing of new drugs. Smith Kline and French, drug manufacturer, has emphasized this point in its August 1962 commentary, “Thoughts on Thalidomide.” The firm points out—and quite correctly—that the additional safeguards needed “can be determined only through a gathering of all the pertinent facts and their careful study by medical authorities.”

In this connection, the drug industry, cognizant of its responsibility and public trust in this area, established in July 1962 a committee on drug safety to find test methods to prevent unforeseen toxic effects of drugs. Dr. Austin Smith, president of the Pharmaceutical Manufacturers Association, stated—

The committee will comprise, for the most part, individuals from leading scientific and medical societies, medical colleges, Government agencies and independent laboratories. They will include specialists in medicine, toxicology, physiology, genetics, and other disciplines.

Perhaps we should review some of the reports on the thalidomide disaster to learn why this committee was just appointed in 1962. The London Times for August 1, 1962 reported—

The tragic occurrence of congenital malformations in children whose mothers have taken the analgesic sedative and hypnotic drug thalidomide creates a new situation in regard to the testing of drugs \* \* \*. In retrospect it is natural to ask, why were no tests made of the teratogenic effects (the production of congenital malformation)? The answer, quite simply, is that the need for such tests in such circumstances had never been made evident before. Testing new drugs is an evolving science and grows progressively more complex and more costly. The need to test for teratogenic effects has now been irrevocably established (though the methods have to be determined) but it would be entirely wrong to say it should have been recognized earlier. Who would care to say what other risks should be provided against now? This is not a matter in which a commercial firm has omitted tests which professional pharmacologists with no commercial interests would have carried out. They would not have carried them out. \* \* \* The particular new risks which thalidomide has shown will clearly be taken into account now in testing drugs. The question of general interest is, however, what, if anything, may be done to avoid other similar distressing incidents?

Ghastly gaps, such as this one, in our knowledge of drug-induced phocomelia must somehow be plugged but not at the expense of research programs. We in the medical-pharmacy research world need to delve deeper into these cause and effect matters. For example, we have long known that insulin, thyroid, cortisone, vitamin A, certain antibiotics, quinine, certain anticancer drugs, tolbutamide and even toxic doses of aspirin have been implicated in either animal experiments or human experience.

We must admit that we know almost nothing about thalidomide's chemistry. What happens to it in the body? We must admit, too, that the lack of this information is not unusual; precisely how the body breaks down aspirin, and how its effects are produced, are not known either.

#### MEDICINE'S POSITION

The Judicial Council of the American Medical Association in a supplementary report, published in 1946, 16 years ago, stated—

In order to conform to the ethics of the American Medical Association, three requirements must be satisfied (prior to human experiments)—(1) the voluntary consent of the person on whom the experiment is to be performed, (2) the danger of each experiment must be previously investigated by animal experimentation, and (3) the experiment must be performed under proper medical protection and management.



Medico-Legal Forms with Legal Analysis—a pamphlet (copyright 1961) of the Law Department of the American Medical Association—carries a form (see box) by which a patient may authorize treatment with drugs under clinical investigation.

.....

**Authorization for Treatment with Drug under Clinical Investigation**

Date \_\_\_\_\_ Time \_\_\_\_\_ a.m.  
p.m.

I authorize Dr. \_\_\_\_\_, the attending physician, to treat \_\_\_\_\_ with the drug \_\_\_\_\_  
(name of patient)

presently identified as \_\_\_\_\_ for the following condition \_\_\_\_\_

\_\_\_\_\_  
(describe symptoms of disease to be treated)

It has been explained to me that the safety and usefulness of the drug in the treatment of patients for the above condition are now being investigated and that the manufacturer or distributor has supplied the drug for the purpose of providing further evidence of its safety and usefulness.

I voluntarily consent to treatment with the drug and release the attending physician from liability for any results that may occur.

Signed \_\_\_\_\_  
(patient or person authorized to consent for patient)

Witness \_\_\_\_\_

The brochure states—

Generally drugs under clinical investigation should be administered only where—

the informed consent of the patient or his authorized representative has been obtained,  
the physician is convinced of the reasonable accuracy of his diagnosis and, if necessary, has confirmed it by adequate consultation,  
existing methods of treatment have proven unsatisfactory.

The voluntary participation of the patient will not excuse a deviation from the physician's obligation to exercise his best skill in rendering the care required of a reasonable practitioner. Furthermore, the physician is advised to confine his clinical investigations of new drugs to those furnished by reputable sources who have supplied him with comprehensive written information concerning animal experimentation, previous clinical investigations, if any, recommended dosages, contraindications, possible side effects to be watched for and the safety and possible usefulness of the drug from existing data.

It would appear therefore organized medicine has done its job well but how well are these ethical principles followed? I suspect in most instances they have been carried out implicitly. But an FDA survey revealed that only 640 testers of the more than 1,000 given thalidomide submitted a statement on their qualifications for testing as required by regulations and fewer than one-third made reports to the company on the results of their "tests," some of these being made verbally to company medical service representatives.

**DENTAL PROFESSION**

The American Dental Association has urged Congress to provide the "necessary regulatory laws and financial assistance" to insure adequate clinical testing of new drugs. An editorial in the ADA Journal stated—



It is the manufacturers' responsibility to market only those drugs which are safe and it is the responsibility of the Food and Drug Administration to see to it that the manufacturers comply. However, the fulfillment of these responsibilities is made difficult by the inadequacy of personnel and facilities for clinical drug testing.

Dentistry, too, is vitally concerned—for in dental research the testing and use of many drugs is necessary, especially therapeutic agents such as the analgesics as was thalidomide.

#### PHARMACY

What role if any have the pharmacists of these United States actually played in this story? The minutes of the December 10, 1956, meeting of the joint committee of the American Society of Hospital Pharmacists and the American Hospital Association read—

A subcommittee composed of Dr. Groeschel and Dr. Francke prepared a statement in regard to investigational drugs. The statement reads in part—Hospitals are the centers for investigations on new drugs. Patient safety and welfare dictate that these drugs should not be employed in an indiscriminate or haphazard manner. Without attempting in any way to control or influence the type of research undertaken, the safety of patients must be protected by establishing certain basic procedures and principles for the handling of investigational drugs. This responsibility could well be assumed by the pharmacy and therapeutics committee.

Then again in May 1957 the joint committee restudied the problem and developed this statement of principles involved in the use of investigational drugs in hospitals—

#### STATEMENTS OF PRINCIPLES INVOLVED IN THE USE OF INVESTIGATIONAL DRUGS IN HOSPITALS

Hospitals are the primary centers for clinical investigations on new drugs. By definition these are drugs which have not yet been released by the Federal Food and Drug Administration for general use.

Since investigational drugs have not been certified as being for general use and have not been cleared for sale in interstate commerce by the Federal Food and Drug Administration, hospitals and their medical staffs have an obligation to their patients to see that proper procedures for their use are established.

Procedures for the control of investigational drugs should be based upon the following principles—

1. Investigational drugs should be used only under the direct supervision of the principal investigator who should be a member of the medical staff and who should assume the burden of securing the necessary consent.
2. The hospital should do all in its power to foster research consistent with adequate safeguards for the patient.
3. When nurses are called upon to administer investigational drugs, they should have available to them basic information concerning such drugs—including dosage forms, strengths available, actions and uses, side effects and symptoms of toxicity, etc.
4. The hospital should establish, preferably through the pharmacy and therapeutics committee, a central unit where essential information on investigational drugs is maintained and whence it may be made available to authorized personnel.
5. The pharmacy department is the appropriate area for the storage of investigational drugs, as it is for all other drugs. This will also provide for the proper labeling and dispensing in accord with the investigator's written orders.

#### NUREMBERG WAR TRIALS

The 10 principles for establishing general rules of conduct for medical research on human subjects developed at the Nuremberg War Trials. Stuart M. Sessoms, Assistant Director, National Institutes of Health, paints the story in this fashion—

Ten principles for establishing general rules of conduct in developing research programs were formulated in 1949 in the judgment of the trials of war criminals by the Nuremberg military tribunal for the medical case. Policies of many research institutions are based on these principles which are sometimes called "The Ten Commandments of Medical Research Involving Human Subjects." They are as follows—



1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice \* \* \* and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. \* \* \* there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problems under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury may occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill, and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Clinton R. Miller, assistant to the president of the National Health Federation, testifying on August 22, 1962, before the Committee on Interstate and Foreign Commerce, the Oren Harris committee, stated—

The Nuremberg war trials did not challenge the matter of testing with human guinea pigs. It did emphasize and establish that voluntary consent is the first prerequisite for human experimentation. When convicts or political prisoners are used in America for human experimentation, it is done with their consent and they may withdraw from the experiment at any time they choose. This same right should be afforded the rest of America.

Concerning the Nuremberg trials, there were 23 defendants at this medical war trial—15 were found guilty; 7 were hanged; 4 of the 7 were physicians. It was freely admitted that in America there were medical experiments similar in nature to those of the accused war criminals but they were all performed with the consent of the human guinea pig. It was the failure to get voluntary consent that made the act of human medical experimentation criminal.

#### RESPONSIBILITY OF PHARMACISTS

Practicing pharmacists through their associations, in the light of recent developments, must now give thought to their public health responsibilities in this area. The American Pharmaceutical Association, for example, has as its first cited reason for being "to insure to the American people drugs and medications of the highest quality." It, therefore, must be concerned with this problem.

In fairness, medicine, pharmacy, and the law cannot expect the drug industry to police itself completely in this area. All of us in the medical complex must be more cognizant of the ASHP-AHA Statement of Principles for the Use of



Investigational Drugs. Also, we must be more alert, more inquisitive in our daily professional activities as we meet suspect adverse drug reactions of not only investigational drugs but drugs already in commerce.

As practicing pharmacists we cannot fear to take a strong stand favoring restrictive legislation or a medicine-pharmacy imposed commission review on this health matter. Nor can we be brushed aside from our purpose of serving the public health and good by such statements as "Government or commission interference with free enterprise" or "death to research" threats. The legitimate pharmaceutical industry would welcome our best thinking in this area. Calculated risks must continue to be taken by man if we are to move forward in medical research, but we must seek an approach that gives the utmost protection possible to the humans involved.

At present, some citizens, quite possibly, with no knowledge on their part, are involved in drug evaluation studies. This is contra to sound medical ethics. We all must bear in mind, or act at our legal peril, the well-established principle that the right of a physician to treat a patient is always limited to the treatment agreed by the patient. Assault and battery and negligence cases with damages against physicians are found in many of our law court decisions testifying to the legal rights of human beings in this regard.

Our responsibility as "medication experts" requires at this time an expression from us—the practitioners of pharmacy, the dispensers of medications in our communities—to restore public confidence in this important work.

#### THE LAWMAKERS

The Federal Register of August 10, 1962, carried this item—"New Drugs for Investigational Use: Notice of Proposal to Amend Regulations." In general, these regulations will concern themselves among other things with keeping the FDA informed on drugs going into clinical trial; having clinical investigations planned properly and executed only by qualified investigators and keeping FDA fully informed of the progress of the clinical investigations. FDA will have the authority to halt or stop any study if the safety of patients so indicates.

Also, the new drug law, passed by the 87th Congress, further strengthens the authority of the Food and Drug Administration relative to the overall control of drugs and medications. This act carries these major features—

1. The Secretary of Health, Education, and Welfare can require that experimental drugs be tested on animals before they are administered to humans.
2. New drugs cannot be tried on humans without their consent, unless physicians deem this not feasible or contrary to their professional judgment. In this respect, the new law requires manufacturers to obtain certificates from investigators "that they will inform any human beings on whom such drugs, or controls used in connection therewith, are being administered, or their representatives, except where they deem it not possible or in their professional judgment, contrary to the best interests of such human beings."
3. The HEW Secretary may order a new drug off the market if he finds it an "imminent hazard to the public health."
4. A new drug will have to be found effective as well as safe, and cannot be marketed without the Secretary's approval. If he denies approval, the manufacturer can request a hearing.

We now hope that Congress will provide the necessary funds for FDA to do this job assigned to it. For laws and regulations without funds to hire the qualified personnel to carry out the obligations so properly spelled out by Congress itself, without funds to educate the people as to the law and its regulations and without funds to employ sufficient personnel to enforce the law are, in fact, valueless laws.

#### ADVERSE DRUG REACTION PROGRAM

FDA's Adverse Drug Reaction Reporting Program is a noncontroversial program in its fifth year of activity. It, in effect, is a national reporting technic being employed by FDA to acquire at a central point in Washington reports on the toxic effects, side effects and other adverse reactions of drugs, new and old. The program is vitally important to the public health. It is an outgrowth of a study conducted by the American Association of Medical Record Librarians, ASHP, AMA, AHA and FDA. Individual hospitals report "any unwanted condition precipitated by a drug regardless of its nature or the circumstances of its occurrence, i.e., toxicity caused by overdosage, allergy, idiosyncrasy, in-



tolerance, side effects, secondary effects or injury from improper method of administration, use of the wrong drug, or error in compounding, labeling or packaging or from other error in the manufacture of the drug or in its preparation for use in the hospital. (Reports of hospital errors are of interest solely because of their value in uncovering deficiencies in the manufacturing, packaging or labeling of a drug)."

Every physician, pharmacist, medical record librarian and hospital administrator in the interest of good medicine should support this program completely. It is in the interest of the public health in the deepest sense of those words.

#### CODE BREAKING AT LOCUS OF PATIENT

A controversial issue exists between some pharmacology research-minded evaluators and physicians involved in direct patient care concerning drug testing on humans. The ASHP-AHA statement emphasizes that hospital authorities, along with nurses and pharmacists engaged in administering, compounding, and dispensing investigational drugs, should have available to them basic information on actions, uses, side-effects, symptoms of toxicity, dosage, and dosage forms.

On the other hand, some clinical investigators and pharmacologists, in their attempt to obtain completely unbiased scientific findings in initial clinical testing, insist upon "remote coding" in connection with "blind studies." Remote coding is a control technic whereby the specific medication administered to a particular patient is unknown to the clinical researcher and his coworkers. These research workers believe that their studies are more objective and scientific if they remove the possibility of any influence on the studies from unsupported statements or data which might intentionally or unintentionally be supplied, without unethical intent, by individuals or concerns with special interests. In the opinion of this group of researchers, this technic of remote testing makes possible the achievement of unbiased objectivity since the individual researcher is unaware of the specific medication (drug, placebo, or standard) administered to an individual patient.

The AHA policy statement provides that vital information needed in the event of an adverse or unexpected reaction of a patient from the administration of an investigational drug be immediately available to the physician. Theoretically, similar information is also readily available in "remote coding" by telephoning the control center and "breaking" the code (often kept in a distant city), but the possibility always exists that communication difficulties may cause dangerous delays and the possible death of the patient. We, in the clinical area, therefore, insist that the code be at the locus of the patient for immediate "breaking" if the condition of the patient so warrants.

And, now you have the story—as told in 1962—"And So a Drug Moves into Human Trials." What will 37 years from now *do* to this story, as we enter "Century 21?" Only the science of tomorrow, not today, can tell us and it is not yet ready to speak.

"Nothing is permanent but change," an old philosopher once said; in today's language we say, the "Gee-Whizzes" of today are the "Ho-Hums" of tomorrow. And so it will be as we witness more and more wonder drugs entering the practice of medicine through properly controlled clinical trials—trials that protect the rights of humans and at the same time do not impede proper research.

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#### EXHIBIT 163

##### ARTICLE BY MORTON MINTZ ENTITLED, "NEW DRUGS: IS GOVERNMENT SUPERVISION ADEQUATE?"

The following article by Morton Mintz, a reporter for the Washington Post and Times Herald, appeared in the Reporter of March 28, 1963, pages 46-52.

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#### NEW DRUGS: IS GOVERNMENT SUPERVISION ADEQUATE?

(By Morton Mintz)

"The more we have examined the handling of the new drugs by the Food and Drug Administration," Hubert H. Humphrey told the Senate last October, "the



more we have been surprised, shocked and disappointed \* \* \*. Often, testing has been going on in a manner which should have sent shivers down the spine of the medical profession \* \* \* drugs intended for use by victims of chronic disease—day after day, year after year—were released by FDA even before—I repeat—before—chronic toxicity tests had been completed on animals \* \* \* shocking reports of injuries and deaths to test patients, as received by drug companies, have often gone unreported to FDA, or have been downgraded by skillfully contrived half-truths, or have been reported accurately to FDA, but virtually ignored \* \* \* Drugs have been approved which FDA now admits should never have been approved. Drugs have been kept on the market long after FDA admits they should have been eliminated \* \* \*."

Senator Humphrey made these disclosures on October 3, 1962, just as the Kefauver-Harris drug-reform bill was being enacted into law. Many of its provisions, such as the requirement that experimental drugs be properly tested on animals before being tested on human beings, go a long way toward correcting the drug abuses that have been making headlines since Senator Kefauver began his investigation of the drug industry 3 years ago. Under the new law, the Secretary of Health, Education, and Welfare (HEW) can order a drug off the market instantly if there is evidence that it is an imminent hazard to the public health; drug companies must list the side effects of their products in their advertising; and a new drug must be proved "effective" as well as safe before it can be marketed. Furthermore, physicians must obtain the consent of patients before giving them experimental drugs, unless this is deemed not feasible or not in the patient's interest.

The FDA, moreover, has been given greater powers for factory inspection and quality control. In addition, tighter regulations for human testing proposed last summer by Anthony J. Celebrezze, the new Secretary of HEW, went into effect this February. These require that the FDA must be notified of *all* clinical (human) trials of new drugs, and that the FDA must be kept fully informed of what happens during testing. The clinical testing must be properly planned and executed by qualified investigators, and again must be based on adequate animal studies.

But the effectiveness of the new law and of the regulations depends greatly on the organization that exists to administer them. Senator Humphrey, the only licensed pharmacist in Congress, is beginning hearings on the FDA this month, but the Senate majority whip has already gathered enough evidence in the preliminary investigation by his Government Reorganization Subcommittee to cast grave doubts on the agency's use of the power it already had, let alone its ability to exercise more. And Senator Everett M. Dirksen, far from being encouraged, found in the belated issuance of the new HEW regulations "an unparalleled example of bureaucratic inertia." The fact is that the FDA could have issued them at any time since 1938.

That year marked the passage of the first significant drug-safety legislation since the FDA was established 56 years ago. It resulted from the disastrous carelessness of a manufacturer who the year before had marketed sulfanilamide in liquid form, using an automobile antifreeze as the solvent. More than a hundred people died. The 1938 law prohibited the sale of any new drug unless the FDA allowed an application for it to become effective. The FDA's decision was to be based on its evaluation of the animal and clinical testing reported by the manufacturer in his application. It was ruled that human testing was to be under the direction of an expert "qualified by scientific training and experience to investigate the safety of drugs." The FDA, however, has never set standards for an "expert" on the debatable ground that to do so would interfere in the practice of medicine. Even if this premise could not be challenged, the fact is that clinical testing is sometimes performed by research scientists who are not physicians. The new HEW regulations, moreover, set higher standards for the initial clinical tests than for those which follow, and their adoption by the FDA would seem to imply that the FDA agrees that it had some rights to set standards without interfering in the practice of medicine.

Though FDA Commissioner George P. Larrick has complained that he could not find a consensus on the definition of an "expert," he has never asked professional or industry groups to help him obtain agreement and arrive at workable definitions. Nor did the FDA regulate or require reports on drug testing on humans.

The FDA was concerned only with the testing done on drugs for which marketing applications were filed. Currently, the agency receives an average of 375 New Drug Applications a year, but manufacturers have been testing 4 to



5 times as many without reporting them. In 1959 alone, manufacturers tested 1,900 new drugs on humans. Since the Second World War the drug industry has expanded tremendously, and 90 percent of today's prescriptions are for drugs that were unavailable 20 years ago. Meanwhile, qualified investigators are in increasingly short supply, and some manufacturers have decided that the mere possession of an M.D. or Ph. D. degree in basic medical science is sufficient for clinical testing. "Nobody knows," Humphrey told the Senate, "how many thousands of drugs have been tested, have caused harm, have been shelved, and never reported, never discussed \* \* \* the most dangerous part of the iceberg has lain below the surface."

#### OF MICE AND MEN

Though the new regulations finally require that the FDA be informed hereafter on all clinical testing while it is in progress, its past performance in evaluating the relatively few medical-research reports it did get has not been reassuring. Even less reassuring has been its anaesthetized response to various cries of alarm.

"We firmly deny," Commissioner Larrick told Senator Kefauver's subcommittee in June 1960, "that New Drug Applications have been allowed to become effective on the basis of inadequate laboratory and clinical investigation work." The 61-year-old commissioner has been with the FDA for 40 years. In 1955, a year after he became head of the agency, a Citizens Advisory Committee had found cause to urge the FDA to develop better methods for evaluating new drugs. In June 1960, Dr. Barbara Moulton, a former FDA medical officer, testified before the Kefauver subcommittee that the situation was "extremely dangerous"; in October of the same year she presented extensive evidence to document her charge, and in September a special committee of the National Academy of Sciences-National Research Council called for remedial action "with the least possible delay."

In July 1961, Dr. Louis Lasagna of Johns Hopkins University gave the Kefauver subcommittee some insight into the quality of animal testing that sometimes preceded the clinical testing: "I have been approached to start human testing of a drug," he said, "with the only information available being the amount of drug necessary to kill 50 percent of mice receiving the drug in one intravenous dose."

There were warnings from the agency itself. In October 1961, an FDA statistician, drawing on 13 years' experience, said in a paper presented at a conference of FDA's top officials: "\* \* \* the low quality of research data in NDA's [New Drug Applications] is general and not isolated \* \* \*. Unfortunately for the medical officers, they must within short periods of time make decisions one way or another \* \* \* they are forced to gamble; the information which they need to reduce almost to zero the risks of an incorrect decision too often is unavailable to them, because of weakness in research methods \* \* \*."

But such criticism had little real impact on the FDA hierarchy or their superiors in HEW—until the scandal about the thalidomide sleeping pill. A number of details in that story, as brought out by Senator Humphrey's subcommittee, amply illustrate the shortcomings of FDA's head-in-the-sand posture about drug testing.

Smith, Kline & French Laboratories of Philadelphia tested thalidomide in 1956-57, without any reported deformities resulting among 875 patients. Not having required that it be informed, the FDA knew nothing of this until March 1962. In September 1960, the William S. Merrell Co. of Cincinnati filed an application to market the sedative. It came out later that Merrell and 3 other subsidiaries of Richardson-Merrell, Inc., ultimately distributed 2.5 million thalidomide tablets to 1,267 physicians for "experimental" use.

About a month after Merrell had first applied to the FDA, it issued to its sales force a manual on how to present physicians with its clinical-testing program for Kevadon, its brand name for thalidomide. "You can assure your doctors that they need not report results if they don't want to," the manual stated, "but that we, naturally, would like to know of their results. Be sure to tell them that we may send them report forms or reminder letters, but these are strictly reminders and they need not reply \* \* \*. Let them know the basic clinical research on Kevadon has been done."

"Don't get involved by selling a basic clinical research program instead of Kevadon," the manual continued. "*Appeal to the doctor's ego—we think he is important enough to be selected as one of the first to use Kevadon in that section*"



of the country \* \* \* Don't forget that you are a salesman, a professional salesman."

Perhaps such an approach to testing helps explain why the former Chief Medical Director of the Veterans' Administration, Dr. William S. Middleton, has found that "the desultory returns from over 1,200 physicians \* \* \* could have no scientific significance or validity. Yet," he added, "this formula for deriving new drug introduction and acceptance has obtained for many years." When the FDA finally investigated last summer, it discovered that only 276 of the 1,267 physicians had reported to Merrell in writing on their clinical trials, and further, that at least one-fifth had not signed the statement of investigative qualifications that FDA regulations required the manufacturers to obtain.

On November 29, 1961, a year after the company had filed its application with the FDA, Merrell learned from West Germany that thalidomide had been associated with birth deformities. The next morning it notified Dr. Frances O. Kelsey of the FDA, who had been withholding approval of the drug. At that point, Commissioner Larrick could have issued a public warning—the very course recommended by Dr. Herman I. Chinn, our deputy scientific attaché in Bonn, in a dispatch relayed to the FDA and HEW in January 1962. Larrick, however, chose to let the company handle the matter.

Why the FDA didn't undertake an immediate effort then to retrieve the drug puzzled Senator Jacob K. Javits, Republican, of New York, among others. He asked Commissioner Larrick, during the preliminary investigation by Humphrey's subcommittee, what happened when Dr. Kelsey got the information.

Senator JAVITS. "Then did you just talk to the company in general?"

Commissioner LARRICK. "It was not conclusively proved at that stage."

Senator JAVITS. "When was it?"

Commissioner LARRICK. "There was strong circumstantial—there would be people who would give you an argument about it now \* \* \* who would say that the problem here has been exaggerated."

Larrick admitted that the FDA could accomplish the retrieval of drugs more effectively than any company, but added that he was "not quarreling" with what Merrell did.

What Merrell did, according to its own report cited by Humphrey's subcommittee, was send a warning letter in early December 1961 to its "active" thalidomide investigators, although the FDA was unaware that they represented only one-tenth of the physicians who had received the experimental tablets. Three months later, Merrell and its affiliates finally wrote all of them asking them to destroy or return the remaining supplies. "At the time," Commissioner Larrick said later, "I thought that was sufficient."

That it was not sufficient has become by now a familiar story. After reports published in mid-July of Dr. Kelsey's achievement in blocking the application of thalidomide, the FDA embarked on a crash program to ferret out the unsuspected numbers of tablets that had got into the hands of the public. A month later, the FDA, finding that substantial quantities were still at large, had to plead with the public to clean out medicine chests and flush all unidentified pills down the toilet. Nearly 21,000 persons in this country had obtained thalidomide from both foreign and domestic sources, and at least 9 women who took it during pregnancy bore babies without arms and legs.

#### DRUGS ON THE MARKET

Recently the FDA has decided that it does have a quarrel with Merrell, and it has asked the company to show cause why its method of distributing the thalidomide tablets should not be referred to the Justice Department for possible legal action. Thalidomide, at least, was never allowed to go on the market. Other drugs that had to be recalled were. One was Marsilid, and in its case the FDA displayed what can be called remarkable patience in dealing with its manufacturer, Hoffmann-La Roche of Nutley, N.J. Marsilid was first approved in 1955 for use, with limitations, in treating critical cases of tuberculosis. Later it was found to have effect as a psychic energizer, or "happiness pill," and the company applied for a supplemental New Drug Application for its use in treating mental depression. But Marsilid also was associated with 246 known cases of hepatitis (liver damage), 53 of which resulted in death. At least 400,000 patients used it.

Hoffmann-La Roche, it would seem from the account given Humphrey's subcommittee by the FDA, was rather casual in reporting some of the hazards of Marsilid. Although it received the first reports of deaths and injuries in con-



nection with the drug in September 1957, it did not mention liver damage to the FDA until half a year later, in February 1958, when it asked permission to change the label. By the end of 1958, the adverse reports on a variety of side effects were mounting and the drug company asked for another supplementary New Drug Application under which a brochure listing new restrictions on its use would accompany the drug. The FDA, in turn, suggested a strong warning to be printed in bold type on the label.

The strong warning was not put on, however, and during the next year the company continued to market the drug. Nonetheless, the FDA approved the supplemental New Drug Application in January 1960. Seven months later, it renewed its request for the stricter warning label. Finally, in September 1960, its request was complied with, but the sale of Marsilid under a proper warning label was short-lived. It was withdrawn from the market the next January, because, as the FDA put it, "drugs with similar therapeutic usefulness but with greater safety were available."

But these drugs had been available and marketed since 1959. Moreover, the five Veterans' Administration hospitals that had tested Marsilid had discarded it much earlier, between December 1958 and June 1960 because of reports of "severe liver damage," "excessive toxicity" and—in a hospital system with more psychiatric patients than any other in the world—"limited usefulness."

Why did the FDA permit Marsilid to remain on sale until 1961? Larrick's explanation is that it was regarded as valuable in "near deathbed cases," but this was true only initially when it was used to treat tuberculosis, not mental depression.

Larrick has said that he is "proud" of the FDA's handling of Marsilid. Dr. Moulton, on the other hand, seemed prouder of the press when she testified about an earlier request to change the label. Marsilid's hazards, she said, "were well known in the Bureau of Medicine long before the newspapers began to carry reports on the subject. When this occurred there was prompt if not entirely effective action by FDA to revise the labeling. Prior to the newspaper publicity, however, we raised our voices in vain."

Another drug that had to be withdrawn from the market was MER/29, a Merrell product intended to reduce the amount of cholesterol in the blood, although the role of cholesterol in heart disease is controversial. Senator Humphrey has called the FDA's handling of the application for this drug "shocking \* \* \* a sharp indictment of the FDA itself—its laxity, its tardiness in seeking to remove the drug from the market, its failure to protect the public interest."

The New Drug Application for MER/29 was filed in July 1959, and was assigned to a 32-year-old FDA physician who had only recently completed his residency in internal medicine. He was promptly contacted by Merrell's F. Joseph Murray. "The company was extremely anxious to get the drug on the market," the young man recalled. However, the report of the FDA pharmacologists on MER/29 was unfavorable. And, the physician said, he was aware that scientists at the National Institutes of Health were concerned about MER/29's effects. (Later, their research showed that in blocking the formation of cholesterol, MER/29 largely defeated its purpose by causing an abnormal accumulation in the blood vessels of a related fatty substance, desmosterol.) The FDA physician felt that MER/29 might be helpful in dealing with arteriosclerosis. Nonetheless, he repeatedly held back approval by judging the application incomplete because it failed "to report clinical studies in full details." But 22 days after he again made such a judgment, on April 19, 1960, FDA's young medical officer let MER/29 be marketed—before, according to Senator Humphrey, the "full details" were in, and even though he regarded its value as "theoretical." The new drug went on sale, not because its effectiveness against heart disease and arteriosclerosis had been established but "solely on the evidence of safety."

By September 1960, the FDA had so many disturbing reports about the effects of the drug—cataracts, baldness, changes in hair and skin color—that it asked Merrell to submit a supplemental NDA and to revise the label to warn against use of MER/29 in women of child-bearing age. Meanwhile the adverse reports continued to pour in. On November 16, 1961, FDA scientists recommended that the drug be withdrawn, but the FDA administrators did not suspend the application. For a total of 2 years the Merrell product, heavily advertised in medical journals, was profitably sold as a prescription drug and taken by more than 300,000 persons. Then in March 1962, by sheer accident, the FDA learned, as it reported to Humphrey's subcommittee, that reassuring data in the NDA from



tests on monkeys "had been falsified." (The FDA investigation of this has been followed up by a Federal grand jury.) In April, Merrell recalled the drug. In May, Larrick cited clinical evidence showing "that the drug was unsafe," and suspended the application. In August, the FDA admitted that the decision to allow marketing had been a mistake.

That decision was made 2 months before Larrick had told the Kefauver subcommittee that it "is extremely improbable" that falsified data would not arouse the FDA's suspicion, and "categorically" denied that the review of New Drug Applications "may in some instances have been superficial." The criterion for release of a drug, he said, is whether "the good in saving lives and alleviating suffering clearly outweighs the hazards."

By a curious aspect of the FDA's decisionmaking machinery, approval of a New Drug Application can be given by a medical officer "on his own initiative, without review by any of his colleagues," according to Dr. Moulton. And as Commissioner Larrick has testified, the medical officer's decision "represents an institutional decision that the drug is safe for use under the conditions and in the dosages prescribed in the labeling." But when a medical officer believed a drug to be unsafe and wanted to deny its approval, the situation was different. According to Dr. Moulton, he had to have "the unanimous support of the Chief of the New Drug Division, the Director of the Bureau of Medicine, the Commissioner, and usually also the Director of the Bureau of Enforcement and the General Counsel's Office."

The agency statistician described an FDA physician's plight quite well in the internal report already cited. "The medical officer," he said, "is in an untenable position because if he were to adopt the view that an application were incomplete unless the research supporting it were properly conducted, he would pass few applications. But this would result in a major shift in FDA policy, and have a far-reaching effect on a major industry. Clearly, a shift of this magnitude is not to be made by the medical officers."

In view of the medical officer's responsibilities, however, it seems strange as Senator Humphrey points out, that the physician handling the NDA for MER/29 "never consulted with the National Institutes of Health *before* the drug went on the market. Nor did NIH initiate such consultation," although it "has been supporting considerable research on cholesterol-lowering substances."

This lack of communication between two branches within HEW particularly irritated Senator Humphrey, who for years has been trying to bring about a systematic exchange of drug data between the FDA, the hospital systems of the Public Health Service and the Defense Department, and the NIH, which "has the greatest pool of drug research information in the world." He has found "little systematic communication," even among the institutes of the NIH. The thalidomide scandal has brought Senator Humphrey some measure of success, however. The NIH, for example, is now methodically feeding the FDA the result of an electronic data-processing survey of 50,000 pregnancy case histories, yet NIH's Director acknowledges that he is "not at all certain we would have done" precisely that if the thalidomide story had not been publicized.

As for the FDA itself, Humphrey claims that its high officials "have apparently been content" to let the agency "stagnate as a scientific backwater," despite the "deep interest of a few extremely talented M.D.'s and pharmacologists." The FDA's isolation has made it dependent, in many cases, on plain luck. The "falsified" MER/29 monkey data came to FDA's attention only because an FDA inspector happened to ride in a carpool with the husband of a woman who had quit her job in Merrell's animal research laboratories. Dr. Kelsey's determination to block the marketing of thalidomide was decisively hardened because she "chanced" to read a letter to the editor of one of the world's 4,000 medical journals, a letter that associated the drug with peripheral neuritis.

Humphrey considers it "a miracle that we learn as much as we do." Though many sources—such as pharmaceutical companies, the FDA, hospitals, the Veterans' Administration, and the NIH—compile data on reactions, they do not cooperate "to any real extent" with each other. According to Humphrey, the individual clinician "tends to be so busy that often his reports are a fraction of what they might be. This is a crucial point: it explains in part a tendency to overvalue fragmentary favorable reports." Although the FDA itself has had a small reporting program, involving at most 150 out of the Nation's 6,000 hospitals, Humphrey's subcommittee has "yet to find anyone who has substantially used this program or anyone at the reporting end who had received useful 'feedback' from it."



Consequently, Humphrey found it "incredible" that the FDA had not made "systematic use" of outside consultants. Although the agency supplied him with a "nominally" long list of outside consultations, Humphrey found it "completely misleading." "It pretends that an isolated telephone call or letter or short visit for a curbstone—I emphasize—curbstone judgment represented 'consultation.'" "I am surprised," he continued, " \* \* \* that FDA states consultation has 'routinely' occurred. The men \* \* \* inside the agency who have fought and begged for outside consultation \* \* \* have been discouraged at worst, or ignored at best, from above."

#### PRESSURE AND PERSUASION

The atmosphere inside the agency apparently has been one of considerable discouragement from above, accompanied by constant harassment from some drug manufacturers. Dr. Moulton has told of cases in which orders came "from above" for medical officers to certify drugs about which they had doubts, the justification being that the manufacturers should "be in a much better position to judge their safety." She contended that in many of its activities the FDA had become "merely a service bureau" for the drug industry.

Dr. Moulton has also complained that manufacturers' representatives spend "3 or 4 days a week in the New Drug Branch offices, arguing each point step by step, wanting to know and being told exactly where the application is at all times and which chemists and which pharmacologists are assisting in its review."

One physician who worked on the application for Marsilid, the "happiness pill" associated with hepatitis, left the FDA shortly thereafter to work for Marsilid's manufacturer, Hoffmann-La Roche. The letter he authorized, while in the FDA, to warn prescribing physicians about Marsilid's side effects did not impress Dr. Moulton, who informed the Kefauver subcommittee that "the important facts were obscured by so much irrelevant material that [it] failed to serve as an effective warning."

The FDA's involvement with the industry was brought home forcibly by the disclosures that the head of its Division of Antibiotics, Henry Welch, was writing articles for professional journals that brought him a profit, as Senator Douglas told Congress last summer, of "approximately \$288,000 \* \* \* from the firms he was supposed to be regulating." Dr. Welch was "allowed to resign" in 1960, when the Kefauver subcommittee fully explored the matter, but even then, as Kefauver found, his superiors "were derelict in the performance of their duty \* \* \* they whitewashed it \* \* \*". He was not even asked by [FDA's top officials] how much his 'honorariums,' as he called them, amounted to. That was an outrageous conflict of interest." (The matter is now before a grand jury.)

When the new drug bill was passed in Congress, both Senator Kefauver and Senator Douglas voiced their concern about the ability of the FDA to administer it, and both called for "an infusion of new blood." Senator Humphrey has made it clear that he has "little reason for confidence in the policy echelons of FDA," but does not attack Commissioner Larrick personally; indeed he calls him "a faithful and dedicated public servant." Last October, however, a second Citizens Advisory Committee, reporting on a year-long study of the FDA, recommended that its top posts should "no longer \* \* \* be held primarily by persons whose backgrounds have been as inspectors, but should include scientists with broad experience as well." The Commissioner's post was specifically included. Larrick, who is not a college graduate, joined the FDA as an inspector in 1923 and rose through the ranks, becoming Commissioner in 1954. His Deputy Commissioner started as an inspector in 1925.

But the chairman of the citizens committee, George Y. Harvey, who has since become a consultant to HEW on FDA matters, blunted what appeared to be a committee attack on Larrick. He told a press conference that the report was directed "to the future," and that Larrick could carry out its recommendations if he takes them "to heart and attracts the right kind of people."

Attracting and holding the right kind of people may prove exceedingly difficult. Dr. Moulton had quit in disgust so that she could speak out. A former scientific director, Dr. Paul L. Day, found life at the FDA impossible after he had criticized the agency for its "lack of sufficient vision of its proper role in the protection of the health of the American people" and "courage to present, adequately, a bold program." He resigned.

In a recent reorganization, Dr. Kelsey was promoted to head a new Investigational Drug Branch, and she has received from the President the Nation's highest



honor for distinguished Federal civilian service. But generally, FDA medical officers have been overworked in thankless, glamorless, paper-pushing jobs. Under the new regulations and the Kefauver-Harris law they will get hundreds of thousands of additional reports a year. More physicians have recently been recruited for the Bureau of Medicine—22 in February—but there will still be too few specialists to evaluate the highly specialized material that will be flooding in, and they still do not have an effective consulting service.

To attract and hold top scientists to the Bureau, Larrick could have pushed for FDA's own research program, as Dr. Day recommended. Larrick could have pressed for exemption of more physicians from civil service salary restrictions, and he could have tried hard to make working conditions more attractive. He did neither.

Since 1957, while enforcement and other FDA branches have stayed put in the HEW Building, the Bureau of Medicine has been shifted from a former nurses' dormitory near the city incinerator to ramshackle structures that were not air conditioned, and from those to a World War II temporary building.

All of these quarters were distant from the Division of Pharmacology, whose work is integral with the Bureau of Medicine because it evaluates the animal testing in New Drug Applications. Yet, as of early March, the Bureau was destined to be moved once more, this time to a converted automobile-servicing garage in one of the most crime-ridden precincts of Washington and at least a mile from the Division of Pharmacology and other FDA scientists with whom the Bureau physicians should consult.

Congress has long treated the FDA shabbily, but Humphrey has said that the price of generous treatment will be a demand for "men with drive, with initiative \* \* \* not just 'going by the book,' by the letter of the law, but by its spirit, its tone, its fundamental purpose."

HEW is assuming that it can put new life into the FDA by teaching the old watchdog new tricks, but in and out of Congress this approach is considered excessively optimistic in view of the past handling of drug problems. Critics believe the FDA can become the great, vital agency Humphrey envisions only if the old watchdogs are replaced by a new breed of scientist-administrators.

The hearings by Senator Humphrey's Government Reorganization Subcommittee this month and next will be followed by more hearings in the House. But it remains to be seen whether the FDA can continue to ignore criticism as it has in the past, or if Dr. Moulton will continue to stand by her testimony of 1960 that "hundreds of people, not merely in this country, suffer daily, and many die because the Food and Drug Administration has failed utterly in its solemn task of enforcing those sections of the law dealing with the safety and misbranding of drugs \* \* \*."

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#### EXHIBIT 164

#### ROLE OF THE PHARMACIST IN COMMUNICATION WITH THE MEDICAL PROFESSION

Communication among the professions of the healing arts has long been an interest of the Senate subcommittee. There follows a column, by the editor of Drug Trade News, as to the role of the pharmacist, in particular, in cooperation with physicians. The column appeared in the March 18, 1963, (p. 70) issue of Drug Trade News and was written by Louis E. Kazin.

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#### YOUR PARTNER THE DRUGGIST

(By Louis E. Kazin)

#### DRUGGIST CAN CLOSE COMMUNICATIONS GAP

Scientific and professional personnel are becoming increasingly concerned with the "communications gaps" appearing in the pharmaceutical field.

In an address before the presidents and secretaries of Allied Hospital Associations, Surg. Gen. Luther L. Terry, of the U.S. Public Health Service, expressed growing concern over this development.

What he had to say in this particular speech was, of course, directed to the hospital group. But it has many ramifications far beyond hospital activities.

As we read the talk, we could not help getting the impression that although



Dr. Terry was speaking to hospital administrators, his real message, in terms of implementation, was directed to the drug industry and to retail and hospital pharmacists.

He said the basic facts of the matter are these:

"1. We are in the midst of an information explosion—in the health sciences and elsewhere in our scientific society. Tremendous quantities of new information are being generated by our massive research effort.

"2. This outpouring of scientific information has overwhelmed our traditional channels of communication, which were developed to meet vastly different conditions.

"3. As a result, much valuable knowledge is not reaching the people who can use it—scientists, practitioners and many other publics.

"4. Consequently, there is a constantly growing gap between what is known and what is done. More specifically and more graphically, people are dying who need not die; people are suffering who need not suffer."

#### NO CRITICISM WAS INTENDED

We can assume, of course, that the Surgeon General was not being critical of any specific facet of the drug industry. Nevertheless the points he made fall directly within those responsibilities referred to in our editorial on page 40 of this issue, namely, increased communications responsibility.

Here is another quotation from Dr. Terry's presentation, which we believe is highly significant:

"Communication implies a message, a sender, and a receiver. In the health professions, the message is usually a new package of knowledge, of potential usefulness in the practice of medicine. The original sender is a research scientist. The desired receiver is a physician, or the staff of a hospital.

"But at this point we strike a snag. Transmitting the message is not the primary interest of the originator; he is more interested in generating further knowledge than in transmitting that which is known.

#### NOT PRIMARY FUNCTION

"Further, receiving new information is not the primary function of the practitioner; his main job is taking care of as many patients as possible, as well as possible, and it's a full-time occupation.

"Thus, at both ends of our communication line, we have people for whom communication is strictly a secondary interest. And since the primary interest of each is all-absorbing, we should not be unduly surprised that the package of information drops off the line somewhere in between."

As an industry executive, how do you feel about Dr. Terry's comment with respect to the originators' and practitioners' failure to transmit and receive, respectively, necessary information? And are you doing your best to make sure the "information explosion" is not just a loud noise, but rather is utilized to the full advantage of the entire scientific community?

If information is not getting through, then we as an industry and profession have failed to do a real communications job.

However, the Surgeon General suggests a solution to this problem. Within his recommendation, the role of "your partner the druggist" can become highly significant.

Dr. Terry says clearly that the process needs a middleman, or several middlemen skilled in the selection of information. Their responsibility would be "the translation of that which is known into a usable and understandable form; skilled in transmission-choosing and using the best channels to reach the right people."

#### ASKS GREATER RECOGNITION

He then goes on to say: "If we are really serious about the importance of this communications problem, we shall not treat these middlemen as second class citizens. We need to give more recognition to those who dedicate their efforts to sifting, abstracting, reviewing, synthesizing, and disseminating health information, with sophistication and meaning."

Well, as far as we're concerned, today's competent and well-trained pharmacist has many of these skills—not all of them, we admit, but enough to minimize the problems stressed by Dr. Terry.

Pharmacists are in daily contact with physicians. Their relationships are personal and friendly, as well as scientific and professional in nature.



In a recent "Your Pharmacy and Mine" column in Drug Topics, we urged retail druggists to study Dr. Terry's remarks in terms of the "middleman approach."

Many are doing just that. On the other hand, among those who still need to be instructed in terms of the Surgeon General's recommendation, there are many who contend that pharmaceutical manufacturers do not provide them with sufficient information either through brochures, pamphlets or journal advertising to enable them to assume the role of skilled communicators.

#### HELP SHAPE PRESCRIBING HABITS

We have long emphasized in this column and others that druggists, through their personal contacts with physicians, do a real job in shaping the prescribing habits of physicians. Many pharmacists go further and, during face-to-face contacts, contribute much to the physician's knowledge of new drug development.

Yet there are many in our field who contend that surveys do not prove this point to be true. Isn't it about time to recognize, if not publicly, the fact that most medical practitioners jealously guard their information sources? After all, it is well known that throughout their educational and medical practice experience, they have been taught never to admit that they need professional people practicing in ancillary areas to help them meet the increasing responsibilities of modern medical practice.

It may be too much to ask physicians to acknowledge this need right now. Despite this, it is imperative that the doctor be provided with as much information about new drugs as possible.

Practically speaking, "your partner the druggist" can do a real job for you. We've said this before, but it's worth saying again. No physician develops his medical practice and knowledge of prescription medication without the help of one or more pharmacists. It's time all concerned recognized this so that all may benefit fully and unreservedly.

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#### EXHIBIT 165

##### ARTICLE IN THE READER'S DIGEST ON DRUG THERAPY

The March 1963 issue of Reader's Digest contained the following article, informing laymen as to the benefits and hazards of drug therapy.

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[From Reader's Digest, March 1963, pp. 99-102]

##### WHAT YOU SHOULD KNOW ABOUT THE DRUGS YOU TAKE

A DOCTOR TELLS WHAT MODERN DRUGS CAN DO, WHAT THEY CANNOT DO; HOW TO USE THEM, HOW NOT TO USE THEM

(By Robert E. Gosselin, M.D., Ph. D.)

The drugs you took—or gave your children—a generation ago could not do much harm; but they did not do much good either. Modern medicines are capable of doing a great deal of good—and an almost equal amount of harm. Many people do not understand that the drug which performs a "miracle" cure does it by radically altering body processes.

Every physician is familiar with the patient who attempts to bully him into prescribing a potent drug for a trivial complaint. A New Jersey engineer, an otherwise logical man, casually brushes aside his doctor's explanation that using a high-powered antibiotic for the sniffles may leave him vulnerable to an infection which is resistant to conventional treatment. An overanxious parent in New York procures a potent hormone to trigger sexual maturity in her 14-year-old son, despite the specialists' advice that he is entirely normal. On the West Coast a college boy has his acne treated with a powerful antibiotic, chloramphenicol—a dangerous drug but an invaluable one in certain serious diseases. Perhaps the drug would have helped the acne, but the boy died of aplastic anemia induced by the treatment.

Modern drugs should be used with caution. For example, you may be—or may become—allergic to even the most common medication. Penicillin is certainly an



effective drug—more than 500 tons are consumed each year—but it is often used indiscriminately. Penicillin shock and other side effects are genuine hazards to those who have become hypersensitive.\* Antibiotics should not be used for a runny nose, to make it possible for a teenager to go to the dance, or to allow her mother to hostess the bridge club.

One source of trouble is that many items purchased without a prescription in a drugstore or supermarket are simply not considered drugs by the public. Many people do not recognize as potent medicine the laxative they take or the sleeping tablet which is advertised as harmless. Still another problem is the casual and usually inappropriate use of drugs left over from a previous illness, sometimes even the illness of another person.

A 17-year-old boy passed out and was rushed to a New York hospital last year. His hemoglobin and red-cell count was down to 15-percent of normal. The doctor suspected a drug reaction, but the boy innocently denied taking any medicine. Later it was discovered that he had consumed enormous amounts of aspirin for headaches, enough to cause near-fatal internal bleeding.

Your physician needs to know *all* the drugs you are taking. A housewife recently came to our hospital for a routine operation. When her medical history was taken, she hid the fact that she had been using large daily doses of a tranquilizer, chlorpromazine, and had smuggled a supply into the hospital with her. This secrecy nearly caused her death. In the operating room the next morning she was given a small dose of thiopental sodium to put her to sleep, and suddenly her blood pressure dropped to zero. Only a heroic effort saved her.

Today with our tendency to move frequently, and with various kinds of medical specialists available, you may find yourself consulting several doctors. If so, you should insist on learning the name of every medicine prescribed, so that you can keep your various physicians informed about the drugs you are taking. The fact that you received a series of antibiotic shots may be as vital a part of your medical history today as the fact that you had your appendix removed.

Drugs may create symptoms, or hide them. Drowsiness may be caused by a hay-fever capsule, sleeplessness by a diet pill. The tranquilizers chlorpromazine and reserpine have a tendency to potentiate some drugs and counteract others. Psychic energizers are capable of interfering radically with the metabolism of various drugs: Taken before or after another preparation, they may multiply its effects or make it useless. A student staying up late studying may get into real trouble when he combines amphetamine with coffee or a cola drink, all stimulants of the central nervous system. The resulting intoxication can mean restlessness, nausea, confusion, delirium, and collapse.

The American Automobile Association says that you should always ask your physician if it is safe to drive when you are taking medication. A tranquilizer, a blood-pressure pill, or a capsule to clear clogged sinuses may make you a hazard on the highway. Statistics are hard to come by because police rarely suspect conventional medicine as the cause of an accident. Safety experts, however, are convinced that "harmless" drugs cause many drivers to use bad judgment or to react too slowly at high speeds.

It is also certain that a number of unintentional suicides are caused by intrinsically safe drugs, each well within the accepted dose, but hazardous when used together or with alcohol. Chloral hydrate, for example, is an old-fashioned sleeping potion. It is now gaining new popularity because of a questionable assertion that it is not as habit-forming as the barbiturates. Mix "harmless" chloral hydrate with alcohol, however, and you have a potentially fatal combination called a "Mickey Finn."

But if it is unwise to take powerful medicines casually, it is equally irrational to refuse to use medication under a doctor's care—as some patients do, sometimes for inexplicable reasons. A colleague told me about a patient of his, a young and apparently intelligent housewife who suffered from malignant hypertension, a condition that was always fatal before new drugs were developed. Her blood pressure reached 240/135, and her heart was distinctly enlarged.

Vigorous treatment with powerful antihypertensive drugs—reserpine, chlorothiazide, hydralazine, and ganglionic blocking agents, all of which were prescribed, singly and in combination—should have reduced the pressure and eased the demands on her heart. Instead, after 9 months she died in convulsions.

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\*See "Why Doctors Hesitate To Prescribe Antibiotics," the Reader's Digest, October 1959.



After the funeral her husband discovered a collection of medicine bottles hidden in a bureau drawer: each of the prescriptions had been filled, but none of the bottles had ever been opened.

Fear is a major reason patients refuse the medicine they need—fear of being poisoned or fear of becoming dependent or addicted. Others regard taking drugs, especially painkillers, as a sign of moral weakness. These attitudes make it impossible for the doctors to treat many patients whose suffering could be eased safely and effectively.

Another common difficulty of the physician is persuading patients to continue drug therapy as long as is necessary. Many drugs do not cure but only control illness. If you have been given digitalis after once suffering from congestive heart failure, thyroid tablets after myxedema, aspirin or hormones for chronic arthritis, eye drops for glaucoma, insulin for diabetes, or other drugs for chronic conditions, it is generally unwise to stop taking medicine without your doctor's advice.

A colleague of mine has a 50-year-old patient with rheumatoid arthritis which responded well to large doses of aspirin. The swelling in her knees subsided and the pain disappeared. She felt so well that after 2 years she decided to discontinue treatment. Within a week she was as disabled as before, and there might have been irreversible joint damage if treatment had not been resumed promptly.

We should accept modern drugs as we do the automobile. Both can do a great deal of harm when they are misused and much good when handled properly. We must not fear drugs but learn to understand what they can and cannot do.

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#### EXHIBIT 166

ARTICLE BY HUGH F. KABAT, PH. D., ON HOSPITAL PHARMACY IN MINNESOTA

In part 1, reference was made to the role of hospital pharmacists. The following article appeared in the official publication of the Minnesota State Pharmaceutical Association and of the Twin City Retail Druggists Association, *Minnesota Pharmacist* (vol. 17, No. 7, Apr. 1963, pp. 29-30, 50). The article was written by Hugh F. Kabat, Ph. D., Assistant Professor of Pharmaceutical Technology, College of Pharmacy, University of Minnesota.

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#### HOSPITAL PHARMACY IN MINNESOTA

(By Hugh F. Kabat, Ph. D.)

Institutional pharmacy has become an area characterized by remarkable growth, by young, vibrant, and interested practitioners, and by an increasing role in the distribution of prescription legend drugs. Today, almost 10,000 pharmacists practice their profession in the more than 7,000 hospitals in the United States.

The hospital is the natural focus of health resources in the community. Its primary function is to assist in the conservation of the Nation's health. The modern hospital, through institutional synthesis, brings together a variety of technical, paramedical, and medical skills in order that the patient may receive the full benefit of present medical knowledge. The pharmacy service has always been an essential component of contemporary hospital care. In the hospital the pharmacy service is that essential professional department which concerns itself with the evaluation, selection, control, distribution, and utilization of drugs.

In an effort to learn more about the current status of hospital pharmacy practice in Minnesota, a questionnaire was mailed to the chief pharmacist of every Minnesota hospital during the summer of 1962. A covering letter was used to explain the purpose of the questionnaire. Almost 60 percent of the questionnaires were returned. It was particularly gratifying to obtain this level of response, since July is a poor month to canvass hospitals for information due to vacation schedules. Many administrators took substantial time to provide the data. Table I summarizes the returns.



**TABLE I.—Minnesota hospitals, questionnaire responses, and percentage response to questionnaire according to bed capacity, July 1962**

Bed capacity	Number of hospitals	Number of responses	Percent
More than 500.....	16	13	81
200 to 499.....	17	15	88
100 to 199.....	32	23	72
50 to 99.....	45	27	60
25 to 49.....	73	34	47
Less than 25.....	40	20	50
Total.....	223	132	59

The smaller percentage of responses from hospitals with less than 100-bed capacity is probably a reflection of the fact that they do not employ a pharmacist. The administrator, in numerous cases, must have discarded the questionnaire, feeling that it did not apply to his institution since he did not employ a pharmacist.

This report is a summary of the level of some selected pharmacy services in Minnesota hospitals as determined by the questionnaire.

**TABLE II.—Percentage of responding hospitals employing a pharmacist according to bed capacity, July 1962**

Bed capacity :	Percentage of responding hospitals employing pharmacists
More than 500.....	85
200 to 499.....	100
100 to 199.....	78
50 to 99.....	18
25 to 49.....	3
Less than 25.....	15
Total.....	42

Table II shows what might have been suspected. Bed capacity almost always determines whether or not it is economically feasible for the hospital to employ a pharmacist on a regular basis. As bed capacity declines below 100 beds, employment of a pharmacist is the exception rather than the rule. The percentage rise in the below 25-bed capacity hospitals is due to a large outpatient activity in some governmental institutions requiring additional personnel. It is rather disconcerting to know that only 42 percent of the respondents retained a pharmacist on a full- or part-time basis to provide pharmaceutical services to their patients.

Minnesota hospitals do not seem to utilize pharmacists in a dual capacity in smaller hospitals as a pharmacist-storekeeper, pharmacist-purchasing agent, pharmacist-central sterile supply director, or pharmacist-assistant administrator.

It might also be possible for two or more hospitals in close proximity to share jointly a pharmacist on a regular basis.

These practices, though not widespread, are existent in other parts of the country. The needs of the hospital to provide pharmacy services are satisfied, yet recognition is given to the economic demands of additional professional personnel. Administrators in Minnesota could well look at their own institution in this light. Perhaps the fault lies with the pharmacist who has not made the administrator aware of the advantages accruing to the patient from such an arrangement.



TABLE III.—*Percentage of responding hospitals with established pharmacy and therapeutics committees according to bed capacity, July 1962*

	Percentage of responding hospitals with P. & T. committee
Bed capacity:	
More than 500.....	92
200 to 499.....	93
100 to 199.....	83
50 to 99.....	48
25 to 49.....	15
Less than 25.....	20
Total.....	51

The pharmacy and therapeutics committee is an advisory committee of the medical staff which serves as the liaison between the medical staff and the pharmacy department. This committee is composed of the chief pharmacist and members of the medical staff. It is a policy-recommending body, both to the medical staff and to the administration of the hospital on all matters related to the use of drugs. The primary purposes of the pharmacy and therapeutics committee are twofold: (1) Advisory, in the formulation of policies regarding evaluation, selection, procurement, distribution, use, safe practices, and other matters pertinent to drugs in hospitals; and (2) Educational regarding the formulation of programs to meet the needs of the professional staff and complete current knowledge on matters related to drugs and drug practices.

Table III indicates the recognition of these important activities performed by the pharmacy and therapeutics committee. Fifty-one percent of the hospitals had such a committee, although only 42-percent employed a pharmacist on a full- or part-time basis. With no pharmacist to supervise drug practices in the hospital, the pharmacy and therapeutics committee has a vital and essential role to perform. Thus, most of the increase in committee activity is in those hospitals which are without full- or part-time pharmacy services. However, it should be a matter of concern that almost 50-percent of these hospitals did not have an active committee. Clearly an active pharmacy and therapeutics committee is essential when there is something less than full-time pharmacy service provided.

TABLE IV.—*Percentage of responding hospitals with automatic stop orders on dangerous drugs according to bed capacity, July 1962*

	Percentage of responding hospitals with automatic stop orders
Bed capacity:	
More than 500.....	77
200 to 499.....	87
100 to 199.....	96
50 to 99.....	89
25 to 49.....	41
Less than 25.....	35
Total.....	68

The Joint Commission on Accreditation of Hospitals requires that hospitals establish written policies concerning dangerous medications. The policies require that these medications, if not specifically prescribed as to time and number of doses, must be automatically stopped after a reasonable time limit set by the medical staff. This is a protection against indiscriminate and indefinite prescribing of an open-end type which can result in harm to the patient, the physician, and the hospital. Especially included are "p.r.n." orders for narcotics, sedatives, anticoagulants and antibiotics.

Table IV shows that almost 70 percent of all responding hospitals recognize the importance of automatic stop orders on dangerous drugs and have instituted policies regarding them. Here it should be noted that smaller hospitals not employing a pharmacist are most frequently lacking this important drug control measure. These same hospitals have the most critical need for measures of this type. It may be that the accreditation requirement is the major factor in the number of hospitals with established automatic stop orders. The pharmacist, full-time, part-time, or consultant, or the administrator (in the absence of



pharmacy service) should introduce the concept of this control measure into their institution. It is an important guarantee of patient safety and protection.

TABLE V.—*Methods for provision of after hours pharmacy service in responding hospitals according to bed capacity, July 1962*

Bed capacity	On-call pharmacist	Night cabinet	Nursing supervisor	Physician	Local community pharmacist
More than 500.....	3	1	7	2	-----
200 to 499.....	-----	4	11	1	-----
100 to 199.....	1	4	12	2	5
50 to 99.....	1	-----	20	-----	6
Less than 50.....	-----	-----	-----	-----	-----

The provision for afterhours pharmacy service has always been difficult for the hospital. Patterns of illness do not appear in 8-hour shifts or 40-hour weeks. Consequently pharmacy service is necessary on a 24-hour basis.

Provision for afterhours pharmacy service does not seem to follow any pattern according to bed capacity. Table V summarizes the replies to the questionnaires from responding hospitals. Most hospitals depend upon the night nursing supervisor to obtain from the pharmacy department the drugs that might be needed on an emergency basis. These are obtained from a night cabinet or are removed from stock containers. The supply obtained is generally only enough to last until the pharmacist is available to fill the order.

In smaller hospitals that do not employ a pharmacist, nursing supervisors generally fill patient orders both day and night. Smaller hospitals frequently depend upon the local community pharmacy to provide this essential afterhours service. The community pharmacy, with its traditionally longer hours of availability, is in an excellent position to provide this afterhours service to the hospital on a regular basis.

Although it has been advocated for years that the community practitioner of pharmacy make his services available to small hospitals, no measure has ever been made of the extent of this relationship. Table VI illustrates the fact that in those hospitals that do not employ a pharmacist, 63 percent do, in fact, avail themselves of the services that one of the local community practitioners of pharmacy is able to provide. This is very encouraging. Even though these institutions have been unable economically to staff the hospital with a full-time pharmacist, they have been able to provide essential pharmacy services to their patients.

TABLE VI.—*Number and percentage of responding hospitals utilizing community pharmacists in the absence of a full-time pharmacist according to bed capacity, July 1962*

Bed capacity	Number of responding hospitals utilizing community pharmacist	Percentage of responding hospitals utilizing community pharmacist
More than 500.....	2	100
200 to 499.....	0	-----
100 to 199.....	5	100
50 to 99.....	16	73
25 to 49.....	19	58
Less than 25.....	8	47
Total.....	50	63



TABLE VII.—*Provisions for pharmacy service in responding hospitals according to bed capacity, July 1962*

Bed capacity	Number of responding hospitals	Number with full-time pharmacist	Number utilizing community pharmacist	Total of last two columns
More than 500.....	13	11	2	13
200 to 499.....	15	15	—	15
100 to 199.....	23	18	5	23
50 to 99.....	27	5	16	21
25 to 49.....	34	1	19	20
Less than 25.....	20	3	8	11
Total.....	132	53	50	103

If one looks at the total picture (that is those hospitals employing full-time pharmacists and those utilizing the community practitioner of pharmacy), it is readily apparent that almost 80 percent of the hospitals in the Minnesota study do, in fact, have the professional services of a pharmacist available to them. This is laudable. However, a concentrated effort should be made to educate the administrators of the remaining institutions (20 percent) to the advantages accruing to the patient and to the hospital from the availability of pharmacy service.

Modern medical therapy requires close supervision to prevent potential dangers of drugs, such as incorrect usage, unwise storage, lack of availability at the moment of need, and failure to recognize untoward reactions. The failure to provide adequate drug control measures often is a result of lack of education concerning the possible or inherent dangers.

The Code of Ethics of the American Pharmaceutical Association delineates the responsibilities of the community practitioner of pharmacy to society in the area of public health, as follows:

(1) "The primary obligation of pharmacy is the service it can render to the public in safeguarding the preparation, compounding, and dispensing of drugs, and the storage and handling of drugs and medical supplies.

(2) "The pharmacist willingly makes available his expert knowledge of drugs to other health professions."

The community practitioner of pharmacy has the moral responsibility of making his knowledge and services available to all parties who would stand to benefit from this relationship. About 20 percent of the hospitals in Minnesota do not have provisions for pharmacy service. Practitioners of pharmacy have an ethical responsibility to make the administrators of these institutions knowledgeable concerning the benefits accruing to the patient and to the hospital through this provision of pharmacy service.

Pharmacy service in the hospital encompasses far more than prescription service. Community pharmacists are able to establish substantial pharmacy programs in smaller hospitals that are unable to obtain the services of a full-time pharmacist. Hospital pharmacists in the larger hospitals have an important responsibility to maintain a very high level of pharmacy service so that patient safety may be insured.

#### EXHIBIT 167

##### EXCERPTS FROM THE MEDICAL LETTER WITH REGARD TO A SERIES OF WARNING LETTERS AND OTHER MESSAGES OF CAUTION ON MER/29 AND OTHER DRUGS

The January 19, 1962, issue of The Medical Letter (vol. 4, No. 2) contained the following comments on pages 5 to 7 with regard to warnings on MER/29 and other drugs.

#### MER/29 AND WARNINGS ON NEW DRUGS

Letters warning against serious untoward effects of new drugs or reporting withdrawal of the drugs from the market have been sent to physicians by several drug companies in recent months. The latest of these letters (all prepared in cooperation with the Food and Drug Administration) comes from the



Wm. S. Merrell Company; it warns physicians that triparanol (MER/29), promoted for use in hypercholesterolemia and coronary artery disease, has caused such injurious effects as cataracts, baldness, loss of body hair, and changes in hair color and texture. Skin changes ranging from dryness, itching and scaling to severe exfoliation and ichthyosis have also been reported. And adrenocortical function may be significantly depressed in patients "who are subjected to stress." Other clinical reports mention four possible cases of leukopenia and scattered cases of abnormal liver function tests, impotence, diminished libido, vaginal smear alterations and vomiting.

**Need for Caution.**—How these injurious effects are produced is unknown; they may be related to the drug's action of inhibiting cholesterol synthesis and accumulation in the blood and tissues of desmosterol (the immediate precursor of cholesterol). The Medical Letter (2:81, Oct. 14, 1960) warned that because of uncertainty as to its safety, the drug should be used only for experimental trial. The Council on Drugs of the AMA (JAMA, 178:574, Nov. 11, 1961) has also urged that " \* \* \* all patients receiving triparanol be maintained under the carefully controlled conditions of clinical investigations \* \* \* " In view of the reported effects, The Medical Letter believes the drug should not be used at all; if the physician considers it advisable to attempt to lower serum cholesterol, a safer means should be employed, such as dietary changes (Medical Letter, 3:85, Oct. 27, 1961).

Other warning notes and withdrawals in recent months include:

**Dithiazanine Iodide (Delvex-Lilly).**—This is a valuable anthelmintic drug but, according to the manufacturer, capable of causing a high incidence of gastrointestinal symptoms and strongly suspected of causing as many as six deaths. The Medical Letter (3:76, Sept. 15, 1961) recommended the use of the drug with suitable caution only in symptomatic *Strongyloides stercoralis* and *Trichuris trichiura* infections (no other agent is effective), and not at all in ascariasis.

**Zoxazolamine (Flexin-McNeil).**—This drug was withdrawn in October 1961 because its use is associated with liver damage. The Medical Letter (3:11, Feb. 3, 1961) warned of "possible hepatotoxicity" from the use of Flexin, and said that until experience is much greater there is no compelling reason to substitute either sulfinpyrazone (Anturane) or zoxazolamine (Flexin) for probenecid (Benemid) as the uricosuric agent of first choice.

**Amphenidone (Dornwal-Maltbie).**—The Medical Letter (3:4, Jan. 6, 1961) appraised this tranquilizer and warned, "The reported \* \* \* absence of side effects is of little significance in view of the small number and the nature of the clinical studies." It was withdrawn in November 1961 because of reports of agranulocytosis.

**Furaltadone (Altafur-Eaton).**—The Medical Letter (2:68, Aug. 19, 1960) warned, "In view of the hazard, and of the questionable effectiveness of the drug, Medical Letter consultants advise against any use of Altafur." It was withdrawn in November 1961 because it is unsafe and ineffective.

**Erythromycin Propionate Lauryl Sulfate (Ilosone-Lilly).**—In August 1961 the manufacturer warned of liver injury and jaundice occurring in some patients (22 cases collected by the manufacturer as of December 29, 1961) usually after more than 2 weeks of therapy. Because of the possibility of intrahepatic cholestasis (probably allergic) after use of the propionyl lauryl sulfate ester of erythromycin, this preparation should be employed only for acute coccal infections not responsive to a penicillin and for not longer than 7 days. Repeated courses should also be avoided. The Medical Letter (1:18, Mar. 20, 1959) said, "Since Ilosone has been used for a relatively short time, the judgment that it is comparable to the older erythromycin in freedom from toxicity and serious side effects must be tentative." However, until it is definitely established that other erythromycins (base, stearate, and other derivatives) are free of the effects observed with Ilosone in prolonged use or repeated courses, no erythromycin should be used for treatment of chronic disorders such as acne and furunculosis or for prophylaxis or rheumatic fever.

**Triacetyloleandomycin (Tao-Roerig; Cyclamycin-Wyeth)** and combinations such as Tain (Dorsey) and others. The manufacturers have issued warnings to physicians of liver injury occurring in some patients taking the antibiotic for more than 2 weeks. The Medical Letter (1:5, Feb. 6, 1959) stated that " \* \* \* the antibiotic has been in use for too short a period to be certain of the range and severity of its side effects." Because the indications for the use of triacetyloleandomycin singly or in combinations are so limited (M. H. Lepper, Med. Clin. N. Amer., 45:1663, 1961), and because of the possibility of liver injury, triacetyloleandomycin products should be avoided.



These warnings and withdrawals reinforce the caution repeatedly expressed in The Medical Letter: except in serious disorders where older and safer drugs are ineffective, no new drug should be employed in practice unless controlled clinical trials and extensive experience have clearly established its effectiveness and safety. Most New Drug Applications are made effective by the Food and Drug Administration on the basis of a company's safety data provided by animal experiments, very limited human toxicity studies, physicians' testimonials and usually uncontrolled clinical trials. Even when controlled clinical trials have been performed, the frequency and severity of toxic, allergic, and other injurious effects are not fully defined until the drug has been in use for several years. All promotion statements that a *new* drug has few, mild or no side effects should be ignored.

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#### EXHIBIT 168

#### EXCERPTS FROM CONGRESSIONAL COMMENTS ON THE RIGHT OF THE CONGRESS TO INFORMATION IN THE NEW DRUG APPLICATION FILES

On page 810, Senator Humphrey referred to the issue of confidentiality of "trade secrets." This issue has arisen in numerous connections in the course of the subcommittee study.<sup>29</sup> The present and succeeding exhibits relate to various aspects of "trade secrets."

This exhibit, includes excerpts from the legislative history of Public Law 87-781, the Drug Amendments of 1962, as regards the right of the Congress to information.

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#### CHRONOLOGY OF EXCERPTS IN THE LEGISLATIVE HISTORY OF DRUG AMENDMENTS OF 1962

#### STATEMENT OF HON. L. H. FOUNTAIN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NORTH CAROLINA<sup>30</sup>

MR. FOUNTAIN. Mr. Chairman and members of the committee, I want to thank you for giving me this opportunity to appear before you this morning. My purpose here today is not to take a position on the general merits of H.R. 11581, but to express my objection to a particular section thereof which would, in my opinion, seriously hamper the work of the congressional committees which have responsibilities with regard to food, drug, and cosmetic legislation or the operations of the Food and Drug Administration. I refer to section 202 of H.R. 11581, amending section 301(j) of the Federal Food, Drug, and Cosmetic Act.

As section 301(j) is presently written, it prohibits "the using by any person to his own advantage, or revealing, other than to the Secretary or officers or employees of the Department, or to the courts when relevant in any judicial proceeding under this Act, any information acquired under authority of section 404, 409, 505, 506, 507, 704, or 706 concerning any method or process which as a trade secret is entitled to protection."

The effect of the amendments proposed in section 202 of H.R. 11581 would be to extend this confidentiality beyond "trade secrets" to include any information acquired by the Food and Drug Administration under the stated sections of the Food, Drug, and Cosmetic Act.

Since only the officers and employees of the Department and the courts are given access to confidential information under section 301(j), passage of section 202 in its present form would, in my opinion, make it virtually impossible for the congressional committees which have responsibilities in connection with food, drug, and cosmetic legislation or the operations of the Food and Drug Administration to obtain the information necessary, for the effective discharge of those responsibilities.

Under the rules of the House, the Committee on Government Operations has the duty of "studying the operation of Government activities at all levels with a view to determining its economy and efficiency."

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<sup>29</sup> On June 26, 1963, at a subsequent hearing Senator Ernest Gruening, as acting chairman of the subcommittee, discussed the issue in connection with testimony by representatives of the American Medical Association.

<sup>30</sup> House Committee on Interstate and Foreign Commerce, Subcommittee on Health and Safety, hearings on Drug Industry Act of 1962, pp. 108-111.



The responsibility for studying the operations of the Food and Drug Administration, as well as those of a number of other Federal agencies, has been delegated by the Committee on Government Operations to its Intergovernmental Relations Subcommittee, of which I am chairman. Our past experience in trying to fulfill this responsibility has shown that on occasion the Food and Drug Administration has used section 301(j) as a basis for withholding access to information which the subcommittee deemed necessary for the proper discharge of its responsibilities to the full committee and to the House. I have copies of two letters of recent date which will, I believe, demonstrate this problem. I would like to read them at this time.

They relate to a situation which arose in late April of this year when two prescription drugs were withdrawn from the market due to the discovery of dangerous side effects. Both drugs had previously been approved by the Food and Drug Administration under its new drug procedure and had been on the market for some time. In an effort to determine whether the Food and Drug Administration had fully and effectively met its responsibilities in the clearing of these two drugs for the market, the subcommittee sent the following letter to Commissioner Larrick:

MAY 2, 1962.

HON. GEORGE P. LARRICK,  
*Commissioner, Food and Drug Administration,  
Department of Health, Education, and Welfare,  
Washington, D.C.*

DEAR MR. LARRICK: In connection with its responsibility for studying the activities of the Food and Drug Administration with respect to efficiency and economy of operation, the Intergovernmental Relations Subcommittee wishes to obtain information concerning two drugs which were recently withdrawn from the market due to the discovery of dangerous side effects. They are MER/29, manufactured by Richardson-Merrell Co., and Flexin, manufactured by McNeil Laboratories.

Will you please arrange for Mr. Donald Gray of the subcommittee's staff to examine your files containing the new drug applications for these two drugs and any other information you may have concerning them.

Your cooperation in this matter will be greatly appreciated.

Sincerely yours,

L. H. FOUNTAIN,  
*Chairman, Intergovernmental Relations Subcommittee.*

I received the following letter from Mr. Larrick in reply:

MAY 10, 1962.

HON. L. H. FOUNTAIN,  
*Chairman, Intergovernmental Relations Subcommittee,  
Committee on Government Operations,  
House of Representatives, Washington, D.C.*

DEAR MR. FOUNTAIN: We have your letter of May 2, 1962, requesting us to arrange for Mr. Donald Gray of the subcommittee staff to examine our files covering the new drug applications for MER/29 and Flexin.

We want to be as helpful as possible to your committee. However, the Federal Food, Drug, and Cosmetic Act imposes certain restrictions on us which we must respect. Under the law, we are forbidden to disclose any information submitted in connection with a new drug application that is entitled to protection as a trade secret. Our regulations further emphasize the fact that all information submitted in connection with new drug applications will be treated as confidential. The reason for these restrictions is to encourage manufacturers to make as full a disclosure as possible when they submit their new drug application, including information involving doctor-patient relationships.

We have uniformly declined to make the files on new drugs available to anyone except employees of the Food and Drug Administration. We are confident, however, that we can prepare a summary of these new drug applications that will contain all pertinent information. We will undertake the preparation of these summaries promptly and they will be sent to you as soon as they are completed.

After you have had an opportunity to review them, we will be glad to arrange for a meeting between Mr. Gray and our personnel who are familiar with these files to clarify any questions you may have. We should point out that even though these drugs have been removed from the market, we are actively investigating both of these cases to determine whether false statements



were made in connection with the new drug applications or whether there was a failure to disclose material facts.

We hope that our suggested handling of your request will be satisfactory. Again let me say that we want to furnish you with all information that we possibly can within the limitations imposed on us by the statutes.

Sincerely yours,

GEORGE P. LARRICK,  
*Commissioner of Food and Drugs.*

Following receipt of this letter, members of the subcommittee staff talked with Assistant Commissioner Rankin and Mr. William W. Goodrich, the Department's Assistant General Counsel, Food and Drug Division. The staff assured Mr. Rankin and Mr. Goodrich that neither they nor the subcommittee were interested in seeing any information entitled to protection by law as a trade secret. I might point out that Mr. Larrick incorrectly states in his letter that his agency has uniformly declined to make the files on new drugs available to anyone except employees of the Food and Drug Administration. The fact is that our subcommittee staff has examined such files in the past, and FDA had not previously in our experience claimed confidentiality for these records.

The subcommittee staff was then assured by Mr. Rankin that, in view of these facts, our request would be reconsidered by the Food and Drug Administration. However, despite numerous telephone inquiries from the staff, no further action has yet been taken on the request; nor have the summaries which Mr. Larrick promised in his letter of May 10 been received.

I have gone into those details merely to demonstrate the difficulty which our subcommittee has encountered in obtaining certain information from the Food and Drug Administration under the existing section 301(j). I believe that the amendments proposed in section 202 of H.R. 11581 translate into law the interpretation which the Food and Drug Administration has already placed upon section 301(j), as outlined in Mr. Larrick's letter of May 10, and which I believe to be incorrect.

In view of the experience which our subcommittee has had under the existing section 301(j), I believe that enactment of section 202 of H.R. 11581 in its present form would be most undesirable and would make it virtually impossible for the subcommittee to perform its duties in connection with the operations of the Food and Drug Administration. For this reason, Mr. Chairman, I would like to propose for the Committee's consideration an amendment to section 202 of H.R. 11581 to read as follows:

"On page 32, line 25, immediately before the period, insert the following: 'and inserting in lieu thereof the following: *Provided*, That nothing in this Act shall authorize the withholding of information from the duly authorized committees of the Congress.'"

This language has been successfully used, I understand, in the organic act setting up the National Aeronautics and Space Administration and in the legislation setting up an Advisory Committee on Weather Control, and, doubtless, in other legislation.

I believe that the adoption of this or a similar amendment would enable our subcommittee and the other committees and subcommittees of the Congress having responsibilities with regard to food, drug, and cosmetic legislation or the operations of the Food and Drug Administration to meet their responsibilities more effectively and with greater dispatch. To me it is unthinkable that information, other than trade secrets, which is available to officers and employees of the Department of Health, Education, and Welfare, as big as it is, as well as to the courts, should not also be available to the Congress, which passes the legislation and appropriates the funds necessary for the Department's operations.

I thank you for the opportunity to be heard on this point which I believe to be of the utmost importance to the Congress. \* \* \*

Mr. Moss. I would like to compliment the gentleman for bringing this to the attention of the committee. As chairman of the Information Subcommittee of Government Operations, the question which underlies the refusal here of the Food and Drug Commissioner to supply the information is one which was exhaustively heard by the subcommittee, I believe, in 1956.

It is an interesting fact that when Congress has intended to limit its own access to information, that it has been eminently successful in stating that in the statute.

There is nothing in the statute upon which the Commissioner relies or in the history of the discussions, either in committee or on the floor, indicating that Congress ever intended that this act as a barrier to the Congress or its committee for this information.



[H. Rept. 2464, 87th Cong., 2d sess.]

## DRUG AMENDMENTS OF 1962

SEPTEMBER 22, 1962.—Committed to the Committee of the Whole House on the State of the Union and ordered to be printed

Mr. HARRIS, from the Committee on Interstate and Foreign Commerce, submitted the following report

[To accompany H.R. 11581]

\* \* \* \* \*

(p. 15)

## CONFIDENTIALITY OF INFORMATION OBTAINED BY INSPECTION, AND SO FORTH

Section 202 of the bill amends section 301(j) of the basic act, which presently makes it a criminal offense for any person to use to his own advantage, or to disclose, other than to the Secretary or officers or employees of the Department, or to the courts, information acquired under section 404 (emergency permit control), 409 (food additives), 505 (new drugs), 507 (antibiotics), 704 (factory inspection), or 706 (color additives) of the basic act, where such information concerns any method or process which as a trade secret is entitled to protection.

In view of the broadened factory inspection authority contained in the bill, the committee amendments to section 301(j) extend the prohibitions of this section to all information acquired under those sections, whether or not the information involves trade secrets.

The committee also added to section 301(j) a proviso stating that nothing in the basic act shall authorize the withholding of information from the duly authorized committees of the Congress. This amendment will remove any basis for a claim by the Department of Health, Education, and Welfare that the Department is prohibited by the basic act from providing congressional committees information which they request.

(*Newspaper Article*)

September 29, 1962

Morton Mintz, in the Washington Post and Times-Herald:

## KENNEDY ASKS FUNDS FOR DRUG CONTROL BILL

(By Morton Mintz, Staff Reporter)

President Kennedy asked Congress yesterday to give the Food and Drug Administration a \$2 million supplemental appropriation to implement new drug safety legislation.<sup>1</sup>

He also asked for \$600,000 to enable FDA to carry out regulations proposed under existing law to insure greater safety in the use of experimental drugs on humans.

The House and Senate have passed basically similar drug bills that are expected to be reconciled in conference Monday, with the resulting compromise apparently assured of enactment.

In a related development, the Department of Health, Education, and Welfare said it "would have no objection" to deleting from the House bill an administration-sponsored revision that could extend certain bans on public disclosure of information to include dangers found in new drugs and additives.

No comparable language is in the Senate bill, which includes factory-inspection provisions approved by the administration.

<sup>1</sup> The first three paragraphs are reprinted for purpose of providing the context; the remaining paragraphs provide additional historical information for the present exhibit. (Editor's note.)



Present law forbids any person from using "to his own advantage" or from disclosing to anyone other than HEW personnel or the courts, information that concerns "any method or process which as a trade secret is entitled to protection."

#### LIMITATION REMOVED

At FDA's urging, the trade-secret limitation was removed. In its report on the bill, the House Commerce Committee said the deletion extends the disclosure prohibitions to FDA information "whether or not (it) involves trade secrets."

Questioned by Representative John E. Moss, Democrat, of California, chairman of the House Government Information Subcommittee, FDA Commissioner George P. Larrick said that:

FDA requested the revision "to make it perfectly clear that \* \* \* there would be adequate safeguards against" an employee's use to his own advantage of information gathered under the broadened factory-inspection powers the bill would grant.

The revision would not diminish HEW's authority to report on investigations involving imminent danger to health or gross deception of the consumer.

FDA intends to continue to giving "a full reporting" of facts that "are in the public interest."

#### INFORMATION TO CONGRESS

At the request of Representative L. H. Fountain, Democrat, of North Carolina, the Commerce Committee added language forbidding the withholding of information from Congress.

In June, Fountain told the committee that FDA had withheld information from his Intergovernmental Relations Subcommittee on two drugs, MER/29 and Flexin, which "were withdrawn from the market due to the discovery of dangerous side effects."

Fountain testified that the subcommittee wanted to find out whether the FDA, which had previously cleared the drugs for sale, "had fully and effectively met its responsibilities."

Fountain said that Larrick refused to make the files on the drugs available, but promised to compile and deliver summaries "promptly." The summaries did not become available until several weeks later.

Fountain also testified that Larrick had "incorrectly" written him that FDA has "uniformly declined to make the files available to anyone except" FDA employees. He said his subcommittee's staff "has examined such files in the past."

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[H. Rept. 2526, 87th Cong., 2d sess.]

#### DRUG AMENDMENTS OF 1962

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OCTOBER 3, 1962.—Ordered to be printed

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Mr. ROBERTS of Alabama, from the committee of conference, submitted the following conference report

[To accompany S. 1552]

\* \* \* \* \*

#### CONFIDENTIALITY OF INFORMATION OBTAINED BY INSPECTION

The House amendment amended section 301(j) of the Federal Food, Drug, and Cosmetic Act with regard to the confidentiality of information obtained by inspection.

The Senate bill did not contain a similar provision.

The conference substitute omits the provision contained in the House version amending section 301(j) of the act. This leaves existing law on this subject unchanged.



Senator Estes Kefauver : <sup>2</sup>

SECTION 202—CONFIDENTIALITY OF INFORMATION OBTAINED BY INSPECTION

The House bill extended the scope of the confidentiality requirements in section 301(j) of the Food, Drug, and Cosmetic Act, but made a special provision to the effect that "nothing in this act shall authorize the withholding of information from the duly authorized committees of the Congress." The conferees decided to strike the confidentiality provision entirely from the bill and to leave the law on this matter as it is.

The Senate Subcommittee on Antitrust and Monopoly has in the past had no difficulty in securing information from the Food and Drug Administration and has never wished to secure information of the type prohibited by the present law, namely information relating to "any method or process which as a trade secret is entitled to protection." It is expected, of course, that since the Congress is not making the law more restrictive on this matter, the FDA will not make its interpretation and administration of section 301(j) more restrictive. Congress and the public deserve to have access to information in the Food and Drug Administration which is not of the nature of a trade secret and is in the public interest.

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EXHIBIT 169

TRADE SECRETS: EXCERPTS OF COMMENTS ON THE ISSUE OF CONFIDENTIALITY OF INFORMATION IN THE FILES ON NEW DRUG APPLICATIONS IN THE FOOD AND DRUG ADMINISTRATION AND ON RELATED ASPECTS IN OTHER FEDERAL AGENCIES

The present exhibit supplements the previous comments with respect to the issue of trade secrets. Two types of information are included herein: (a) excerpts of comments on the specific issue of the confidentiality of information in the files on New Drug Applications in the FDA, and (b) by way of general background, excerpts of comments on the issue as it affects other Government agencies, particularly the Department of Agriculture. The latter excerpts begin with comments by the President's Science Advisory Committee as regards the issue of confidentiality of information in pesticide applications. This latter subject is at present under consideration by the Senate subcommittee as part of its study of interagency coordination in environmental health hazards.

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May 19, 1958.

F-D-C Reports—"The Pink Sheet": <sup>31</sup>

Opening of NDA analytical methods for medicated feeds to state feed officials is still under consideration by the Food and Drug Administration (FDA) and a compromise between mfrs. and state officials may be in the works. The controversial proposal had appeared to be dead because of opposition by Am. Drug Mfrs. Assn. (ADMA), Animal Health Institute (AHI), Abbott, Pfizer, Am. Cyanamid, and Dow ("FDC" Nov. 18, 25). Opposition was based upon the traditional confidentiality associated with New Drug Applications (NDA). But state officials have been plugging away at a compromise, and recently FDA-ers met with representatives of ADMA, Pfizer, Am. Cyanamid, Abbott, and Lilly, and with the State Feed Official's Quackenbush.

This group is believed to have drawn up a plan for a compromise, which will be presented to the state feed control officials in Chicago, May 19. The compromise may involve opening assay methods to state officials only after an NDA becomes effective. Under the original proposal, the material would be opened up by FDA before the NDA was made effective. In their filings last year, AHI, Am. Cyanamid, and Dow all indicated they would go along with the compromise now indicated.

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<sup>2</sup> Congressional Record, p. 20870. (Description of the decision by the Senate-House Conference Committee.)

<sup>31</sup> Vol. 20, No. 20, pp. 20-21.



September 12, 1962.

Drug Research Reports—"The Blue Sheet":<sup>82</sup>

Full texts of memos and letters from the Food & Drug Administration's (FDA) files, now available for the first time, fill in significant details on the story of the thalidomide New Drug Application (NDA) that was never cleared by the govt.

The Humphrey subcmte. volume also will reprint in full various statements made by the Merrell company or its officials, including the Merrell thalidomide chronology, or "sequence of events," that was sent in a letter from President Frank Getman to all M.D.'s. \* \* \*

The thalidomide chronology—as seen through FDA's eyes—requires careful study by everyone interested in medical research, drug investigation and clinical evaluation. To the knowledgeable, it provides a vast amount of data—some of which has been ignored or glossed over in the natural emphasis placed on certain aspects in political discussion and lay newspaper writing.

The basic data provided by the chronology is vital to serious consideration of the many issues raised by the "close call" which the thalidomide episode represented for the medical profession—researchers, educators and practitioners, for the entire pharmaceutical industry, for FDA and, most importantly, for the American public.

The chronology also is a rare document in that it provides a hitherto unavailable insight into the practical operation of the govt.'s NDA procedure for clearing new drugs to the market. Because the drug law imposes a cloak of confidentiality on NDA material, the thalidomide chronology represents the first time that even the non-confidential documents in a specific NDA file have been released for public study.

December 19, 1962.

Pat Barnes, Drug News Weekly:

#### FDA WILL LIFT SECRECY ON NEW DRUG APPROVALS

(By Pat Barnes)

WASHINGTON.—The Food and Drug Administration plans to lift much of the secrecy from one of its most vital functions—the approval of new drugs for commercial marketing, Drug News Weekly learned.

FDA legal adviser William Goodrich said the agency plans to release, perhaps each month, some data on new drugs which it approves as being safe and effective.

Since 1938, FDA has considered it "a matter of policy" not to divulge names of new drugs, but the agency has never had legal justification for withholding this information, he said.

FDA has meted out this information to State food and drug officials for years, but would not permit general release of the information.

A member of FDA's New Drug Division explained the reasoning behind its traditional policy on new drug information. He pointed out that drug firms don't always immediately market products upon FDA approval. Sometimes these drugs are held for what the firm considers a strategic introduction time. "If FDA let the cat out of the bag, it might give his competitor unfair advantage," he said. He added that some drugs approved by FDA are never marketed.

Asked why FDA is reorienting its policy, Commissioner George P. Larrick said the agency feels it is a good thing to bring as much of its scientific work into the open as possible.

Greater recognition of FDA scientific work was urged by the Citizens Advisory Committee earlier this year; at the same time, the group blasted FDA for being what is considered too tough on industry.

CAC chairman George Y. Harvey is now a paid consultant to the Health, Education, and Welfare Department on FDA matters.

Mr. Goodrich said it has not been decided just how much new drug information will be released. He said FDA is uneasy about the fact that it is a criminal offense for a drug firm to advertise FDA approval of a drug (since it might imply

<sup>82</sup> Vol. 5, No. 36, pp. 397-398 S.



to laymen Government endorsement of a product). This underlines a question of fairness, he indicated.

FDA attempted a number of years ago to make new drug information public but was overruled by industry protests.

The Pharmaceutical Manufacturers Association could not be reached for comment.

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February 15, 1963.

Arthur Ruskin, M.D.,<sup>32a</sup> Acting Director, Division of New Drugs, Bureau of Medicine, Food and Drug Administration:

Personally, I think all of us should strive for the day when the drug firms and the Food and Drug Administration will be able to make public all the evidence, positive and negative, of all drug investigations, short of vital manufacturing secrets.

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May 15, 1963.

President's Science Advisory Committee:<sup>32b</sup>

As an administrative principle, tolerances are set by FDA at 1/100 of the lowest level which causes effects in the most sensitive test animals whenever data on human toxicity are not available. However, tolerances have been set for some compounds such as dieldrin, aldrin, heptachlor (epoxide), and chlordane, although a "no effect" level in animals has never been determined. After reviewing the data on which tolerances are based, the panel concludes that, in certain instances, *the experimental evidence is inadequate*. Recent review by FDA has also demonstrated several such examples and the tolerances are being reassessed.

*The panel believes that all data used as a basis for granting registration and establishing tolerances should be published, thus allowing the hypotheses and the validity and reliability of the data to be subjected to critical review by the public and the scientific community.*

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(Illustrative Letter and Attached Articles on Related Instances as to Federal Secrecy)

June 14, 1963.

F. J. Schlink, president and technical director, Consumers' Research, Inc.:

CONSUMERS' RESEARCH, INC.,  
Washington, N.J.

DEAR SENATOR HUMPHREY: You will recall that some time ago you requested that we send you any comments our medical advisers might wish to make in the drug area, concerning psychopharmacologicals, etc., with special reference to any aspect of poor coordination or judgment in the marketing of new drugs. I have now received a delayed reply from one of the doctors to whom we wrote, and I am sending you a copy of his letter for your subcommittee's file.

I was especially interested in Dr. Howorth's comments about the practice of the Government agencies in waiting until a danger has been proven to be very serious before official agencies go to work on the problem. This is the long history of Government controls in the food additives, pesticides, and air and water pollution fields. As we understand the problem, it is not so much that there is a lack of needed means for legal control, but rather that in important instances such controls have been exercised in an ineffective and half-hearted fashion, with a long time lag between learning of a danger and acting upon it. We may hope that such instances as the Department of Agriculture's behavior that was brought to public notice by Senator Ribicoff in connection with the names of producers who were selling pesticides under protest registration will never again occur, or that when and if they do, there will be someone like yourself or Senator Ribicoff on hand to put the officials concerned into the same uncomfortable position that Department of Agricultural officials were placed, as a result of their evasion in the matter of protest registrations of several dangerous pesticides.

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<sup>32a</sup> Drug Topics Publishing Co., Transcript of Conference on New Drug Regulations, p. 6.

<sup>32b</sup> "Use of Pesticides," report, p. 17. [Italics added.]



We had a similar instance in the matter of butylated hydroxyanisole. Scientists' reports which gave some of the basis for the approval of this preservative for wide use in food products were unavailable until someone raised Cain about it; instead of admitting they were wrong in suppressing the basis of approval, the Food and Drug Administration pretended that they always had followed a policy of "open covenants" on matters relating to the toxicity of additives. This was a false and misleading position and one which has been characteristic of Federal food and drug operations for a considerable number of years, and which continues currently. (See especially page 29 of Consumer Bulletin for August 1962 (tearsheet enclosed).)

In respect to the field of pesticides, there is a great amount of information that is unavailable to practically everyone but "insiders," and the insiders do not include consumers, as you are well aware. The very technical nature of this subject and that of food additives and the needless complexities in the Government's handling of these topics have made easy the concealment of essential information and have put effective barriers in the way of those who wish the material to be available to the consumer. The industries have means to get what they need; the rest of us are left outside, looking in.

No one should have to beg for this kind of information or go to any special trouble to get it or have to get it through one of his State's Senators or a Congressman. It should be *published* in a form available to everyone, either free or at nominal prices to cover printing costs. In some cases, taxpayers have paid directly for the work; in other cases, the findings are a part of submittals of data by manufacturers or processors to the Government. In either case the information should be in the public domain and should belong to the citizens as a right, not as a privilege to be grudgingly accorded or refused because it might embarrass some Government agency that was asleep at its post or neglected to do *and to publish* necessary research.

The President's Scientific Advisory Committee's recent report on the Use of Pesticides puts the matter very clearly, and the same principles apply to food additives, color additives, new drugs, etc. " \* \* \* all data used as a basis for granting registration and establishing tolerances should be published, thus allowing the hypotheses and the validity and reliability of the data to be subjected to critical review by the public and the scientific community."

Sincerely yours,

F. J. SCHLINK.

Beckett Howorth, M.D., Stamford, Conn., June 4, 1963.

Mr. F. J. Schlink,  
*Consumers' Research Inc., Washington, N.J.*

DEAR MR. SCHLINK: I am sorry to have delayed answering your letter of March 12th regarding food and drugs control. I have been overwhelmed with 6 meetings for which I have had to prepare for the past 5 months, as well as getting ready for the meeting of the American Orthopedic Association this month, of which I am president.

I do not have enough specific information to be of much help in answering your question, as drugs are not really my field. I did see some of the babies deformed from thalidomide when I was in Sweden last September and it was tragic indeed. However, perhaps I can give you some thoughts and statements of principles.

The protection of the public from impure food and drugs, as well as poisons and pesticides is indeed a proper function of Government. Our laws and our enforcement of them have lagged so far behind that they are almost obsolete. As you have so well said, confiscation of a small quantity of dangerous foods and drugs without effective control of their production and distribution or punishment of a conscious malefactor is of little or no value. The time lag is also quite important. False advertising is of course closely bound to protecting the public. The vast amount of flagrant, misleading and dishonest advertising is still a cause for grave concern.

The approach has been all wrong. The Government has seemed to sit back and wait until it is proven that enough people have died or been deformed by food or drugs to exercise control. It seems to me that our approach should be just the opposite, that it should be required that any new drug, synthetic or preservative, pesticide, etc., should not be used until it can be proven safe, within some reasonable doubt. As example, regardless of the relations of fat in the diet, heart



trouble, artery trouble and cholesterol, I think the present widespread over-fattening of animals for human consumption is wrong and dangerous, especially when it involves the use of hormones and drugs like aureomycin, and should be stopped. The widespread use of pesticides, such as those dumped from airplanes or into rivers is certainly to be condemned. More and more evidence is accumulating not only of the destruction of birds, fish and animals, as well as making them dangerous for human consumption, but of the direct dangers to people themselves.

I shall be much interested in further developments.

With best regards.

Sincerely yours,

BECKETT HOWORTH, M.D.

#### CRITICS OF FOOD ADULTERATION GIVEN THE BRUSHOFF<sup>32c</sup>

GOVERNMENT OFFICIALS REGARD AS CRACKPOTS AND CULTISTS THOSE WHO OBJECT TO BEING DOSED CONSTANTLY WITH UNWANTED AND POISONOUS CHEMICALS—CHEMICALS WHICH THE INDIVIDUAL CONSUMER HAS NO WAY OF AVOIDING

One of our subscribers, Mr. Guy A. Bagley of Petersham, Mass., wrote some months ago to the head of the Department of Health, Education, and Welfare, expressing concern for the safety of the American food supply and citing the disturbing facts about food adulteration brought out in the book, *The Poisons in Your Food*, by William Longgood (reviewed in the May 1960 Consumer Bulletin). Mr. Bagley referred to the "spotty record" of the Government and of the Food and Drug Administration in regard to the risks to consumers' health through manufacturers' use of chemical additives and the presence of various contaminating poisonous substances in our food. Mr. Bagley asserted, quite correctly, that instead of fighting to close the door firmly against any and all foreign substances in our diet, governmental agencies have participated in a policy which "permits known poisons and carcinogens, plus items of questionable safety, to enter our food supply."

Mr. Bagley's letter to the Secretary of Health, Education, and Welfare observed that the Food and Drug Administration seems to feel that it has a dual responsibility—to the public and to the food industry—whereas the obligation of the Food and Drug Administration should be to serve only the public welfare and "to take the lead in stemming and turning back the tide of chemicals in our foods and the deterioration of nutritive values in our foods."

The letter went on to say that foods should contain "no adulterants of any kind where there is the slightest question of absolute safety for human consumption. \* \* \* Moreover, why should the Government collaborate in a use of chemicals which makes a product appear better or more nutritious than it really is? That is a fraud!"

Mr. Flemming did not himself reply to Mr. Bagley's letter. The answer came from a member of the Food and Drug Administration's public relations staff. This reply ascribed to Mr. Longgood the conclusion that "the American public is being poisoned on a wholesale basis" and described that conclusion as being "false and irresponsible." The writer cited a review of the Longgood book by a biochemist, Dr. William T. Darby of Vanderbilt University, as evidence that the Food and Drug Administration need give no weight to Mr. Longgood's criticism of the state of our food supply; actually Mr. Longgood's book was a well written, well documented study. Dr. Darby had disposed of the Longgood thesis in his review in *Science* by charging the author with sensationalism, muckraking, with being a cultist favoring natural over synthetic foods, and with basing many of his conclusions on information derived from a variety of dietary quacks and cultists. Dr. Darby urged that people should pay heed only to the pronouncements based on source material from official bodies, U.S. governmental and United Nations agencies. (It just happens that Dr. Darby is an officer of one of the official agencies.)

A most important fact is that the toxic qualities of a number of now-condemned food dyes and other additives were not discovered by governmental agencies, but by private investigators more concerned with the public's welfare and loyal to the professional obligations than many a Federal or State official chemist or toxicologist.

<sup>32c</sup> Consumer Bulletin, Apr. 1961, pp. 24-28.



In a second letter to the Secretary, Mr. Bagley noted the suspicion that attaches to public relations services in and out of Government and expressed his disappointment at getting the type of reply such an agency would prepare. He continued, "You *must* know that the extensive and growing use of additives and contaminants in food has aroused deep concern in many quarters and certainly raises many disturbing questions and problems. If you do not know this and are not deeply concerned about it every day of your life, then I suggest that you resign your office (with Mr. Larrick [head of the Food and Drug Administration] to follow suit, if he is also so benighted). If you had simply written and said that you appreciated my concern, that you too were aware of the serious questions and problems raised by Mr. Longgood, and that you were earnestly striving toward a better situation, you would have earned my respect. Instead I feel that I have been told that we live in the best of all possible worlds and that only a few 'cultists' and odd-balls fail to realize this.

"\* \* \* To state Mr. Longgood's thesis correctly, contrary to your public relations division's falsification of it, I think it is as follows: Large numbers of chemicals are being used in growing and processing foods. Many of these chemicals are known to be poisonous or carcinogenic. Many have not been properly tested. Therefore it is reasonable to fear that subtle and serious damage is being done to the health of the American people. Mr. Longgood also states that chemicals are being used to grow food of greater abundance but poorer quality (would you deny this?) and it is reasonable to fear that our food supply is not as nutritious as it should be. Now there is certainly nothing rabid, unreasonable, or irresponsible about all this. On the contrary, Mr. Longgood's deep concern is to be applauded. It is the kind of concern we should all have. There are undeniable and damning facts throughout the book. Dr. Darby, who seems to have been picked to represent the Government's official view, addressed himself to none of the problems, but simply attacked Longgood as a cultist. Is it any wonder that my faith in you and in the FDA is less than it was and that I feel a sense of frustration in writing to you. \* \* \* We are using people as guinea pigs. We do not know that safe tolerances really are safe (after all, some of them have been revised). The FDA cannot detect all food shipments that violate safe tolerance limits. Farmers cannot all be expected to read and follow directions in using pesticides. The whole 'safe tolerance' concept in foods is very questionable, first because safe tolerances are really only informed guesses, and second because it is just too hard to control the situation so that no one gets an unsafe dose. We do not know the subtle, long-range effect of many additives and contaminants. Little is known about the cumulative effect of *all* these chemicals ingested day after day, year after year (practically all studies, I believe, relate to a single chemical in isolation). The FDA has made serious errors before, may it not be making some now?

"Instead of being in the tradition of 'bloodthirsty pen-pushing,' to use Dr. Darby's emotionally charged phrase of name calling, it may well be that Longgood is in the tradition of crusaders through the ages who have fought for more intelligent policies which have eventually come to replace established policies. Certainly we have no right to scoff and sneer at people who seek to apply their intelligence toward safeguarding their welfare just because what they say threatens to arouse people from a false sense of security and suggests that Government and industrial policy is lacking. \* \* \*

The next letter to Mr. Bagley came from an assistant to the Secretary of Health, Education, and Welfare, who reiterated the official disregard for the Longgood thesis, and who in effect said that the Food and Drug Administration was doing a good job, and was possessed of "knowledge and experience." Mr. Bagley thereupon wrote again to Secretary Flemming.

"My correspondence with you (or rather with your subordinates) has been most disheartening. Here we have a vast organization, facing tremendously complex and controversial problems, unwilling to admit that it is anything less than completely satisfied with the way things are and unwilling to admit that an entire book devoted to problems (or what others see as problems) of this department has in it one shred of merit. \* \* \* Perhaps this apparent impregnable smugness is why we of the public too often have to leave it to other, non-official sources to alert us to dangers.

"Fortunately we seem still to live in a society where every citizen has a right and a duty to criticize. I am surprised that you people seem so hurt about it—as though you felt this threatened your security."



A recent report of the Food and Drug Administration clearly indicates the limitations of the value of its work to the public. Their report for 1959, recently available, notes: "Samples of beans, peas, and fish from Peru have been analyzed for radioactivity during 1959. The results will serve as a guide for greater selectivity in import sampling." That is all it says about the produce from Peru! Why were the results not made available to the public, for its information regarding the safety of beans, peas, and fish from Peru and such inferences as might reasonably be drawn on radioactivity of food products from other sources, foreign and American?

In another paragraph of the FDA report the following appears: "Increased consumer protection from excessive pesticide residues on fruits and vegetables was provided by the planned collection and analysis of over 2,000 samples of crops from all commercially important growing areas and constant surveillance of the pesticide spray practices of growers." Why should not the public be told *the specific findings* on the 2,000 samples? That is information far more worthy of publication than most of the large and general tracts that come from the Government Printing Office.

The next paragraph of the same annual report mentions the finding of excessive DDT residues on packages of spinach being frozen *for nationwide distribution*, but omits the name of the place and the packing plant and fails to state *how much* DDT residue.

Another paragraph mentions a carload of lettuce which carried "*parathion and fluorine* in excess of the tolerance," but failed to state where this incident occurred and *how much* parathion and fluoride were present and how exceedingly toxic these chemicals are.

These instances do show clearly that there is a serious problem of exactly the kind exposed by Mr. Longgood and that farmers and others who handle these extremely poisonous materials do not, in the diffuse and unsupervised nature of farming operations, take all needed precautions against contamination of food materials. In one spraying or dusting operation in California, a State government department reports that of 10 safety precautions listed by the manufacturer for safe handling of his product *not one* was being applied, and operators were in some cases without protective clothing and were following "sloppy and hazardous procedures." There are over a thousand cases a year in one State of injury or "occupational disease" of workmen through highly toxic agricultural chemicals. These errors due to ignorance, misunderstanding, and carelessness may, of course, result in injuries to an unknown number of thousands of unsuspecting consumers who handle or ingest the treated produce.

The Administration's report of the year's activities cites case after case of harmful and dangerous food materials without giving names, places, or other details, all on the assumption that in spite of these instances involving as much as 25,000 pounds of one food product, and 465 tons of grain, we should simply place our trust in the Government's food control operations as completely safeguarding consumer interests. We are supposed to have this confidence in the Government's food control operations, even when the Government does not report its findings to the public (except in large, vague, and general terms of no specific use to anyone).

The Administration's report shows that when they do detect and act on a problem, it is often after the situation has gotten to be extremely dangerous or has brought about a fatality, as in the case of a death from sodium nitrite used to adulterate flounder fillets in the Philadelphia area a year or two ago. In this case, State and Federal controls were both obviously lax, and it was sheer good luck that only one person died of those who were taken ill from the poison. Other seizures of fish products containing sodium nitrite were subsequently made, but we were not told any details except that they were "mainly imported."

A recent incident involved the highly toxic food dye called Red No. 1, which had long been used with Government approval in maraschino cherries, ice cream, frankfurters, and certain other types of sausages.

Of 250 rats being fed this toxic dye, 116 died, while none of the 27 animals on control diets died (diets not containing the dye). Gross liver damage showed up in animals fed the dye. Some of the feeding studies have shown malignant tumors in rats, and work not yet completed on this dangerous dye may ultimately show after 15 months or so of further testing that the dye is a cancer-causing agent or carcinogen (other food dyes have been!).

The prior official acceptance of this harmful dye is but one of a substantial number of errors made in previous judgments of the Food and Drug Admin-



istration—errors that may have caused most serious harm to human health, or brought death to citizens, whom the Government has not even warned of the undesirability of consuming foods containing coal-tar dyes. (Who needs jelly, candies, and cakes colored with strictly synthetic coal-tar-derived dye materials, anyway?)

There are scores of ways in which the activities of the Food and Drug Administration should be corrected and strengthened to make the agency a more effective guardian of the public welfare.

The difficulties and dangers from a consumer's standpoint would at least be mitigated to some extent if the Food and Drug officials would adopt a policy of issuing complete, timely, clear, and straightforward public statements on what they find, and if they would readily grant the possibility of error, and the importance of continuous and intensive research. The list of chemical substances that may contaminate foods or be added to them continues to grow rapidly; 2 to 3 thousand are now employed. The most vital need is to move speedily toward drastically shrinking this huge number, so that the problem of determining the safety of additives and controlling their use may be reduced to proportions which researchers may hope to deal with successfully.

#### THE MYSTERY OF THE BUTYLATED TWINS <sup>22d</sup>

CONSUMERS' RESEARCH TRIED TO FIND OUT ABOUT THE SAFETY OF TWO WIDELY USED CHEMICAL ADDITIVES FOR USE IN FOOD, BUT FOUND FEW SOURCES OF INFORMATION. IN THIS FIELD, THERE'S A STARTLING BARRIER OF GOVERNMENTAL SECRECY

The names of two fat preservatives which are used in a very large number and variety of grocery items stand out in every study of food package labels by Consumers' Research. We are safe in saying that a typical homemaker of today buying a week's supply of packaged groceries would be very likely to include some products that contain butylated hydroxytoluene or butylated hydroxyanisole. Indeed, *both* are present in some food products, including certain packaged raisins and breakfast foods.

Of the two butylated fat preservers, BHA (butylated hydroxyanisole) has apparently been more popular among researchers. Two citizens who asked what tests had been made to determine the safety of these ubiquitous chemicals were given identical lists of references by a Government agency (see reproduced letter), and only one item, the first, turned out to be about BHT (butylated hydroxytoluene); the long chemical name given in the title of that paper is a synonym for BHT. All the remaining papers listed are about BHA.

In a near-by university library, we had no difficulty obtaining the cited issue of *Agricultural and Food Chemistry* and the two listed issues of *Biochemical Journal*.

Interestingly enough, each of the three scientific papers in these journals gave in its list of references the "Summary of Toxicity Studies on Butylated Hydroxyanisole," third item in the F. & D. Administration's list. Nonetheless the library could not supply that publication. We wrote to the American Meat Institute Foundation, listed in the reference as its publisher. Back promptly came the reply: \* \* \* sorry \* \* \* but no copies of [this] AMIF publication are available for distribution."

#### A "PUBLICATION" THAT WAS NOT PUBLISHED

Puzzled that a large library and now apparently even the publisher could not supply this item, we asked for more information: Just what was the "Summary," a book, pamphlet—possibly part of some larger publication?

The "Summary," cited as a reference source in at least 3 learned papers, actually, according to the Meat Institute Foundation, "was not published"! "It was," they said, "information submitted to the Bureau of Meat Inspection of the U.S. Department of Agriculture at the time butylated hydroxyanisole as an antioxidant for food fats was under consideration by the U.S. Department of Agriculture."

Told of the difficulties in obtaining the "Summary," the Food and Drug Administration was of little help. Said the agency, "we are sorry that this

<sup>22d</sup> Consumer Bulletin, Oct. 1961, pp. 18-20.



paper is not available and apparently should not be listed among our references on this subject. \* \* \* We are not in a position to make our copy of the paper available."

With this polite but decisive bureaucratic brushoff ringing in his ears, the patient put persevering inquirer wrote to the Meat Inspection Division of the Department of Agriculture. Their reply was astonishing and disquieting.

Said the Meat Inspection Division, "Both the antioxidants which you mention [BHA and BHT] have been exhaustively studied by comprehensive animal feeding studies. \* \* \* the toxicity studies were not conducted by a Government agency but by private companies \* \* \* under the direction of this Division. \* \* \* The data resulting from the feeding experiments is in our files but is not available for distribution since it was furnished to us in confidence. We do not know whether the results of these studies have been published. \* \* \* We do not have a copy of the paper to which you refer, entitled, *Summary of Toxicity Studies on Butylated Hydroxyanisole*." [Italics ours.]

So, this was the end of the long and time-wasting search for the much cited "Summary." The agency to which it was supposedly submitted did not have a copy—and what information they did have about the toxicity of BHA was "confidential." Another tax-supported agency which did have a copy was "not in a position" to make its copy available, meaning that the agency did not concede that consumers have any right to read and judge the validity of information which the Government thinks good enough to provide a basis for adding a more or less poisonous substance to hundreds of items in our food supply.

It is very disturbing to know (1) that the Government's basic data from which was decided the "safety" of BHA and BHT were supplied from private sources which have an evident commercial interest in the products, (2) that these scientific data and the reasoning whereby they were interpreted are not available for critical examination by any person outside the Government service, and (3) that the Meat Inspection Division which originally approved use of these chemicals in food is so backward in its studies of relevant scientific literature that they "do not know" what has been published on the subject.

The chances are good for the general correctness and truthfulness of *published* scientific studies, or for their fairly prompt correction if wrong in some major respect, because papers published in scholarly journals are often read critically by experts in the fields concerned, and normally by some experts who have no financial stake in the matters discussed. This safeguard, of course, can not apply to studies which emanate from commercial sources and are kept as secret information in the files of a Government bureau, available only to Government officials and administrators, or perhaps to certain representatives of industry.

References listed as sources at the end of a published scientific paper are assumed, unless stated otherwise, to be available to interested persons. Listing of the secret "Summary" by authors of the papers on BHA was a violation of a sound and widely accepted rule. It is hard to account for, except on the assumption that there is something that needs to be kept from public review. One wonders whether the secret paper was at any time made available to the various authors of papers which cited it (and if so, by whom), or whether they relied on abstracts, merely, or other second-hand reports about its contents.

As the number of chemical additives tolerated in foods keeps rising (well over 3,000 now), it becomes increasingly urgent that all experimental work claimed to show their safety be exposed to public scrutiny and review by *any interested independent expert*. Governmental authorities should give no weight at all to data on toxicity which are supplied "in confidence," or to information which is restricted in any way so that it cannot be made freely available to anyone interested. This does not mean that secrets of manufacturing methods need be publicly disclosed—but no chemical product should even be considered for addition to food unless its exact chemical formulation is known and the results of tests alleged to show its safety are made generally available at any and all times to all who may be interested.

#### HOW SAFE ARE BHA AND BHT?

The papers we were able to find revealed some interesting facts and judgments about BHA. The earliest of the references was to a study, published in 1956 by three scientists in New Zealand. "Although studies of the conventional type on acute and chronic toxicity have been made," the authors said, "no studies on metabolism [how the material is utilized or is changed in the body] have been



made." Concluding their own study of BHA's metabolism in rabbits, the authors point out certain reassuring facts about metabolism of BHA, but say also that some of their findings are less satisfactory, notably the observation that "four or five daily doses of one gram to a rabbit have cumulative and lethal effects. This shows the need for further studies \* \* \* at lower dose levels. \* \* \*

And note that these views about the need of further investigations were published some 8 years *after* use of BHA as a preservative in edible fats had been approved.

A report published in 1960 on the metabolism of BHA in rats, according to its authors, "approaches closer to human-usage doses than any previous study of antioxidants." (We wonder how the author can be sure; perhaps on this point, too, the story of some relevant previous work is locked somewhere as a "classified document" in a bureaucrat's files.) The paper concludes, "No evidence has so far been presented which suggests that BHA is not largely absorbed and largely excreted at these very low doses." In other words, no one is *known* to have shown it's bad for you; presumably then it's OK—but this presumption is based on the belief that whatever investigators have found out has been *published* for other scientists to read.

The one paper in F. & D. Administration's list which reports about the other butylated preservative, BHT, was published in 1955 and describes tests in which the drug was fed in various dosages to rats, rabbits, guinea pigs, and dogs. The amounts of single doses sufficient to kill the animals were determined, as were the amounts that could be tolerated in repeated feedings for periods as long as 2 years. In these latter tests, some deaths of animals were noted, but the fatalities seemed to bear no relation to the amount of BHT ingested. Even some control animals that ate no BHT died. *Because of this conflict of evidence* it was "believed" that BHT had not caused the deaths, and that it "could be used without any public health hazard."

It was on this basis, apparently, that the Federal regulatory agencies allowed the use of BHT in foods. Incidentally, the scientists who made the report last cited were financed in their studies by 3 chemical manufacturers; all were commercially interested in the sale of BHT.

Perhaps, by the time BHT has been in common use for another 5 years or so, the Food and Drug Administration will be able to refer inquirers to reports of necessary studies of BHT's metabolism that demonstrate its probable safety—or its danger to health on a long-term basis.

There seems persuasive, though not conclusive, evidence that BHA is comparatively harmless in very low concentrations. We wonder, however, about the cumulative effects of ingesting a little here and a little there—in each of perhaps a dozen foods a day if one's diet happens to consist mainly or largely of factory processed foods (a common situation for many consumers).

As to BHT, what evidence we found tends to be favorable, but we would like to see comprehensive studies by other investigators, and the evidence on which Government agencies decided the compound was safe as an additive.

We are convinced of the need for continuing scrutiny both by the general public and by scientific experts of the evidence that is offered to "prove" the safety of any and all chemicals in food. There should be no cases whatever of blind acceptance of decisions by Government pundits based on secret reports by commercially interested proponents of various materials. Every scientist who experiments on the effects of any chemical food additive on animals or humans should feel morally obligated to publish his data and findings, and expose them to the fire of criticism by his peers in research. Certainly, when such material is submitted to a Government agency in support of an application for official action, the experimental findings and the data underlying them—every word of those records and observations—should become part of the public record, freely available to any inquiring citizen.



MYSTERY OF THE BUTYLATED TWINS—A FURTHER REPORT<sup>32a</sup>

THE FOOD AND DRUG ADMINISTRATION SAYS ITS POLICY "HAS ALWAYS BEEN TO MAKE AVAILABLE TO PUBLIC SCRUTINY" INFORMATION OF A SORT WHICH IT DENIED EARLIER TO AN INQUIRER. BUT THE AGENCY'S ACTIONS AND ITS OWN RULES SAY OTHERWISE

Events followed quickly upon our report, in Consumer Bulletin for October 1961, of difficulties in obtaining for study a paper entitled "Summary of Toxicity Studies on Butylated Hydroxyanisole."

Indignant readers, including several physicians, wrote about the matter to the Food and Drug Administration; to Health, Education, and Welfare Secretary Abraham Ribicoff; and to their Senators and Congressmen. An influential big city newspaper, the Philadelphia Bulletin, editorialized about the "new example of suppression by the Government of information in its files to which the public has a right of access."

On the same day as the newspaper's editorial appeared, Deputy Commissioner John L. Harvey of the Food and Drug Administration sent off two letters. One went to the editor of Consumer Bulletin and said in part:

"We agree with your premise that data on which we make decisions to permit use of chemicals in foods should be available to public scrutiny, and regret that there has been a misunderstanding of our policy on the matter. \* \* \*

"Since it has developed that the 'Summary' is not available elsewhere, we are glad to furnish you—and anyone interested—a photocopy of our file copy."

The other letter of which we have knowledge that Mr. Harvey wrote on that day was addressed to a Consumer Bulletin subscriber, who kindly sent us a copy. There was an interesting additional remark which we have italicized below:

"On the general principle, however, we agree with you completely that the scientific information on which we base decisions on whether to permit certain chemicals in foods should be made available to public scrutiny. *This has always been our policy* except where the law specifically protects confidential information provided to us by manufacturers."

Mr. Harvey became more explicit as time went on. In a letter to a Congressman about 2 weeks later, he wrote (*italics ours*):

"The article submitted [Consumer Bulletin, October 1961] does not so state, but in the case of the American Meat Institute 'summary' *as soon as we were advised* that the inquirers were not able to get the material from the American Meat Institute, we made photocopies of our file reference and supplied these."

Consumers' Research is pleased to know about the Food and Drug Administration's policy of freedom of information, but we cannot allow to pass without challenge the implications by Deputy Commissioner Harvey that this policy has always been followed by the agency.

About 6 months before the dates of Mr. Harvey's letters quoted above, a citizen wrote to the Food and Drug Administration, told the agency that the "Summary" could not be obtained from the American Meat Institute Foundation, and asked aid in obtaining or even borrowing a copy. (The inquirer was interested in the paper because the Food and Drug Administration previously had cited it to him as a source of needed information.) Following, in full, is the agency's answer to the citizen's request:

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,

FOOD AND DRUG ADMINISTRATION,

Washington, D.C., May 18, 1961.

DEAR MR. ———: This replies to your letter of April 28 about the Wilder paper on butylated hydroxyanisole.

We are sorry that this paper is not available and apparently should not be listed among our references on this subject. You might inquire of the Meat Inspection Division of the Department of Agriculture, since your information indicates that the studies may have been made for that agency.

We are not in a position to make our copy of the paper available.

Sincerely yours,

DOROTHY H. KOEGLER,

Consumer Inquiry Branch, Division of Public Information.

<sup>32a</sup> Consumer Bulletin, Aug. 1962, pp. 28-29.



We direct attention especially to the date of this letter *and to the closing sentence*, and urge the reader to decide for himself whether or not the Food and Drug Administration has "always" followed the policy of making such material as the Wilder paper "available to public scrutiny."

As to the "general principle" enunciated by Deputy Commissioner Harvey that scientific data on which the agency bases decisions about food additives should be accessible to the public, and the assertion that "this has always been their policy" except where the law specifically prohibits it, we suggest that Mr. Harvey re-read the regulations of his own agency [section 121.51(h)].

"Data in a petition regarding any method or process entitled to protection as a trade secret will be held confidential. \* \* \* *Other data* [italics ours] in the petition will not be revealed to persons other than the petitioner and persons engaged in the enforcement of the act beyond that which is necessary [for a notice 'in general terms,' and for any regulation issued]."

The law does require protection for trade secrets as to methods and processes (and many would hold this protection to be a proper one). However, that is the *only* element of secrecy that we can find which is provided for by law, so far as food additives are concerned. (An amendment now before Congress and supported by FDA officials would, if adopted, greatly extend the area of legally imposed secrecy.)

What, then, are the "other data" that the Food and Drug Administration will keep secret according to its own regulation, even though such secrecy is not established by any provision in the law? Among these other data that will not be revealed in full as presented by the petitioner are: composition of the additive; its physical, chemical, and biological properties; stability data; data as to physical or other technical effect; and *reports of investigations as to safety*.

It is remarkable that the Administration would maintain its right and duty to hold in confidence even those parts of manufacturers' food-additive petitions which deal with the composition and chemical and biological properties and impurities of any potentially toxic additive that tens of millions of consumers may be expected to consume daily with their meals and snacks. And how can the full reports of investigations as to safety be kept confidential, and at the same time "be available to public scrutiny," as Deputy Commissioner Harvey has written that they should be?

Consumers' Research is pleased to have played a part in causing the Food and Drug Administration to affirm the position that the scientific data upon which the acceptance of food additives is based *should* be available to scrutiny by interested scientists and by the public at large. We shall be pleased, too, when we can say with assurance that the agency's actions and its official regulations have been brought into agreement with its asserted policy in this regard.

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FROM PRESIDENT KENNEDY'S MESSAGE OF MARCH 15, 1962, TO THE CONGRESS, ON  
"CONSUMERS' PROTECTION AND INTEREST"

\* \* \* \* \*

These rights include—

(2) The right to be informed—to be protected against fraudulent, deceitful, or grossly misleading information, advertising, labeling, or other practices, and to be given the facts he needs to make an informed choice.

\* \* \* \* \*

Second, that the head of each Federal agency whose activities bear significantly on consumer welfare designate a special assistant in his office to advise and assist him in assuring adequate and effective attention to consumer interests in the work of the agency; to act as liaison with consumer and related organizations, and to place increased emphasis on preparing and making available pertinent research findings for consumers in clear and usable form (pp. 6, 7).

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(Note by editor: Additional comment on "trade secrets" with specific reference to drugs will appear in subsequent subcommittee volumes.)



## EXHIBIT 170

PROPOSED NATIONAL DRUG INFORMATION CLEARINGHOUSE: CHRONOLOGY OF  
COMMENTS AND ACTIONS ON ORIGINS OF THE PROPOSAL

There follows a chronology with respect to the interest of the Senate Subcommittee on Reorganization and International Organizations in improved coordination of drug information.

The excerpts indicate the overall framework of the subcommittee's interest—the strengthening of all types of biomedical communication. Within this broad framework, the excerpts narrow down to specific activities on coordination of drug information, per se.

Certain of the references which follow are reprinted elsewhere in the subcommittee's series; therefore, they are referred to herein merely by a brief bibliographic reference; where, however, pertinent quotations are not available in the subcommittee's other volumes, they are reproduced in full, or in large part, on the pages which follow.

The chronology has been limited to a period of 3 years. As in the instance of any other major concept, however, the antecedents of plans for drug coordination can naturally be traced back much further. For the purpose of illustrating early origins, a single article is presented, at the outset. It describes one component of a clearinghouse concept—the central coding of compounds and their biological properties. This concept was the foundation for an organization which had existed during the 11-year period 1946 to 1957—the Chemical Biological Coordination Center.<sup>1</sup>

## ARTICLE ON CHEMICAL-BIOLOGICAL COORDINATION CENTER

*March 18, 1957.*—Chemical and Engineering News<sup>2</sup> describes the closing of the Chemical Biological Coordination Center.

## NEEDED: AN "ANGEL" FOR CBCC

CHEMICAL-BIOLOGICAL COORDINATION CENTER TO CLOSE IN JUNE; INSUFFICIENT FUNDS  
GIVEN AS CAUSE

The Chemical-Biological Coordination Center will close in June. The National Academy of Sciences—National Research Council says CBCC will close because "sufficient financial support to permit it to operate effectively hasn't been found" (C&EN, March 11, page 7). Every effort will be made to keep CBCC's files intact, says NAS.

During the 10 years of its existence, more than \$1.5 million has been poured into CBCC, says S. D. Cornell, NAS executive officer. These funds have come from the Departments of the Army and the Navy, National Institutes of Health, Atomic Energy Commission, American Cancer Society, and the National Science Foundation.

The decision to close CBCC was not made lightly, says Cornell. With the need for money constantly rising and income dropping, NAS had to face hard business facts.

CBCC was established in 1946 as the successor to the Insect Control Committee of the Office of Scientific Research and Development. Its purpose: to collect, store, and correlate chemical-biological data, develop methods of converting this information to a coded form that could be recorded and sorted by machine methods, and make the data available to scientists.

<sup>1</sup> See Seitner, Philip G., Livingston, George A., and Williams, Ann S., "Biology Code of the Chemical Biological Coordination Center," and "Key to the Biology Code of the Chemical Biological Coordination Center," National Academy of Sciences—National Research Council Publications 790 and 790K, Washington, D.C., 1960.

For additional background, see Livingston, George A., and Welt, Isaac D., "Chemical Structures and Responses of Organisms to Applied Chemicals," in "Advances in Documentation," edited by Shera, Jesse, Kent, A., and Perry, J. W., Inter-Science Publishers, New York, 1957, vol. II, ch. 16, pp. 250–270. Welt, Isaac D., "Aspects of the CBCC Biology Code of Interest to Chemists," *Journal of Chemical Documentation*, 1, 19, 1961, pp. 19–21. Wood, G. Congdon and Welt, Isaac D., "A Multi-Indexed Machine-Sorted, Punch Card System for Pesticide Metabolism Data," *Agricultural and Food Chemistry*, vol. 4, No. 10, pp. 886–888, October 1956. (Footnote by editor of this volume.)

<sup>2</sup> P. 34.



Here is what CBCC has accomplished since it was born:

Developed and published (1950) a chemical code. Over 63,000 chemicals have been coded and indexed by name, code serial number, and molecular formula.

Evolved a biological code. More than 212,000 pieces of biological information have been coded and filed. The code has been in use since 1951 and publication is planned soon.

Screened over 10,000 untested compounds for biological activity. These compounds were submitted by industrial firms, universities, and individuals. The screening was done by 35 cooperating laboratories. CBCC acted as a middleman, collecting and distributing samples and getting back information which it included in its files. Much of the information relating to these chemicals and their activity is unpublished and available only from CBCC's files.

Received over 1,300 questions from industry, universities, and individuals. Most of the questions were answered. No fee was ever charged.

Coded, cross-referenced, and put on nearly 2 million IBM punch cards chemical-biological data it compiled.

Published summary tables listing preliminary results of biological tests on the chemicals in its screening program.

Anywhere from less than \$100,000 to over \$1 million per year would be needed to operate CBCC efficiently, Cornell says. If work were limited to research on methodology, \$100,000 per year might be enough. At the other extreme, says Cornell, it would probably take over \$1 million a year to search all the world's literature for reference to chemicals having biological activity and develop correlations from these references.

CBCC has followed a middle course, says Cornell. This involves an attempt to provide the basis for discovering chemical-biological correlations by reviewing a small but selected portion of the world's scientific literature. Cost of this course—around \$250,000 per year, says Cornell.

Several observers agree with Cornell's figure for the middle course. Income has averaged around \$175,000 per year over CBCC's 10 years. In recent years, however, income has been declining, says Cornell, "despite many efforts to maintain and increase it."

People all agree that CBCC is a desirable thing, says Detlev W. Bronk, NAS president. But when the chips are down, he says, nobody seems to want to put up the necessary money. A year ago, says Bronk, the National Science Foundation made a special grant to keep CBCC in operation when other funds ran out before the fiscal year ended.

A special advisory committee met in September 1956 to consider the future of CBCC, says Cornell. This committee recognized that CBCC's work is important, suggested activities to be emphasized, and recommended that CBCC be continued—provided an adequate staff and stable financing were available. Otherwise, the committee said, CBCC should be suspended or ended.

#### "DEPLORABLE"

The decision to close CBCC came as a shock to many interested parties. The feeling is that CBCC is built on sound concepts and that it has done a good job. Many close to the situation say that a more vigorous effort to raise money for CBCC might have been successful.

"Deplorable," says an academic observer. "This is what happens when a good idea is not sold aggressively."

"It's too bad CBCC is closing," says Dow Chemical's Donald D. Irish, "but it accomplished two big things: It opened up the subject of handling large amounts of scientific data and thereby speeded up recognition of the problem; and CBCC took some positive forward steps toward showing what can be done with the data handling problem. CBCC is probably a little ahead of its time." Irish was a member of the special committee which met in September 1956 to consider the future of CBCC.

Another special committee member, Olin Mathieson's Charles H. Hofrichter, is "thoroughly disgusted" at the closing of CBCC. "In closing CBCC, NAS has undermined its charter in not following through with the promotion of basic sciences which deal with basic biological problems that confront mankind." Commenting on CBCC's financial problems, Hofrichter says that if an organized effort had been made to raise money from industry, it probably would have been forthcoming, provided CBCC's screening function and the question answering service were preserved. In fact, says Hofrichter, the committee was told not to worry about money, that if more money were required, it could be found some way.



## CRITICS

P. K. Smith of George Washington University Medical School is frankly critical of CBCC. He feels CBCC has been badly managed. CBCC, he says, "is riding on the coat tails of NAS-NRC prestige." He charges "clumsy, awkward management by people lacking the proper background" led to its downfall. Smith feels the operation went into far greater detail in the coding than was necessary. He would preserve CBCC's master files but destroy the rest of the data.

James G. Horsfall of the Connecticut Agricultural Experiment Station, also a member of the committee which met in September 1956, says CBCC didn't demonstrate any real worth to industry. Horsfall says industry wanted CBCC to be a sort of Chemical Abstracts—only maybe a little faster. CBCC's biggest contribution, says Horsfall, is the biological code.

Another spokesman felt there had been constant fluctuations in policy. "One day CBCC was run as a repository for chemical-biological information. The next, it was expected to be a service agency and answer questions. A clear-cut policy wasn't spelled out."

## WHAT NOW?

NAS intends to publish the biological code, and as soon as is practical. Also, NAS hopes to publish a history of CBCC. Money for this work, says NAS, may come from NSF.

## CHRONOLOGY ON DRUG CLEARINGHOUSE—1960-1963

*August 11, 1960.*—Senate Subcommittee on Reorganization and International Organization conducts hearing on "Interagency Coordination of Information on Current Research." The hearing considers the extent of cooperation between all of the principal Federal agencies which support biomedical research. The subcommittee considers, in particular, the relationships (if they exist at all) between individual agencies and what was then known as the Bio-Sciences Information Exchange.

*August 19, 1960.*—Senator Hubert H. Humphrey, chairman, addresses an inquiry<sup>3</sup> to the Food and Drug Administration. The letter inquires, along the line of the hearing, as to whether or not FDA registers information on its current drug and other research with the exchange. The letter also inquires as to arrangements for "interagency coordination including 2-way flow of information on current research," and whether the FDA is "actually collaborating on any particular research with another agency, e.g., through joint planning, joint funding, and/or joint implementation."

*September 30, 1960.*—George P. Larrick, Commissioner, Food and Drug Administration, responds.<sup>4</sup> He states that in the 1960 fiscal year FDA supported \$922,300 worth of research (of which all but \$38,300 was intramural). The agency does not, he states, register its projects with the exchange.

*June 20, 1961.*—Senator Hubert H. Humphrey testifies before the Senate Appropriations Committee on the need for centralized abstracting-indexing on all drugs.<sup>5</sup> He points out that only the National Heart Institute is centrally abstract-indexing its drug literature. He points out further the duplication and waste which occur when, entirely independently, other institutes or other sources later scan the very same journals for information on similar or other drugs.

*March 20, 1962.*—Senator Humphrey writes to the Secretary of Health, Education, and Welfare, pointing out that there is still no comprehensive, departmentwide information system.<sup>6</sup>

*May 14, 1962.*—Senator Humphrey releases a 52-page mimeographed report, "An Action Program for Strengthening Medical Information and Communication."<sup>7</sup> The report is submitted to Senator Lister Hill, Chairman, Senate Appro-

<sup>3</sup> Senate Committee on Government Operations, Subcommittee on Reorganization and International Organizations, "Coordination of Activities of Federal Agencies in Biomedical Research," hearing, Aug. 11, 1960, pp. 195-201.

<sup>4</sup> *Ibid.*

<sup>5</sup> Reprinted in Senate Committee on Government Operations, Subcommittee on Reorganization and International Organizations, hearings on "Interagency Coordination in Drug Research and Regulation," pt. 1, p. 140.

<sup>6</sup> *Ibid.*, pp. 141-143.

<sup>7</sup> Release S 5-4-62, by Subcommittee on Reorganization and International Organizations, "An Action Program for Strengthening Medical Information and Communication," pp. 4, 14, 18.



priations Subcommittee, for the Departments of Labor-Health, Education, and Welfare.

Part 1 of the report contains these 12 recommendations for improvements of biomedical communication as a whole:

- "1. Increase information cooperation among Federal health agencies.
- "2. Establish a modern, coordinated research information system in HEW Department.
- "3. Strengthen information resources and competences in HEW Department.
- "4. Convene a series of action-oriented conferences on communication.
- "5. Strengthen research in communications and mobilize private advice on how best to do so.
- "6. Broaden and deepen resources and competences for medical uses of electronic data processing throughout the Nation.
- "7. Expand statutory authority for National Library of Medicine.
- "8. Encourage the formation of a national "network" of specialized information centers.
- "9. Cooperate with the profession in strengthening postgraduate medical education.
- "10. Foster increased use of audio-visuals, including educational television.
- "11. Establish a council on processing of clinical information.
- "12. Modernize and increase international cooperation in exchange of research information."

\* \* \* \* \*

[Of the 12 detailed recommendations, only No. 2 is reprinted at this point.]

#### "ACTION RECOMMENDATION :

#### "2. *Establish a modern, coordinated research information system in HEW Department*

"Request the Secretary of Health, Education, and Welfare to submit a report to the Committee on Appropriations, containing plans for a more modern and coordinated research information program throughout the Department.

"HEW's research information 'arm' should become the strongest, most modern such service in the Federal Government's health sphere. HEW's information services should serve not merely routine information purposes, but the most advanced needs of administrators and bench scientists.

"The proposed report to be transmitted by the Secretary should include plans for improving the information services of all the major HEW research-supporting units. These include the Food and Drug Administration, Office of Vocational Rehabilitation, Office of Education, and Social Security Administration, but particularly, the largest and most rapidly evolving organization—the U.S. Public Health Service.

#### "REASONS FOR RECOMMENDATION

"The House Committee on Appropriations has requested (p. 43) a report on 'a unified, coordinated' program of information within the Public Health Service. I had personally been happy to recommend such a program to the House committee, but in a broader context. I suggest that the improvement is needed: (a) on a Governmentwide and HEW Departmentwide basis and (b) with respect to all types and channels of research communication.

"The situation is as follows at present: throughout the Department, as a whole, research information is splintered in a multiplicity of heterogeneous, largely obsolete and incompatible systems. The information systems of the major departmental units are not, therefore, individually or collectively, in a position to serve the broad needs of: (a) the administrator of any given organization, e.g., PHS, OVR, etc., or (b) other research administrators (i.e., in other HEW units), or (c) the bench scientists who are supported intramurally and extramurally by PHS or other sources."

\* \* \* \* \*

<sup>1</sup> "See my letter of February 17, 1962, reprinted in House of Representatives, Committee on Appropriations, hearings on Department of Labor, Health, Education, and Welfare appropriations for 1963, 'Statements by Members of Congress, Organizations, and Interested Individuals,' pp. 572ff."



Part 2 of the 52-page statement contains this statement by Senator Humphrey on overall problems of medical communication:

"1. *A crisis does exist in medical communication. It is part of an overall crisis gripping all rapidly evolving fields of science and technology. The crisis grows more serious with each passing day.*

"(See, for example, the statement by one observer who not only confirmed the existence of the crisis but added 'the crisis has passed; the vast flow of scientific information has already inundated all scientists \* \* \*'

"2. *The crisis in medical communication is neither new nor simple; it is a complex of crises. Every phase of medical communication is involved—medical writing and editing, reviews, audio-visuals, etc.*

"(I may illustrate by pointing out the communication problem in one vast field—*mental retardation*. This multi-phased problem costs this Nation not less than \$1½ billion in tangible costs alone in a single year. Yet, *research information* here (or other fields) is widely scattered in *primary journals*, is unsatisfactorily abstracted and indexed in *secondary journals*, is woefully deficient in *critical reviews*, is poorly organized as regards cataloging of *audio-visuals*, is sadly lacking in systematic *international communication*, etc.—according to our staff.

"3. *There is no so-called 'cure-all' for the complex of communication crises; instead, interdisciplinary remedies must be sought in each and every phase and for the communications system as a whole.*

"4. *Answers to needs for improved communication will come from medicine's adapting the best of proven, traditional techniques with the best of bold, new techniques. For example, person-to-person communication must be strengthened. But excellence must be fostered in usage of advanced systems which represent 'collective memories.'*

5. Biological and medical communications represent problems of the profession, not of the *Federal Government*, per se. U.S. Government funds support the preponderant share of American biological and medical research; the U.S. Government, thus, bears a heavy responsibility. But it must consult and catalyze; it must neither pre-empt nor dictate. The professions and their chosen instruments—the societies—must continue to bear principal responsibility. Thinking observers do not question the absolute necessity of the professions' continued freedom and independence in information or in other areas.

"6. *There is a vast ferment of interest throughout the land in improved communication. One of the areas of greatest ferment is in strengthening of post-graduate medical education. A number of somewhat parallel forces can be seen converging in this area, in improved processing of clinical information and in other fields.*

"7. *Whenever an expert group attacks a medical problem, e.g., heart disease and cancer, environmental health, it tends to come up with bold information proposals. Unfortunately, these proposals are usually treated in isolation by Government agencies, instead of being fitted into a coordinated, total information program, which would prove useful to a wide range of disorder and disease problems.*

"Finally, this issue must be kept in perspective. *Medical communication is but one of many important problems confronting Federal research administrators; they face scores of other important problems, as well. On an overall basis, agency research administrators have performed an outstanding job; this Nation has every reason to be grateful for their integrity, dedication, and skill. Everything can hardly be accomplished at once. We should not miss the 'forest' (overall Federal research achievements) by seeing only the 'trees' (this particular issue of medical communications, important though it is). Dollar for dollar, Federal medical research represents one of the finest investments in the entire U.S. budget.*

\* \* \* \* \*

(The 52-page report contains the views of many distinguished authorities, including the following comments:)

Geo. P. Hager, Dean,<sup>2</sup> College of Pharmacy, University of Minnesota, Minneapolis, Minn.:

\* \* \* \* \*

<sup>2</sup> Letter of March 24, 1962, to Senate Subcommittee on Reorganization and International Organizations.



"My personal experience in modern methods of using scientific data stems from my work as Head of the Structure-Activity Coordination Unit at Smith Kline and French Laboratories. I was instrumental in establishing the unit during the years, 1955-1957, before I came to Minnesota. I became fully aware of the fact that laboratory data, handled by classical procedures, yielded only a part of the potential dividends from investments in research. Such data are useful in answering the specific question that prompted their collection. *With proper communication, they may also furnish answers to other questions current at the time of the investigation. With proper documentation, they may be used in providing, in the future, answers to questions as yet unasked.* In any case, the versatility with which laboratory data should be handled, the expedience of their combination and permutation in a great variety of searches, their integration into the total body of knowledge (present and future) with which they are homogeneous require the use of highly sophisticated, modern methods made possible by punched cards and computers.

"The relatively small investment required for handling data in this way, in comparison with the great expenditures for their collection, is, I am confident, fully justified by the potential role of modern methods of handling information in deriving maximum yields from investments in *laboratory* research.

\* \* \* \* \*

"I sincerely hope that your constructive efforts in this general field will lend proper emphasis not only to the obviously important problem of medical communication, but also to the equally important problems related to the communication and documentation within the ancillary sciences of pharmaceutical (or medicinal) chemistry and pharmacology."

\* \* \* \* \*

*August 1962.*—At hearings of the Senate Reorganization Subcommittee the Director of the National Institutes of Health concedes that only 3 of the then 7 categorical institutes have a substantial drug information program.<sup>8</sup> NIH reveals no plans as regards the other 4 institutes, nor plans for an overall inter-institute system, such as Senator Humphrey had urged.

*August 15, 1962.*—Senate Reorganization Subcommittee gathers information on the operation of Mediphone, Inc. For 3½ months this service had provided 24-hour-a-day, physician-to-physician information on any of 9,000 drugs—on contra-indications, toxicity, side effects, etc.

*September 21, 1962.*—The Director of the National Institutes of Health announces at Senate subcommittee hearings the beginning of a more comprehensive drug information program.<sup>9</sup>

*October 12, 1962.*—Julius N. Cahn, Staff Director, Subcommittee on Reorganization and International Organizations, Senate Committee on Government Operations, urges<sup>10</sup> establishment of a "Network of Drug Information and Evaluation Centers."

Portions of his statement follow:

(As in the case of other excerpts in this chronology, certain overall observations are reprinted. They establish the broad framework within which drug information progress would hopefully be made.)

#### NEED FOR A LONG-RANGE PLAN

" \* \* \* in medical communications, our needs have grown much faster than—

our understanding;  
our actions;  
our resources;  
yes, even our plans.

"We do not even have 'on paper' the blueprints with which to cope with the medical information problem of 1965, much less of 1970.

<sup>8</sup> "Interagency Coordination in Drug Research and Regulation," pt. 2, pp. 591-604.

<sup>9</sup> Senate Committee on Government Operations, Subcommittee on Reorganization and International Organizations, "Interagency Coordination of Information," pt. 1, p. 115 ff.

<sup>10</sup> Release H 10-12-62 by Subcommittee on Reorganization and International Organizations.



"Why, it may be asked at this point, should we think in such long-range terms, when we admittedly face such immediately pressing problems?"

"The answer is clear.

"There is a very long 'leadtime' both in training and retraining men, as well as in developing systems which will constitute definitive advances.

"Lacking a long-range plan, we may *drift*, at worst, or *crawl*, at best.

"We must do neither.

"This Government has a bold 10-year plan to reach the moon. The plan embraces a vast governmental-industrial-military-international complex.

"A Medical Communication Plan for the next decade should prove far less difficult to prepare or to implement. Its beneficial consequences for the human race may, in their own way, be no less profound.

#### A MASTER PLAN AND ITS COMPONENTS

"MCP.—A Medical Communication Plan—is both feasible and desirable.

"Actually, *the* plan would really be a *complex* of plans. Communication problems in the health sciences are too many and too varied, embrace too many organizations at home and abroad—to be subject to a *single, centralized* strategy of response.

"The challenge is, instead, threefold: to encourage each professional group to plan for its communication needs in the world of today and tomorrow; to make certain that for its plans, each draws upon the competence and looks to the needs of related groups in the health sciences and in the communications system; to have representatives of the foremost groups join democratically in developing a plan of plans, in which the parts could be harmoniously fitted.

"The time to begin is now.

\* \* \* \* \*

#### "INFORMATION ON DRUG REACTIONS

"One area calling for action has been referred to earlier—information on drugs, particularly on drug reactions. Immense talents are available here; much has been done; but, it falls far short of what is needed in the form of a comprehensive 'network.'

"Many sources are involved:

- drug companies;
- clinical testers;
- practitioners;
- Federal, State and local agencies;
- hospitals, etc.

in addition to their foreign counterparts.

"Masses of information, particularly as to drug reactions, are generated, processed, printed, disseminated. Infinitely more information is unnecessarily lost at every one of the many steps in the chain.

"Many services, journals, indexes, abstracts, books, monographs, exist—not to mention data processing systems, as such. Most of the latter exist in virtual isolation and with little, if any, compatibility with other systems.

"On the Federal side, recent Senate hearings<sup>15</sup> documented the paucity of coordination among such official systems as exist, much less between public and private systems.

"In effect, the same distressing conditions pervading other areas appear in sharp focus here:

- saturation of 'messages';
- enormous gaps in available information;
- wide overlap between such systems as exist;
- incompatibility of systems;
- obsolescence of most systems;
- underevaluation of data, etc.

"Few informed observers underestimate either the need for improvement or the difficulties in doing so. The problems of voluntary coordination are formidable, but not insuperable.

<sup>15</sup> Senate Committee on Government Operations, Subcommittee on Reorganization and International Organizations, "Interagency Coordination in Drug Research," hearings of Aug. 1 and 9, 1962, pts. 1 and 2.



"Necessary restrictions will, of course, continue to prevail as regards confidential doctor-patient information and proprietary information.

"A great opportunity confronts the drug industry, the medical profession, Federal agencies, the World Health Organization, and other interested sources.

"Their response is eagerly awaited.

"It is not too much to expect that the types of expert skills and dedication which have enriched mankind with so many lifesaving medications will be paralleled by equal brilliance—and fervor—in improving drug communications.

"It can be done. 'When' and 'how' are the real questions.

"Bear in mind, the greatest torrent of medical research and medical care knowledge is still to come. Time is running out in which to prepare for it.

#### "'COMMUNICATIONS AS USUAL' MEANS BEING PRODIGAL

"It is incumbent upon the distinguished leaders of medical and allied science to realize that a casual policy of 'communications as usual' will not serve to meet the rising challenge.

"'Communications as usual' tend to be inadequate communication, wasteful communication.

"Neither we, nor any other nation, can afford this waste. We have been prodigal long enough:

prodigal with *research findings* which we permitted to disappear or to remain unevaluated, albeit published.

prodigal in handling *negative results* which might have provided uncounted leads,

prodigal with *medical records*, with exhibits and with virtually every other form in which knowledge reposes.

"Scientists have spent lifetimes extracting fragments of knowledge from reluctant nature—only to have their painful investment of sweat and tears dissipated by breakdowns in communication.

"All of us owe too much to medical science to stand idly by while it does not have the best system of communication that money, skill and dedication can possibly provide.

#### "ADAPTING AND INTEGRATING INNOVATIONS IN PHYSICAL SCIENCES

"In the physical sciences, the sheer urgency of military-space needs has required that *order* be brought out of information *chaos*.

"Much is to be learned from how the physical sciences have responded to their challenge.

"Indeed, in any plans for improving communication in the health sciences, the fullest effort must be made to *integrate innovations* with those projected in other disciplines.

#### "A PROGRAM OF CHANGE

"But, what innovations are to be regarded as desirable for medical science?

"Let me submit just three broad possibilities. I shall do so in terms of the context within which the Committee on Government Operations operates—that is, in terms of *inter-agency*, *inter-disciplinary*, *policy-level* actions.

#### "A PROGRAM OF 'NETWORKS'

"Elements which should be incorporated in a national and international program should include:

"1. *Federal Clearinghouses*.—The establishment within the 10 agencies of the United States Government which support health-related activities, including biomedical research, of a clearinghouse capability. This would include provision for cross-seeding administrative knowledge, for indexing current research, for providing retrospective searches of Federally sponsored report literature and for indexing meetings.

"All this should be part of a larger clearinghouse capability, embracing agency interests in the *physical*, *mathematical*, *engineering* and *social sciences*.<sup>16</sup>

<sup>16</sup> See Crawford, James H., Chairman, Task Force to the President's Special Assistant for Science and Technology, "Scientific and Technological Communication in the Government," Apr. 1962, a working paper, discussed in hearing of Senate Committee on Government Operations, Sept. 21, 1962, op. cit.; but not, in itself, released, as yet, for public distribution.



"2. *National Center*.—The establishment in conjunction with the National Library of Medicine of a National Center for Communication in the Health Sciences. It would be devoted to all phases of health communications (other than those phases handled by a strengthened National Medical Audio-Visual Center at the Communicable Disease Center at Atlanta).

"The new national center should be the focal point for the coordination of expanded communication programs of the U.S. Public Health Service and for the management of certain extramural operations. The latter should include, once the appropriate statutory authority has been approved, grants<sup>17</sup> for library construction, for training of inter-disciplinary manpower, for comprehensive support of critical reviews, etc. The center would be the ally, not the control, of nongovernmental information resources.

"*Research-related* operations should, of course, be carried on in closest conjunction with the National Institutes of Health; *service-related* tasks in closest liaison with the Bureau of State Services; *documentation* aspects in closest relationship with the Office of Documentation, National Academy of Sciences—National Research Council, and the National Science Foundation's Office of Science Information Service.

"3. *National Networks*.—Support for the establishment of an intercommunicating series of networks, including:

a network of specialized Scientific Information Evaluation Centers,<sup>18</sup> *organically* related to *university* and other research;

a network of drug information and evaluation centers;

a network for automated biomedical information processing;

a network of registers of medical case histories.<sup>19</sup>

#### "THE DIFFERENCE BETWEEN NETWORK AND STATION

"The concepts—'clearinghouse,' 'system,' 'network'—must underlie all future action.

"By contrast, the past tendency has been to endlessly proliferate individual systems or 'stations' which could hardly even 'talk' with one another.

"The result has been a series of anarchic 'Towers of Babel.'

"Not even the medical computers which are starting to multiply throughout the Nation, talk the same language.

"Of course, absolute *uniformity* in computer language, or in almost anything else, is neither desirable nor attainable.

"But, *heedless disuniformity* is also intolerable; so is *indifference* to the needs at the vast interface between centers, stations, disciplines and systems.

"The interface between the three great national libraries—the National Library of Medicine, the Library of Congress and the National Agricultural Library—likewise bears attention.

"In turn, each national library can be a still greater center, 'transmitting' to stations throughout the Nation more rapidly, more clearly, more completely than ever before. There is encouraging indication of the desire of each of these admirable institutions to do so.<sup>20</sup>

<sup>17</sup> For a survey of financial, space, personnel, and other needs of these nations' medical libraries, see Bloomquist, Harold, assistant librarian, Harvard University Schools of Medicine and Public Health, "The Status and Needs of Medical School Libraries in the United States," a report prepared for the National Library of Medicine, Boston, Mass., Oct. 1962.

<sup>18</sup> For a discussion of the role of such centers in all the sciences and technology, see Sullivan, Ralph H., Office of Science Information Service, National Science Foundation, "Science Information Centers—Their Present and Future," presented before Reference Division, Potomac Chapter, American Library Association, Washington, D.C., May 10, 1962, 9 pages (photocopy).

<sup>19</sup> For illustrations of current efforts to study and improve management of many types of clinical records (in addition to health-related records strewn today among many community resources) see (a) Moore, Frederick J., M.D., Professor of Public Health, University of Southern California, "Health Information Systems, vol. 1, Narrative Description of Record Procedures in Current Use in Three Public Institutions," 1962; and (b) Best, Wallace H., Ph. D., lecturer in public administration, Department of Public Health Practice, Harvard School of Public Health, "Health Records Are a Top Management Problem and Opportunity in Public Health, Medical Care, Mental Health, Rehabilitation, Research, and Protection," Sept. 1962, 8 pages, mimeographed.

<sup>20</sup> For an indication of the continuing deep interest of the National Library of Medicine in adapting its services to the broadest variety of uses, see Kurth, William H., Reference Services Division, National Library of Medicine, "Survey of the Interlibrary Loan Operation of the National Library of Medicine." (To be published.)



## "TRANSMITTING SIGNALS OVER SWITCHBOARDS"

"In the future, to use another analogy, as in the case of a long distance phone call, an inquirer should be able to tap into the 'switchboard system' everywhere. The signal should be switched from 'board' to 'board' until the right contact is made with the right source or sources—no matter where they are.

"Does all this sound 'impractical?' Before you answer 'yes,' turn your thoughts to the number of space satellites which may, at this very moment, be whirling over your head, circumnavigating the globe in 'the miracle' of 90 minutes.

"You may still be skeptical. You may still say, 'Congress or the professions will never provide the money.' But, first try to answer the question, 'When has Congress or anyone else been told of the real need—the real waste which exists at present—and been asked for the money to end the waste?'

## "CONGRESS BESIEGED BY REQUESTS FOR FUNDS"

"Make no mistake—obtaining financial resources will be no easy problem.

"Requests for funds for communication must compete, on their merits, with requests for funds for a thousand other vital purposes.

"The Congress *has* heard 'a story' before; indeed, hears it every year at appropriations time, that 'money is urgently needed' for this or that 'essential purpose.'

"The Congress has the right to say, 'Show me.' It has the right to expect strong proof of need, including economic justification in dollar and cent terms. Such substantiation can and should be mobilized in depth for submission to the Bureau of the Budget, Congressional Appropriation Subcommittees, boards of directors of private foundations and other trustees of other people's funds.

"Each source of funds must, incidentally, be apprised of the fact that what we seek is not to flood users with documentation, but rather to give them the most useful information that they want and need to do their job efficiently and economically.

## "THE PRICE TAG ON INFORMATION OR LACK OF INFORMATION"

"How much will a Federal clearinghouse capability, a national communications center, and a series of networks cost, directly and indirectly, for establishment and for maintenance?

"A good deal.

"But, this country has to make up its mind whether it chooses to pay for information or to pay infinitely more for lack of information.

"The price tag on lack of information is unbelievably large. It is growing larger.

"How much larger? No one knows. After all, how much is time worth in the battle against one disease, much less a hundred?

## "NO EXCUSE FOR WASTE"

"Fortunately, a trend is underway toward paying our information bill by *action* rather than by *default*. Support of communication is now becoming 'fashionable.' That is no excuse, however, for its becoming prodigal.

"The fiscal obligations of the U.S. Government are too heavy to permit the needless waste of a dime.

"Every proposal for communication improvement must be analyzed as to:

- (a) The ratio of anticipated costs to anticipated benefits.
- (b) The relative urgency and *priority*."

\* \* \* \* \*

November 5-8, 1962.—Surgeon General's Conference on Health Communications takes place. The conference urges "Cooperation of all groups, governmental and nongovernmental, concerned with drug information" to establish a "worldwide drug information system."<sup>21</sup>

(Pertinent portions of the conference report follow. Once again a few of the excerpts relate to broader phases of biomedical communication than drugs, per se. Drug information would, however, form an important component in the actions contemplated under these overall recommendations.)

<sup>21</sup> U.S. Department of Health, Education, and Welfare, "Surgeon General's Conference on Health Communications," Feb. 1963, p. 24. Ibid, pp. 12, 13, 22-24, 115-117.



## SURGEON GENERAL'S CONFERENCE ON HEALTH COMMUNICATIONS

\* \* \* \* \*

## RECOMMENDATIONS

The proposals which follow were selected by the chairmen of the four panels as the major recommendations made by the conference participants. Additional suggestions and more detailed counsel are in the panel reports, in the notes of the panel recorders, and in the tapes of the panel sessions and the general meetings.

The Conference on Health Communications recommends that the Public Health Service:

\* \* \* \* \*

10. *Establish science information evaluation services to satisfy urgent needs for specific information.*

Precise, comprehensive, and up-to-date information pertinent to the current research activities of individual scientists is not readily available from existing sources.

Science information evaluation services should be initiated which would satisfy these needs by selecting precise information from large bodies of knowledge.

As in all endeavors, caution must be exercised against adopting too hastily any large-scale information operations which have been inadequately planned.

11. *Support pilot studies of the problems involved in collecting health data.*

Pilot studies are suggested as prerequisite to establishing a register of medical case histories. Independent studies can provide consideration of alternate methods of setting up a register.

Adequate safeguards for the privacy of the individual were emphasized as important in any register of medical case histories. Such a register could be a valuable source of information for health studies.

12. *Support efforts on behalf of more effective international communication of research results.*

Methods of improving international communication which should be considered include:

Make selected translations available through cooperation between the Government and research groups,

Support abstracting, indexing, and preparing critical reviews, in cooperation with appropriate national and international agencies,

Gather and disseminate internationally information on health programs.

Language differences in biomedical data throughout the world constitute an obvious barrier to communication. Therefore a uniform machine language is needed for processing, storing, and retrieving data from information systems. The Public Health Service should be aware of this problem and support any efforts to cope with it that appear feasible and appropriate.

The Public Health Service should not become involved in research on machine translations at the present time in view of existing programs which are already heavily supported.

13. *Support research and development directed toward establishing a coordinated network for automated biomedical information processing.*

The vast amount of biomedical communication which needs to be carried out in the future can probably be facilitated by the radically new electronic means for information processing, storing, and retrieval now being developed. Eventually a coordinated network with central storage and local "browsing" and retrieval may relieve the increasing pressure on libraries and speed the flow of needed information to scientists, practitioners, health administrators, and the public.

It is urged that steps be taken to determine whether such a system is feasible and practical, and if so, to implement it.

14. *Take the urgent action necessary to establish a worldwide drug information system.*

Cooperation by all groups, governmental and nongovernmental, concerned with drug information will be essential for a successful program.



## REPORT OF PANEL I

## SCIENTIST-TO-SCIENTIST COMMUNICATION

\* \* \* \* \*

*International Exchange of Information*

There is a need for more effective communication of the results of research between foreign and American scientists. Existing programs should be evaluated and the effective ones broadened and strengthened. New means to effect this exchange should be considered.

The means of accomplishing this exchange include:

1. Selected translations, converting and republishing significant research results, would be made available to scientists through cooperative channels involving government support and cooperative planning of research groups.

2. Abstracting, indexing, and the preparation of critical reviews would be vigorously supported in coordination with other national and international agencies.

3. Information would be obtained and kept up-to-date on international health-related programs and research, necessary staff, continuing functions and permanent records, to be established in this connection.

4. Information relating to the organization and conduct of medical research would be placed in the hands of medical scientists for their better understanding and appraisal of international contributions to their fields of research.

*Specialized Information Services*

The panel recognizes a need for specialized information services but is reluctant to support hasty adoption of a large-scale center operation in the biomedical field.

The panel is convinced that biomedical scientists need an information "commodity," or service, that is not available or generally effective in the scientific community at the present time.

This service should satisfy the scientist's urgent need for specific information that is pertinent to his current research activity and is *precisely selected* from the large body of recorded knowledge. His need for such selected information will be satisfied only as it is supplied in a *comprehensive way*, and as he is kept up-to-date on new information in the circumscribed field of his particular research project.

Precise, comprehensive, and up-to-date information pertinent to the current research activities of individual scientists is not readily available to the scientific community-at-large from existing sources. It may well be supplied by a new type of information service. Some isolated services of this general nature are known to be operating at various levels of sophistication and effectiveness for the benefit of relatively few scientists in biomedical research. These should serve to some degree as pattern prototypes or guides in developing special services for the benefit of all biomedical scientists.

Development of such a service should be initially confined to a fairly narrow segment of biomedical science for which the information required for productive research can be processed for the above purposes within a reasonable trial period, reflecting areas of paramount interest to the Public Health Service. Continual evaluation and appropriate modification of this demonstration project can lead to the orderly and economical extension of such a service to other areas of interest.

Limitations of scientific manpower and resources, as well as concern for proprietary interest, militate against (the provision of) services of this kind by most nongovernmental agencies.

The panel, therefore, recommends that the Public Health Service undertake the implementation of such a pilot demonstration on the new information services outlined above.

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Three proposals as outlined in the preconference working document came under careful scrutiny by the panel: Information clearinghouses, No. 8; Drug Information Management System, No. 9; and A Coordinated Network for Automated Biomedical Information Processing, No. 17.



After full and thorough discussion, and based upon the information currently available in the technical communications fields, it was decided to hold in abeyance at this time, any discrete recommendations that would imply a ready-made answer to these complex areas of biomedical communications.

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REPORT OF PANEL 2

SCIENTIST-TO-PRACTITIONER COMMUNICATION

DRUG INFORMATION

The panel unanimously approved proposal 9, Drug Information Management System, after considerable discussion relating largely to the proper role of the Federal Government and the necessity of assuring coordinated cooperation by all groups, governmental and nongovernmental, concerned with drug information. Although there was concern about the problem of the Government making judgments on the effectiveness of individual drugs, there was finally general agreement that the Government must take the leadership in seeking order and the urgent action needed.

CONFERENCE AGENDA ITEMS

*Proposal Number 8*

INFORMATION CLEARINGHOUSES

Encourage the development of clearinghouses, modeled after those already established by the National Institutes of Health, to serve the information requirements of specialized mission-oriented areas of research or applied science.

*Proposal Number 9*

DRUG INFORMATION MANAGEMENT SYSTEM

Establish a drug information management system that will rapidly acquire and appraise new knowledge of the biological effects of particular drugs and make the results known to a variety of users of such information.

*Proposal Number 10*

HEALTH INTELLIGENCE AND REGISTER OF MEDICAL CASE HISTORIES

Undertake a definite and concentrated effort to improve the number of health intelligence activities, their individual scope and usefulness, and their format and distribution capabilities.

Develop a national register of medical case histories containing significant basic health information for every registered individual.

Develop standard personal health records for the use of all individuals and health agencies, one inducement for extending the use of the standard public health record being the provision of record blanks at Federal expense to all applicants.

*Proposal Number 17*

A COORDINATED NETWORK FOR AUTOMATED BIOMEDICAL INFORMATION PROCESSING

In anticipation of radically changed methods of handling information establish a program of study, experiment, and demonstration projects to aid in preparing for the changes that will take place in the transition to completely automated health information processing which can locate not only articles and books but individual facts in them.

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November 14, 1962.—Trade publication, Drug Research Reports, describes<sup>12</sup> recent events with respect to drug information.

<sup>12</sup> Vol. 5, No. 45, pp. 1, 3.



(Title Page)

REVOLUTION IN SCIENTIFIC INFORMATION COMMUNICATIONS OUTLINED FOR USPHS  
MEETING: 50 INFORMATION EVALUATION CENTERS, DRUG REACTION REPORTING  
PLAN

Senator Humphrey's demands for quick progress reflected in two key proposals—(1) evaluation centers to select, analyze, evaluate, abstract, reject and critically review unpublished as well as published data in major research fields; and (2) drug information management system to quickly collect and disseminate data on side effects from all Government facilities.

"Doubting Thomases" at the USPHS' 4-day Airlie House conference question whether computer hardware can handle medical research data. Even if it can, is "mechanized boondoggle" worth the cost? they ask. The hardware is available, conferees are told, and the doubters have little chance to stem the revolutionary tide being swept up by Senator Humphrey from the flood of research data.

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REVOLUTION IN SCIENTIFIC INFORMATION COMMUNICATIONS OUTLINED FOR USPHS  
MEETING: 50 INFORMATION EVALUATION CENTERS, DRUG REACTION REPORTING  
PLAN

Two of the 22 proposals advanced by the U.S. Public Health Service (USPHS) in the working paper prepared for its semiprivate conference on medical research communications were specifically designed to satisfy and quiet Senate Government Operations Subcommittee Chairman Humphrey (D-Minn.), the Capitol Hill pressure man for modernization and mechanization of scientific information exchange.

The two proposals, in fact, were tailored out of the wordy suggestions made by Humphrey during hearings of his subcommittee last summer and by Julius N. Cahn, his subcommittee staffer, in a detailed exposition of his unofficial, individual judgments, delivered before the American Medical Writers Association meeting in Washington last month.

The two key proposals in the USPHS working paper—the ones most likely to get the Capitol Hill boost and go-ahead next year—provide for:

(1) Establishment of up to 50 information evaluation centers to select, analyze, evaluate, abstract, reject, and critically review unpublished as well as published data in major fields of medical and biological research interest.

The residue would be fed to a centralized, mechanized storage and retrieval facility that would supply information in specified areas to regular users and also would answer queries from ad hoc users. \* \* \*

REVOLUTIONARY IDEAS MAY STAGGER SCIENTISTS, BUDGET AND USPHS, BUT NOT  
SENATOR HUMPHREY

(2) Operation of a drug information management system that would quickly collect and disseminate data on side effects from Government medical research centers, the Food and Drug Administration (FDA), USPHS, other Government agencies and extramural research supported with Government money. Said USPHS:

A computerized system wherein drugs, chemicals, food additives, and like substances are characterized, possibly according to their formula would probably be developed. Considerable groundwork related to computer input already has been done in this field of classification and identification of drugs. Biological effects of selected substances can be programmed for input, related in the computer's memory system to identification of the drug, and selective retrieval of this information rapidly obtained.

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The revolution in scientific communications may stagger the imagination—and the budget—but Humphrey has captured the "spirit of 1963" and he has virtually insured the funds to get the new movement on the road. He has served notice to USPHS and other research agencies—and more importantly, to the White House's Budget Bureau—that he will fight to send back every appropriations bill that doesn't contain specific "line items" for special programs in scientific communications.

And Senator Humphrey is in a strategic position to do this. He's not only chairman of the Government Operations subcommittee that can call a hearing



and put USPHS and NIH officials on the griddle any time the Minnesota Senator wants to light the fire, but he also is a member of the Senate Appropriations Committee and Assistant Majority Leader of the Senate.

In addition, as a party leader, Humphrey goes to the White House for breakfast once a week when Congress is in session.

Senator Humphrey's message apparently hasn't been wasted on USPHS Surgeon General Terry. In his remarks November 12 before the Association of Military Surgeons' convention in Washington, he referred to the scientific communications conference and declared: "We hope to implement as many of these recommendations as are feasible as rapidly as possible."

U.S. Air Force Surgeon General Oliver K. Niess indicated to the Military Surgeons' meeting that the Air Force's Capitol Hill radar system also is working. In a speech outlining the size of his medical program, he said: "The Air Force Medical Service now is processing in-patient records with electronic computers. We have extensive possibilities under study for further application of this type of processing."

Another one of the proposals placed before the USPHS conference was the development of a "national register of medical case histories." USPHS' working paper for the conference said: "Now, with the development of computers and automated information management systems, a national register of medical case histories has become feasible."

#### "DOUBTING THOMASES" AT USPHS' AIRLIE HOUSE CONFERENCE FAIL TO CATCH "SPIRIT OF 1963"

Julius Cahn, the Humphrey subcommittee's key staffer, forecast all the imaginative recommendations made in the USPHS working paper 5 weeks before the Government convened over 50 people at Airlie House, an estate in the foothills of the Blue Ridge mountains, near Warrenton, Va.

In his October 12 speech before the American Medical Writers Association, Cahn virtually told them that their publications were outdated as a means of conveying medical research information. He called for: (1) Specialized information evaluation centers (the same name used at the USPHS conference); (2) a system for collecting data on drug reactions; and (3) a register of medical case histories.

The USPHS' 4-day conference at Airlie House held semipublic opening and closing sessions, but the closeup work was done by four panels that held executive meetings for 2 days. (Names of the "outside" experts and Government officials who participated in the panel sessions are listed on the back page of the supplement to this issue of "The Blue Sheet.")

There were "doubting Thomases" at the Airlie House conference. Some doubted whether existing computer hardware was ready to handle medical research data. Others were inclined to the view that the whole program was a "mechanized boondoggle" which would cost more money than Congress was ready to appropriate and the job could be done better and cheaper by humans than by machines.

The "doubting Thomases" who used the cost as the basis of their bearish views on the revolution in research information apparently overlooked the performance of Congress in recent years on research appropriations—particularly when spurred on by an interested, energetic and articulate Senator with a convenient subcommittee in the palm of his hand.

Apparently no one pointed out what Senate Appropriations Subcommittee Chairman Hill (D-Ala.) had done to the now-forgotten Bayne-Jones Report on Medical Research, dated July 1958. This committee of learned consultants to the HEW Department declared that the Nation's maximum capacity for absorbing medical research funds would reach the \$1 billion mark by 1970.

The Bayne-Jones report said that the Government's contribution to the \$1 billion research spending in 1970 should be \$450 to \$500 million. Of this amount, NIH would get \$350 million. ("The Blue Sheet" July 23, 1958.) The fiscal 1963 congressional appropriation for NIH totaled \$880.8 million.

The "doubting Thomases" who contended that computer hardware wasn't ready to handle a medical research data program apparently didn't read or believe all the material passed out by USPHS at the Airlie House conference.

USPHS' working paper was accompanied by two reports from the Training Materials and Information Services Division of McGraw Hill Book Company. One of the reports, submitted to USPHS on October 18, outlined a Biomedical



Research Information System. The second report, submitted 4 days before the conference, gave a general description of a computer-based information retrieval system. It concluded with the assurance that:

In short, as this report suggests, there is nothing in the anticipated computer processing requirements of the proposed Biomedical Research Information System that cannot be supported by the present state of the information systems art using available computer hardware and programming techniques.

#### THALIDOMIDE EPISODE ASSURED GIANT GOVERNMENT SYSTEM FOR RAPID REPORTING OF DRUG EFFECTS

The centralized and possibly "computerized" system for rapid reporting of drug effects was the subject of extensive debate in one of the panel sessions. But it wasn't endorsed, or even mentioned, during the semi-public general sessions. The thalidomide episode had already assured the development of a giant Government drug reporting system.

USPHS told its Airlie House conferees that the proposals in its working paper were designed to provide only a basis for discussion. But NIH Director Shannon had disclosed plans for a drug reporting system when he testified before the Humphrey subcommittee on September 21 ("The Blue Sheet" Sept. 26).

The Food and Drug Administration was represented at Airlie House by Dr. Oral L. Kline, new Assistant Commissioner for Science, and several others. Dr. Kline, however, wasn't listed as a conference participant by the USPHS, sister agency to FDA in the HEW Department.

Each of the 4 panels endorsed a proposal calling for more research on communications, per se. NIH had also acted on this one before the conference. It will shortly announce the establishment of a communications research branch. The man for the branch chief job is Dr. F. Ellis Kelsey, husband of FDA's thalidomide heroine. He planned the Airlie House conference.

The panel on research in communications, per se, was the only one that came back to the conference on the final day with a written statement of its views. It voiced the thoughts of the "doubting Thomases" in somewhat the same language that USPHS, itself, had used in the opening part of its working paper.

The panel questioned the wisdom of moving quickly into a program involving expensive mechanical equipment. It cited the need for more research before undertaking "vast and expensive" programs of mechanization. "No single phase of communication should be exploited without regard to its effect on other parts of the system," the panel said.

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*January 10, 1963.*—A Panel on Information of the President's Science Advisory Committee issues a comprehensive report.<sup>13</sup> It suggests that each NIH institute "consider establishing what would amount to a very elaborate specialized information center with services available to the entire biomedical community."

*January 23, 1963.*—A specialized panel of the President's Science Advisory Committee comments on the great potentialities of computers in the life sciences. It states that "new information technologies would appear ideally suited to prompt recording, analyzing and reporting of any untoward effects" from drugs.<sup>14</sup>

*March 16, 1963.*—Senate Reorganization Subcommittee releases<sup>15</sup> report, "The Nature and Magnitude of Drug Literature." The report, prepared by the National Library of Medicine at the subcommittee's request, estimates that 200,000 original papers in the pharmaceutical literature are prepared annually and describes other problems of "elusive" drug information. (See also notation as to release of printed version of this report on Aug. 30, 1963.)

<sup>13</sup> President's Science Advisory Committee, "Science, Government, and Information," The White House, p. 49.

<sup>14</sup> President's Science Advisory Committee, Life Sciences Panel, "Some New Technologies and Their Promise for the Life Sciences," The White House, p. 5.

<sup>15</sup> Release H 3-5-63 by Subcommittee on Reorganization and International Organizations.



March 20, 21, 1963.—Witnesses testify at Reorganization Subcommittee hearings on imperative necessity for improvement in drug information and evaluation resources.<sup>16</sup> The former head of Mediphone estimates to the press that for \$200,000 he could provide its type of service on a contract basis to Federal agencies and the Nation's scientific community. He reports, however, virtually no previous interest in Mediphone on the part of any agency but the Veterans' Administration.

March 21, 1963.—F. Ellis Kelsey, Ph. D., Special Assistant to the Surgeon General for Scientific Communication, states that the "broad concept" of a "National Drug Information Clearinghouse" is "now being carefully explored for its general feasibility in the Department of Health, Education, and Welfare, and in its several agencies."

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[The full text of Dr. Kelsey's address follows.]

#### A NATIONAL DRUG INFORMATION CLEARINGHOUSE

(By F. Ellis Kelsey, Ph. D., Special Assistant to the Surgeon General for Scientific Communication)

In light of the fact that the National Library of Medicine is the host institution for this, your sixth annual meeting, your program chairman has asked me to extend a formal welcome to you on behalf of the Surgeon General.

First, I bring to you most hearty greetings from Dr. Terry. He has asked me to assure you of his personal interest in your group and the activities of the organizations you represent. The Public Health Service has long had heavy commitments in scientific communications; in fact, many of our programs have as their main purpose the more effective use of health science information by scientists, by health practitioners, and by the general public.

As for myself, I was particularly happy to have this opportunity. I want to describe for you a broad concept which is now being carefully explored for its general feasibility in the Department of Health, Education, and Welfare, and in its several agencies. This is for the establishment of a National Drug Information Clearinghouse.

This concept calls for a very high degree of collaboration among many different groups. Among the most crucial are those represented here—the individuals who are specially skilled in science abstracting and indexing.

The premise which is basic to the system I am about to outline for you is that a more systematic approach to drug information handling is urgently needed, that the volume of the drug literature is great and growing, and that much valuable information is being unnecessarily delayed in its application.

Drug information handling systems operated separately, by various groups, are, at present, insufficient in their coverage. The National Library of Medicine, for example, is able to provide an index to only 2,200 scientific journals, although many more are in existence. Letters to the editor, and minor notes in journals, are not indexed. Even the largest drug companies attempt to cope with only a fraction of the published literature. The American Medical Association plans to monitor thoroughly only some 500 journals for current information about drug toxicity. Pharmacists find it difficult to keep up with regulatory actions by the Food and Drug Administration, which in turn has its well-known scientific information problems. Within the Public Health Service each institute and division has, or is planning to undertake, science information programs in its own field of responsibility, with inevitable duplication of effort.

However, probably the greatest deficiency lies in the fact that present-day attempts to handle substantive information about drug research-in-progress are unorganized and inadequate, even though collections of such information do in fact exist.

It is now technically feasible to establish a Centralized Drug Information Clearinghouse, responsible for total collection of all drug information, published and unpublished, and for the switching of organized blocks of such information to each user-group according to its predefined area of interest, for repackaging and distribution to individual users within that group. In this concept, the user-groups would include various Government agencies; for example, each

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<sup>16</sup> "Interagency Coordination of Drug Research and Regulation," pt. 4 (to be printed).



institute or division in the Public Health Service, and the Food and Drug Administration. They would also include such nongovernment organizations as individual drug or publishing companies and their associations, research institutions and societies, professional societies such as the American Medical Association and other organizations of health practitioners, and international organizations and individual foreign countries. Each of these user-groups would establish and maintain an Information Service Center, with its own search and retrieval facilities, using, among other information sources, duplicate tapes and microforms from the clearinghouse. Each such Information Service Center would organize and consolidate further such specialized information as would be pertinent and timely for dissemination to individual users in that group, as a kind of "retailer" of information.

A first step toward establishing a clearinghouse is a detailed study of the kinds of information needed by each class or type of user-group.

Concurrently, the volume and sources of drug information should be determined, in preparation for a systematic, active, acquisitions program. Potential sources and methods for the collection of information not ordinarily available in traditional publications must receive particular attention.

Existing abstracting and indexing services must be utilized to the fullest possible extent to provide, in an economic and coordinated way, the necessary basic analyses of scientific materials.

The shortage of trained abstractors and indexers may become a limiting factor. It has been suggested, however, that careful coordination may result in substantial savings in both manpower and money. In support of this, for example, is the statistical analysis made for the British Society for International Bibliography in 1950. This study indicated that two-thirds of the scientific papers published each year are never abstracted, each of the others being abstracted, on the average, 3 times. This brings up, of course, the matter of the so-called "slanted" abstracts, those produced for the peculiar needs of specific audiences, and the general desirability, or necessity, of these.

An even more complex set of problems may be found in the specialized Science Information Evaluation Center concept. Four or five hundred of these are now in operation, although relatively few of them are in biology or medicine.

Such specialized Information Evaluation Centers, responsible for evaluating and synthesizing new information, through such mechanisms as critical reviews and monographs, will probably be established in much larger numbers than now exist in the life sciences fields. Their development will be greatly simplified by taking advantage of the experiences gained in the operation of the many specialized Information Evaluation Centers in other areas of science.

In a fully-operative clearinghouse system, selected incoming information materials would be microfilmed and copies distributed, as appropriate, to the decentralized Information Service Centers. Second, each scientific information item would have assigned to it broad descriptor terms for computer preparation of indexes, as in the MEDLARS operation. Third, abstracts would be obtained, with finely focused descriptor terms to permit more definitive searches and precise matching with user-defined interest profiles.

One of the earliest general policy decisions to be taken is the specific system for line notations to be used to convert both chemical structures and biological activities to machine language. Fortunately, a considerable amount of attention has already been given to this by the Chemical Abstracts Service, as well as certain other organizations.

Another decision that should be taken early is the system to be used for control of terminology. Probably MESH (Medical Subject Headings, developed over the years by the National Library of Medicine for Index Medicus) would be the most suitable general frame.

Custom-built blocks of information, in the form of indexes and abstracts, would be provided periodically to each user-group, or Science Information Service Center, as well as to such specialized Science Information Evaluation Centers as may be established. The evaluation centers would thus have readily available to them their appropriate portion of the total drug information materials to facilitate their evaluative functions. Critical reviews, general purpose summaries, monographs, and similar digests would be produced by each evaluation center. Each could also be responsible for answering individual inquiries, since it would have all necessary information at hand through replicate tapes and microform copy from the central clearinghouse.



Such a clearinghouse-based system would require, at Science Information Evaluation Centers and at most Information Service Centers, satellite, compatible, machine-based information handling systems. Such locally controlled systems would often contain information of a proprietary or other nonpublic nature. Each drug company, for example, generates certain information in which it maintains proprietary interests. As time goes on, some of this loses its peculiar value to the originating company, whereupon it could enter the general system and become available to all. Other examples of information that must be held confidential can be found in the applications and notices concerning new drugs submitted to the Food and Drug Administration, or in grant applications and progress reports submitted to the Public Health Service.

Preliminary discussions with a few potential user-groups, information sources, systems designers, and information equipment manufacturers lead to a tentative confirmation of needs, values and general feasibility. However, the continued development of this concept requires active, thoroughgoing collaboration among many Government and nongovernment agencies and organizations, and among those who produce, process, or use scientific information.

This, then, in very broad outline, describes a nationwide system for the more effective management of information about drugs. Clearly, however, there are many international aspects as well. It is essential that information about drugs travel freely across national boundaries. Many of the steps necessary for establishing an International Drug Information Clearinghouse could be taken concurrently with developments in our own national system. It is quite possible that some of the international features of a drug information exchange would not involve great expenditures over and above the programs being carried out within the participating nations.

Discussions already have occurred in the World Health Organization on the need for pooling of information about drugs. The Public Health Service has made clear to the World Health Organization its wish to cooperate in every practical way in the planning and establishment of such an international program.

The essence of the system as described is the organizing function of the clearinghouse—to minimize unnecessary duplication of effort, to improve in-depth coverage, and to speed up to the total communications process. Many studies have been made of abstracting and indexing, and of methods for their financing. There seem to be relatively few financial problems for the processing of information which is mission- or project-oriented. The centralized clearinghouse, as a switching system, must utilize fully the information processing efforts of the mission-oriented groups, encouraging the extension of these efforts, and filling in the gaps where they do exist.

For example, at the present time the Public Health Service supports abstracting services for water pollution, public health engineering, cancer chemotherapy, psychopharmacology, venereal disease, and influenza. This type of program is likely to increase rather than decrease. It is not at all certain, however, that the actual abstracts produced with these funds are put to maximal use by the discipline- or profession-oriented groups such as Chemical Abstracts, Biological Abstracts, or Excerpta Medica.

One potential value of the Drug Information Clearinghouse System lies in its serving as a prototype or precursor for an even larger Clearinghouse System, one to be concerned with all scientific information which relates to health. However, rather than develop this aspect any further, I will close these remarks by asking each of you for your help, individually and collectively, to explore further the possible values, the mechanisms and interrelationships, and the probable pitfalls, of such a Drug Information Clearinghouse.

I am certain that many of you can foresee a number of serious difficulties, particularly in the technical areas. I have made passing reference to some of these; the others must first be identified and then, hopefully, overcome. However, management and policy problems seem even more difficult, especially those which arise because of the necessarily collaborative nature of the project. One of the recommendations made at the Surgeon General's Conference on Health Communications, held last November, advises the Service to "Take the urgent action necessary to establish a worldwide drug information system," and adds the following counsel: "Cooperation by all groups, governmental and nongovernmental, concerned with drug information will be essential for a successful program." With this counsel I most thoroughly agree. Thank you.



*April 2, 1963.*—Senator Hubert H. Humphrey comments<sup>17</sup> in the Senate on the subcommittee's hearings of March 20-21, 1963. He commends the address which had been delivered by F. Ellis Kelsey, Ph.D., on March 21, 1963, indicating that a National Drug Information Clearinghouse was under consideration.

[The full text of Senator Humphrey's address follows.]

#### AN IMPORTANT MILESTONE IN PROTECTING THE PUBLIC HEALTH—PROPOSAL FOR A CENTRALIZED DRUG-DATA INFORMATION SYSTEM

On Thursday, March 21st, the Senate Government Operations Subcommittee on Reorganization and International Organizations heard important testimony on, among other topics, the critical need for a centralized system of drug information.

Coincidentally, that very morning, I received an advance copy of a welcome statement which was to be delivered that day before the National Federation of Science Abstracting and Indexing Services.

The statement was prepared by F. Ellis Kelsey, Ph.D., Special Assistant for Scientific Communication to the Surgeon General of the United States Public Health Service. Dr. Ellis Kelsey is the husband of Dr. Frances Kelsey, the medical officer of the Food and Drug Administration who has been honored for her success in preventing the commercial introduction of thalidomide into the United States.

In his statement, Dr. Ellis Kelsey proposed the establishment of a National Drug Information Clearinghouse.

The full text of Dr. Kelsey's excellent speech will be printed within the subcommittee hearing record—part 3.

#### CONGRATULATIONS TO ELLIS KELSEY

I should like to congratulate Ellis Kelsey for his vision and enterprise.

It will be recalled that it was he who had arranged, on behalf of the Surgeon General, Dr. Terry, the successful Conference on Health Communications, held at Airlie, Va., in November 1962.

I had personally urged the calling of such a conference in a public statement 6 months earlier—on May 14, 1962.

#### OPPORTUNITY CONFRONTING SURGEON GENERAL

It is gratifying to note that Surgeon General Terry is moving ahead expeditiously in this field of better communication.

The Surgeon General confronts many other problems and challenges. We, of the Congress and of the Nation, expect a great deal of him.

But, I believe that if he and his staff continue to spearhead this particular drive, we will all have great reason to be proud of the results which will accrue to medical and pharmaceutical science.

#### PROBLEMS OF A CLEARINGHOUSE

Bringing Dr. Kelsey's proposal into reality will require men, money, materiel and time.

A "clearinghouse" implies cooperative arrangements between a wide variety of sources, both as to input and output. These sources would have to include, for example, the Food and Drug Administration, the National Institutes of Health, the National Library of Medicine, the Veterans' Administration and other agencies, as well as a wide variety of nongovernmental sources—the American Medical Association, specialty medical organizations, pharmaceutical companies (to the extent they feel it feasible, without endangering their proprietary rights), the American Pharmaceutical Association, and others.

The time to proceed on this effort is now. Too much time has already needlessly elapsed. Much of that time was lost, speaking very frankly, because the leading Federal agencies were, for so long, relatively indifferent to the problem.

<sup>17</sup> Congressional Record, pp. 5119 ff



The medical research agencies contended this was "not a research function;" the medical-care agencies contended it was "not a service function;" most agencies looked to private efforts; private sources looked to supplemental Government efforts.

Month after month, year after year, I personally reiterated to all of them (in statements in committee, on the Senate floor, in the press and before public assemblies) the absolute importance of affirmative action.

What does the record show?

Who actually did what and when?

Who did not do what and when?

Let us see a few of the principal actions, step by step, over the past 2 years.<sup>1</sup>

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#### A LARGER SYSTEM OF SYSTEMS

This is where we now stand. Obviously, we still have a long way to go. But, let's not lose any more time. Let representatives of the principal drug information sources—the generators, "packagers" and users—work out together a common program.

And, let them plan it, as Dr. Kelsey rightly urged, as a part of a much larger, i.e., drug and nondrug, health clearinghouse system.

To that I may add, let the Clearinghouse for Health Sciences be recognized as an integral part of an overall system for all the sciences—the physical, social, mathematic, engineering and life sciences.

This is no idle dream. The fact is that parts of an "all-science" system already exist and are already functioning, but on a relatively uncoordinated, disuniform basis. I refer to:

the very modern NASA system;

the system of the Atomic Energy Commission;

the system of the Armed Services Technical Information Agency;

the Science Information Exchange, etc.

The present patch-work should be transformed into a rational "system of systems," such as this subcommittee—its Members and staff—have long proposed.

#### GREAT POTENTIAL ON USEFUL DRUGS

I predict that there will be a Drug Information Clearing House and that it will be a great boon to medicine and to pharmaceutical science.

It should be pointed out, too, that in much of the advance thinking about a clearinghouse, its value has been mentioned as a means of calling attention to adverse drug reactions. The fact of the matter is, however, that the clearinghouse could serve for just the opposite objective also. It could and would call prompt attention to the beneficial effects of the vast number of efficacious and safe drugs.

And, it would provide varied information for the widest variety of "audiences"—for basic and applied researchers, administrators, drug companies, practitioners, pharmacists, other members of the healing arts, etc.

The clearinghouse could help further raise the high and well-justified confidence of the American people in the healing arts, including pharmaceutical science.

The type of dedication which Ellis Kelsey has evidenced should be paralleled by dedication on the part of all sources whose cooperation will be so vitally necessary. Exactly where the clearinghouse or system of clearinghouses will be established, under whose auspices, whose financing, whose "language" system, etc. are important but hardly insoluble problems. Let us get on with the task.

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*July 18, 1963.*—Dr. Ellis Kelsey testifies before the House Committee on Education and Labor Ad Hoc Subcommittee on Research Data Processing and Information Retrieval Center, under the chairmanship of Congressman Roman Pucinski of Illinois. Dr. Kelsey elaborates on the concept and plans for the proposed clearinghouse.

[The full text of his address follows.]

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<sup>1</sup> The chronology, as published in the Congressional Record, is reprinted in expanded form in the present exhibit.



## STATEMENT OF F. ELLIS KELSEY, PH. D.

Mr. Chairman, I appreciate the invitation to appear before your committee as you consider legislation to establish within the Federal Government a national center for research data processing and information retrieval. This is a timely subject of nationwide and international significance. Few matters facing the scientific community today are as urgent as improved communication of scientific information. The health and well-being of millions of Americans depend on the speed, accuracy, and comprehensiveness with which scientific information reaches professional groups and the public. I am indeed gratified, therefore, that this committee is seeking a national solution to a national problem.

I am on the staff of the Surgeon General of the Public Health Service, as his Special Assistant for Science Information. I should make clear at the outset, however, that I am appearing before you today in a personal capacity rather than as a spokesman for the Public Health Service or for the Administration.

Briefly, my professional background includes 23 years in medical school teaching and research in biochemical pharmacology; author or coauthor of over 50 scientific papers dealing with cholesterol metabolism, antimalarial drugs, radioactive isotopes and drug metabolism in general; membership in the American Society for Pharmacology and Experimental Therapeutics and the Society for Experimental Biology and Medicine; and 3 years in administrative work with the Public Health Service. My experience in science information programs is, therefore, largely based on the needs and user habits of scientists and teachers. This past year, however, I have been responsible for planning and coordinating a broad survey of the health-sciences information-handling programs of the Public Health Service and for collecting information about possible extension, expansion, or revision of present efforts.

It is my firm conviction that neither old nor newly generated knowledge in the biomedical sciences is being thoroughly exploited at the present time because of our failure to take full advantage of modern information-handling devices and systems.

The President, in his special health message to Congress last February, stated: "Last year I pointed out that the accumulation of knowledge through research is of little use unless communicated in useful form to those who need to use it—to other scientists, educators, practitioners, administrators, and the public. There is now wide recognition that improved scientific communication is an urgent goal, and action is being taken. With the assistance of information developed by congressional studies, I have asked the Department of Health, Education, and Welfare to take the lead in developing new methods and systems of utilizing and making effectively available more health research results and information."

The President's Science Advisory Committee Report of January 10, 1963, entitled "Science, Government, and Information," carries a number of far-reaching recommendations for improving science information handling. I would like to quote one sentence: "An operational analysis of the process of technical discovery made by the panel suggests that the individual theoretical scientist will, on the average, maximize his overall productivity if he spends half of his time trying to create new scientific information and half of his time digesting other work and communicating his own."

This is obviously an approximation which needs more detailed examination. It does suggest that, each year, information handling may be costing us hundreds of millions of dollars worth of our biomedical scientists' time and effort. Surely then, this is an area where time-saving devices, and the use of specialists to do specialists' work, promise significant increases in productivity. Since we seem to be approaching a natural limit as to the percentage of our people and of our gross national product that can be devoted to research and development, such productivity increases are vital.

Since 1958 the National Science Foundation has been the major mechanism for public support of research on science information methods and systems, theory and practice. Much has been learned. Some kind of a systems-oriented, machine-based science information data processing and retrieval center is, in my opinion, practical, necessary, and inevitable. The only question is one of timing. This will, by-and-large, be determined by the level of financial support the program is given.

I think it is too early to define any such center in detail. In fact, I would prefer to refer to it as a National System, rather than as a National Center. Actually, we have a national system at this time—made up of a complex of many



diverse elements: solo scholars, colleges, journals, libraries, secondary publishers, professional societies, transient conferences, information centers, and so on. These are interdependent in their functioning but usually autonomous in their operations. More efficient use must be made of all of these components if they are to continue to cope with the increasing amounts of newly-generated scientific information.

Each of these subsystems presents its own set of needs but the greatest need is for their coordination, their joining together to exchange resources and assets, to minimize unnecessary repetition, to divide an almost overwhelming task according to the peculiar skills and abilities of each.

New scientific information must be recorded, collected, abstracted, indexed, evaluated, summarized, and related with that which was previously known. Then it must be transmitted to the people who need it. This is the clearinghouse function.

The ultimate goal, as I see it, is the complete automation of science information handling, an international network for processing, storage and retrieval of biomedical articles, books, and documents of all sorts. The full documents would be abstracted and indexed in various ways by machine or by human abstractors, translated as necessary, and stored electronically.

The original articles, the abstracts, and the critical evaluations would be made available for retrieval of individual facts contained in them as well as for total retrieval, at dispersed places throughout the country and perhaps abroad. This retrieval might be accomplished over ordinary long-distance telephone lines, or perhaps over a special network established for the purpose, if that appeared more efficient.

Consideration of the following points is implied in the planning of this system for biomedical information handling.

1. Optimum methods for searching for stored information.
2. Alternative coding systems for identifying information.
3. Alternative forms of machine and human abstracting.
4. Alternative information storage rationales.
5. Developmental work required on new information processing equipment and machine programs.
6. Developmental work required on techniques for remote transmission of information so that it can be available on demand to users who may wish to browse, in either a directed or in a random fashion.
7. Techniques for automatic suggestion to the searcher about secondary materials relevant to his interests, to increase the likelihood of that creature association of seemingly unrelated facts or concepts which is so important.
8. Programs to enable the machine to learn from users how to adjust filing and coding procedures for greater efficiency.
9. Searching techniques which will automatically teach the user how to operate the system most effectively.
10. Procedures which will take the initiative in notifying users of new items of possible interest to them.

Such a system has been studied by many of the major corporations in the electronic and data processing industry. In general, the major and more experienced companies seem to be confident of its feasibility.

Last November the Surgeon General called together a group of 39 nongovernment experts for a 3-day conference on health communications. A report of this conference is now available as Public Health Service Publication No. 998. A number of important recommendations were made by the conferees. One such recommendation, to support research and development directed toward establishing a coordinated network for automated biomedical information processing, has since been developed in some detail. It has not been evaluated fully within the executive branch and certainly no recommendations to this committee are to be inferred. I include a discussion of it here only in illustration of the type of examinations now underway.

In its present form, the proposition calls for the development of a thorough-going system design plan, including needs, feasibility, and costs.

This feasibility and planning study should include a careful estimate of the size of the information center and extrapolations concerning its growth during the next 10 years. Analysis should be made of the needs of the users. Alternate possible components produced by current manufacturers should be evaluated as well as alternate system configurations. Attention should be paid both to machines and programs which are available now, as well as to those which can reasonably be expected in the next 2 or 5 years.



The alternative values of gradual development of information processing techniques from the present procedures to more advanced ones, versus the immediate undertaking of advanced systems, should be considered. Centralized versus decentralized storage and administration should be compared. The most promising system configuration should be checked by simulation methods, which are currently available. An implementation schedule should be worked out, with the timing of all necessary steps clearly shown. It should be possible for a drug information clearinghouse system, for example, to be operating within 2 years of the letting of the contract for it, for a biomedical scientific information processing system to be operating a year later, and for a medical records information processing system to be operating a year after that. Careful cost analyses of all alternatives should be included in the primary study.

For each of the systems the following types of inputs should be used: cards, paper tape, magnetic tape, keyboard, typewriters, printed and handwritten sheets (with high speed optical readers at least at 2,000 characters/sec.), and voice.

Storage should be modular. Ultimately memory techniques should work toward electronic storage of the total task, but early versions of the systems would probably use microform. A central memory capacity of  $10^{12}$  bits is probably essential. Complete search of such a memory should be possible in 6 hours and random access to any address in a few milliseconds. Centralized buffer memories up to  $10^6$  bits will probably be needed.

Special attention should be paid to the methods for storing either microform or electronic information, and the system should gradually move from one to the other.

Among the output media should be all those considered under input media. High speed electrostatic printers going at a speed of as much as 280,000 characters/second and making possible facsimile transmission are particularly important. So are small local printers which can produce a page of hard copy a second and which should be available for less than \$1,000 each.

Long line components including telephone, telegraph, radio, laser, microwave, coaxial cable, Telpak, and Telstar should be compared. It is probable that the Government telephone system will be adequate for most purposes as well as cheapest. Up to 8,000 bits/sec. may be transmitted on good telephone wires.

The search mode will be, perhaps, by document title or depth key word but, ultimately, by natural language search. The search time should not be longer than a second, if possible; the time for search and distant arrival of a complete record should be a maximum of 20 minutes.

Operations should be planned to develop in the direction of using electronic storage and transmission, since the electron is unquestionably in the long run the marker for information which is cheapest, easiest to manipulate, the fastest to transmit. Systems should also be planned to isolate the individual fact from unneeded materials in the document or book in which that fact is located, in order to shorten the time required for the user to get to the fact he wants and to decrease the mass of information which must be transmitted to him so that he can get the single fact he wants.

The study should also consider such matters as formatting, abstracting, indexing, techniques for informing users of new materials, and translating. Abstracting and translating probably can be largely automated within 5 years.

It is critical that extensive attention be given to methods whereby the different systems and probable future systems can be made compatible or convertible in order to decrease the cost of later changes in coding, storing, and other procedures.

This is a bold and imaginative program which some will dismiss as visionary. But, as must be apparent, I am personally convinced that these things are possible, that the basic discoveries have already been made, and that no theoretical roadblocks remain. On the other hand, such a system cannot be bought off-the-shelf as yet; a vast amount of problem-solving research and development remains to be done in both the technical and the socioeconomic areas. Clearly such ambitious programs as these cannot be undertaken without real and substantial evidences of their national importance, in competition with many other national programs.

Even so, it is impractical to expect early overall solutions in this complex field. In the interim, certain practical and urgent problems must be attacked and solved, at least in part. In my view, one of the most important of these concerns the better management of scientific information about drugs.



The drug information clearinghouse concept is among the many possible programs of potential value which are being given thorough study before any recommendations will be made. With this distinct reservation, I will try to explain this concept at its present stage of development.

The purpose of a drug information clearinghouse would be to coordinate, extend and supplement present activities in the collection, organization and distribution of scientific information relating to the pharmacological and toxicological properties of chemicals, including drugs, pesticides, and all other chemical hazards in our environment.

The clearinghouse would serve also as a model for the possible future development of a similar system for handling scientific and technical information in all of the life sciences and related fields.

Justification for the support of a drug information clearinghouse is based on the expectation that improved management of scientific information will increase the yield from investments in biomedical research and development by reducing the time scientists now spend searching the scientific literature, by helping in the identification of information gaps, and by hastening the widespread application of research results to the solution of health problems or to additional research efforts.

The general concept of a drug information clearinghouse encompasses many activities by several agencies within the Federal Government, notably the Public Health Service and the Food and Drug Administration, as well as the pharmaceutical industry and profession, universities, medical schools, hospitals, and other organizations engaged in drug research and development.

Four classes of individuals, each with specific information needs, would be served by the clearinghouse: research scientists both public and private, health educators and practitioners, the general public, and administrative managers.

Three kinds of information services would be required: (1) *current awareness* services, including both selective dissemination of information regarding drugs, chemicals or situations, and for browsing for fresh or unforeseen associations; (2) *retrospective searching*, for those entering new fields or subfields for the location of new methodologies or to test new hypotheses, for efficient and complete identification of pertinent source materials for writers of critical reviews or for program analysts, and for obtaining new correlations or previously unrelated data including relations between chemical structure and biological activity and relations between environmental hazards and the incidence of disease; and (3) *prospective searching*, to follow up on specific theories so as to permit updating of knowledge in a given field or to checking on how well an older observation, therapy or conclusion has stood the test of time on the evidence of subsequently published information confirming, condemning or extending such theories.

The first product of such a clearinghouse would probably be a body of informative abstracts, written to uniform specifications and produced with a minimum of delay after primary announcement or publication. The text of the abstracts should be coded on magnetic tape and their indexes on magnetic random access devices, to facilitate prompt selection and printing in response to individual demand. Special collections could be printed in microform on a periodic basis to serve the continuing interests of specific mission-oriented groups.

These abstracts should be regarded as a national resource, to be used to supply various mission-oriented organizations with such abstracts as may be selected by them, for independent printing and distribution according to the needs of their patrons. Such a policy would make possible a continuing assessment of the usefulness of the central abstract collection as well as to reduce the need for multiple abstracting of the same primary documents, with its attendant waste of both manpower and funds.

The second product might be microform reproductions of relatively unobtainable publications. Present and future bibliographic resources, such as Index Medicus, are or will be of great value in locating the titles of articles which may be pertinent to individual problems. The use of such indexes, however, often results only in long lists of such titles. This requires an excessive effort to locate each abstract or original paper, so that it may be examined for its actual pertinence to the problem at hand. With the deep indexing made possible by machine-stored abstracts, and the sophisticated use of weighted inquiry terms, roles and links, precise answers are more easily obtained. The problem of rapid availability of the original texts so located can be solved with modern microform techniques.



The third product would be a new series of critical review articles and monographs, summarizing present knowledge in selected fields. Selection of subject matter areas, and authors, will require extensive use of expert panels. Certain of these projects might be expected to lead into the development of specialized information evaluation centers, for the continuing production of evaluations of specific data or information, current summaries of technical trends, comprehensive state-of-the-art analyses and identification of information gaps.

Other information services contemplated include specialized research personnel identifications, assessments of research program productivity, and special analyses of chemical-biological reciprocity.

A conservative approach to the immediate and long-range task of exchange of information about drugs and chemicals would include the careful and detailed identification of the information requirements of scientists and practitioners and also of the several sources of scientific information which will be required to satisfy these needs. Specifications for a working system analysis and design study could be established this year. A comprehensive system design would require another 8 months at least.

Certain technical aspects require intensive study and careful definition before operations can begin. These include:

1. Chemical and biological coding systems development.
2. Thesaurus or language control principles.
3. Abstract specifications.
4. Collection methods, especially for foreign information.
5. Microform specifications and production methods.
6. Machine storage and retrieval system selection.
7. Development of organizational and technical guides for information service center operations.

The primary goal is the production of useful information tools at the earliest possible time. In its first phase, the drug information clearinghouse would have to be a document-switching operation, a fairly simple extension of the Medical Literature Analysis and Retrieval System (MEDLARS) now being installed at the National Library of Medicine. In fact, MEDLARS should probably serve as the basic system, to provide clues to the identification of the most significant scientific publications for deeper indexing and abstracting. At the same time, provision must be made for more efficient dissemination of informative abstracts, or complete documents, according to need, since MEDLARS can do no more than provide a bibliography, with no substantial information beyond a few key words and the title of each document.

During the first phase of development of the clearinghouse, steps should be taken to standardize names, codes, and formats to facilitate eventual automation of the information system. Ultimately, we should strive to retrieve information itself, rather than just the documents which contain the information. Realistically, it will be many years before an effective information system of this type can be in operation. Nevertheless, certain aspects of the relationships between chemical structure and biological activity can be handled electronically by present methods and equipment. This has been demonstrated by the drug information systems operated by certain of the drug companies. These are extraordinarily powerful tools for research even in small systems. From a file of information concerning 50,000 chemical compounds, for example, it takes only a few minutes to select those compounds with a certain substructural configuration which also have certain biological properties in common. From either a toxicological or a therapeutic standpoint, such information is of great practical value.

There appear to be 4 identifiable activities which are necessary for a clearinghouse: the collecting of information, from published or unpublished sources; the procuring of abstracts, critical reviews and summaries; the indexing and organizing of all of these materials; and the dissemination of information, indexes, abstracts or documents according to the defined needs of users.

A somewhat different approach than that used for the discipline-oriented drug information clearinghouse, where information is organized according to the traditional divisions of science, is that of the mission-oriented National Clearinghouse for Mental Health Information, where information is organized according to the needs of people working in a given problem area. Now being established, the Mental Health Information Clearinghouse will incorporate and extend the work of the Science Information Unit of the Psychopharmacology Service Center. This unit services research workers in the field of mental health through such publications as Psychopharmacology Abstracts. Some 5,000 copies are



distributed to individual research workers and librarians each month. The center also prepares special-purpose bibliographies and answers direct scientific inquiries from a central store of information consisting of more than 20,000 scientific documents. When this service center becomes a clearinghouse, its audience will be increased to include practitioners and the public, and its information collection will include everything that might be pertinent for workers in all of the mental health fields.

At last November's Conference on Health Communications, which I referred to earlier, discussions revolved around the 3 major classes or groups of information users, scientists, health practitioners, and the general public.

Scientists need information for their work, and information is the end product of their work. Improvement here would save time, thereby reducing costs, and improve the quality of research.

Health practitioners also both use and produce scientific information. Improvements here would save lives and reduce pain and suffering. As the participants in the conference pointed out most emphatically, "the communication of new knowledge to the practitioner must, in fact, be education, if it is to affect the behavior of the practitioner and bring about changes in his practice to the health benefit of the patient, which is, after all, the primary purpose of all medical research."

The panel on "Scientist-to-Public Communication" was quite vigorous in its condemnation of that title to express the two-way process necessary to effective communications among all the health professions and agencies and the public. It was suggested that the concept be broadened to include health planners and administrators as well as scientists. It was also pointed out that the "public" consists of a variety of publics, with different aims, content, and levels of understanding. All of these publics must be reached and informed in the interest of sound health action by individuals, families, groups, communities, and the Nation as a whole.

As a former laboratory scientist and medical school teacher, I often find myself remiss in my appreciation of science information programs which are oriented toward the rest of the so-called public. Yet as I look back on this period of my life, I recall the ways and means by which I kept informed about general scientific events and progress. At the risk of seeming to be still unsympathetic to this problem, I will say that of these 3 groups, scientists, practitioners, and the public, I think the best job is being done by and for the public.

Much more can and should be done, of course. For example, we are only beginning to appreciate commercial television as a medium for communication of science information. The enormous viewing audience offered by this still developing medium has been insufficiently employed in the public service. Documentary television, making widely available to the public, developments in research and in the application of research findings to the health needs of people, can be of substantial assistance in widening the spectrum of biomedical communications.

However, in my judgment, the most pressing needs are for better methods for bringing new knowledge to practicing physicians, dentists, nurses, and all of the others whose job it is to minister to our health needs. Much more could be done now, with present methods and media, given adequate resources.

Finally, in this high-points only, overall review, I have alluded to a too-large number of possible new programs in the general area of science information. Decisions must soon be taken about these. Selections, and the assignments of priorities, must be on the basis of values as well as costs.

Costs for new information systems are relatively easy to estimate. Values are not. The most satisfactory way to evaluate the feasibility, usefulness and costs of new health information processing techniques is to assess them in pretests conducted in the most realistic possible situations. This could be accomplished by the establishment of a proving ground in a community including physicians, dentists, nurses, public health nurses, and other medical personnel in practice, a university medical school, civilian and government hospitals, and medical library. This proving ground should try out a wide range of new communications techniques and do the necessary research and development related to them. These techniques should include new forms of machine processing and also experiments with conferences, classes, programmed learning techniques, open- and closed-circuit television, audiovisual aids, and other procedures designed to improve biomedical communication in the community.



Careful evaluations of the comparative benefits and costs of these different procedures could then be made.

In summary, I have given you my personal views as to the long-range feasibility of a Science Information Data Processing Center, some further descriptions of other essential components of a truly national system, and outlined certain possible, logical steps that could lead eventually to the adoption and implementation of this vital concept.

Thank you.

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(EDITORS' NOTE.—Additional comment on drug information will be found in the committee print, "Drug Literature" which was formally issued by the subcommittee on August 30, 1963. The print contained numerous appendixes including letter from the Food and Drug Administration on difficulty of "keeping up with the literature."

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EXHIBIT 171

SCIENTIFIC INFORMATION PROGRAM IN THE FOOD AND DRUG ADMINISTRATION:  
REPORT BY THE AGENCY'S COMMITTEE ON SCIENTIFIC INFORMATION

In December 1962 O. L. Kline, Assistant Commissioner for Science and Chairman of the Committee on Scientific Information of the Food and Drug Administration, conveyed a report on the agency's program to Commissioner George Larrick. A copy of the report was requested by the subcommittee and was furnished by the agency. The report follows.

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, FOOD AND DRUG  
ADMINISTRATION

REPORT TO THE COMMISSIONER OF FOOD AND DRUGS

by the

FDA COMMITTEE ON SCIENTIFIC INFORMATION

DECEMBER 19, 1962.

To: Mr. Geo. P. Larrick, Commissioner of Food and Drugs.

From: O. L. Kline, Assistant Commissioner for Science.

Subject: Report of FDA Committee on Scientific Information.

On October 1, 1962, you asked me to form and to head a group within FDA entrusted to achieve the following:

1. Followup on FDA's commitments to participate with the Science Information Exchange.
2. Develop recommendations within 60 days to promote and improve the processing and dissemination of scientific data processing within FDA.
3. Evaluate FDA's current Adverse Reaction Reporting Program.
4. Consider FDA's overall need to exchange all kinds of scientific information with outside organizations.
5. Represent FDA with the growing number of outside persons and groups working in the area of scientific data collection, coordination, and dissemination.

Transmitted herewith is a report of this group's accomplishments up to this time. It includes:

1. Recommendations for improvements in the processing and dissemination of scientific information within FDA, including the establishment of a permanent group to deal with agency-wide scientific data handling problems; and
2. Recommendations concerning the exchange of scientific information with the Science Information Exchange and other outside organizations.

The Committee is still studying the Adverse Reaction Reporting Program currently operated by the Bureau of Medicine. We will submit specific recommendations concerning this particular program at a later date.



It is the belief of the Committee on Scientific Information that its efforts so far to study the scientific data and information exchange activities of FDA have been of considerable value. We have found that FDA is not lagging behind other organizations interested in the dissemination and utilization of medical and scientific information and knowledge and that, in many ways, FDA stands in the forefront of those organizations that have demonstrated an appreciation of the important role that information dissemination plays in the execution of sound scientific programs. Some of our past and present programs and projects stand as evidence of this fact.

However, the Committee has also found that improvements are in order and that much more must be done to develop more information sharing within FDA, acquire more data from the outside, and exchange such data with organizations both in and out of Government, not only in this country but abroad.

One encouraging aspect of the Committee's study has been the almost unanimous desire on the part of FDA staff to cooperate in every way possible in developing a better scientific information exchange operation. Another point of encouragement has been the Committee's finding that there already exists in FDA a solid base for developing such an improved operation. This base consists not only of an awareness and appreciation of the problem but also of actual programs and projects either now in operation or now being planned that would contribute directly to a more effective information exchange program.

The members of the Committee and I are available to discuss the enclosed report with you in more detail should you desire.

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#### FDA COMMITTEE ON SCIENTIFIC INFORMATION

##### Chairman

Dr. Oral L. Kline, Assistant Commissioner for Science

##### Members

Dr. Daniel Banes, Deputy Director, Bureau of Biological and Physical Sciences

James B. Cardwell, Acting Director, Division of Management Systems

Reo Duggan, Chief Chemist, Bureau of Field Administration

Dr. Frances O. Kelsey, Medical Officer, Division of New Drugs, Bureau of Medicine

Dr. Irwin Siegel, Deputy Director, Bureau of Medicine

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#### REPORT OF FDA COMMITTEE ON SCIENTIFIC INFORMATION

December 19, 1962

##### I. CONTENTS OF THE REPORT

This report deals with the following subjects:

1. Recommendations for improvements in the processing and dissemination of scientific data within FDA, including the establishment of a permanent group to deal with agencywide FDA scientific data handling problems.

2. Comments and recommendations concerning the exchange of scientific information with the Science Information Exchange and other outside organizations.

##### II. PROPOSAL TO IMPROVE THE PROCESSING AND DISSEMINATION OF SCIENTIFIC INFORMATION WITHIN FDA

###### A. Background

Among its assignments, the FDA Committee on Scientific Information was requested by the Commissioner of Food and Drugs to furnish specific recommendations for the promotion of and improvements in the processing and dissemination of scientific information within FDA. In carrying out this assignment, the Committee took into consideration (1) the requirements of the several organizations and programs of the agency which depend on valid scientific information and (2) efforts already underway within the agency to improve the processing, distribution, and dissemination of scientific data and information. The Committee also took into consideration the findings and recommendations of the recent National Bureau of Standards study.



In considering the various activities and programs that depend upon, and in many cases create, valid scientific data and information, the Committee gave primary attention to the following processes:

1. The New Drug Application process;
2. The evaluation of investigational drug testing programs;
3. The establishment of safety tolerances for food additives, color additives, and pesticide residues;
4. The review and evaluation of labels for hazardous household substances; and
5. The premarket testing and certification of insulin, colors, and antibiotics.

The Committee recognizes that almost all FDA programs depend upon the availability and application of current scientific information and that many programs produce technical and scientific results which have an informational value to scientists outside FDA. However, the Committee considers the above to be the most significant and is of the opinion that improvements in these areas will also result in better availability and utilization of data and information in FDA scientific programs generally.

### *B. Findings*

Following are the major findings of the Committee:

1. FDA scientists and program managers have a strong and basic appreciation of the part that valid and current scientific information plays in the conduct of sound science programs.

2. An awareness of the need to update and improve the exchange and application of current scientific and technical information throughout FDA and the scientific community in general already exists among FDA scientists and program managers.

3. Many FDA scientists and program managers are enthusiastic supporters of serious efforts to bring about reforms and improvements in this area.

4. A number of steps have already been taken to improve the processing of scientific information and data within FDA. These include:

- (a) The establishment in 1960 of the FDA Drug Adverse Reaction Reporting Program. The workings of this program and the part which it plays in the overall scheme of FDA's medical information efforts are to be the subject of a later report.<sup>1</sup>

- (b) The establishment in 1961 of a separate organization and staff to work on improved information and data systems. This unit, the Data Automation Branch of the Division of Management Systems, is still in the formative stage. It has a staff of seven employees, five of whom are professionals in the field of automatic data analysis, retrieval, and processing. The capacity of this unit to bring about necessary improvement in FDA's overall scientific information efforts was given special consideration by the Committee. On this point, the Committee finds that the Data Automation Branch is not now prepared to undertake, nor does it include in its present mission, responsibility for the development of either bureauwide or agencywide unified systems. Instead, this unit operates currently on the principle of identifying to the various bureaus and divisions the capacity and potentialities of automated systems and, once this is done, it waits for the individual organizational unit to propose a particular project. This is not to say that the Data Automation Branch has not on occasion suggested and even urged the initiation of specific projects. On the other hand, it should be noted that the Data Automation Branch holds as one of its main responsibilities the task of coordinating, wherever possible, individual efforts to achieve uniformity in equipment and to establish multipurpose systems wherever practicable.

- (c) The acquisition in 1962, in collaboration with the Department of Health, Education, and Welfare, of an operating computer.

- (d) The undertaking, during the period 1961 to date, of 10 special projects designed to develop new or improved FDA information and data handling techniques.

Not all of these projects have to do with indexing and storage of information for later use. However, they do represent serious attempts to systematize the flow and use of information and, in the opinion of the Committee, they provide a base on which to build an integrated

<sup>1</sup> Note by editor of this volume: see an earlier report on adverse reactions, exhibit 157, p. 1108 and the later report, p. 1127.



FDA-wide scientific information handling program. The 10 projects are summarized in appendix A to this report.

5. The Committee finds that, aside from the establishment of the Data Automation Branch itself, to date no specific personnel have been assigned (or appear to be available) within either the Bureau of Medicine or the Bureau of Biological and Physical Sciences to initiate scientific data and information handling improvements. Personnel have been assigned on a limited ad hoc basis to represent these two Bureaus. It should be noted, however, that specific positions are included for this purpose in the 1964 budget.

6. The Committee finds little coordination among the various efforts to improve the processing, dissemination, and utilization of scientific information within FDA. The present procedure for updating and modernizing information handling systems depends upon the initiative and ingenuity of the individual organizational unit to identify its own needs and suggest its own improvements. As indicated by the projects summarized in appendix A, to date most efforts to improve have been centered at the Division or Branch level. No real evidence exists at this time of a well-organized and unified effort at the Bureau level in either the Bureau of Medicine or the Bureau of Biological and Physical Sciences, nor is there any evidence at this time of a tangible agency-wide system designed to correlate the informational requirements of the various scientific activities, particularly activities of the Bureau of Biological and Physical Sciences and the Bureau of Medicine. While there has been some effort to coordinate the information requirements of FDA's field laboratories with those of headquarters units, such efforts have been limited in both number and scope.

7. One finding of particular concern to the Committee is that, due to staff and technical limitations, the present order of priority governing the participation of the Data Automation Branch in new data automation and systems improvement projects places last emphasis on the development of data retrieval<sup>2</sup> systems. (See memorandum dated Feb. 7, 1962, issued by the Office of the Commissioner, subject: "Planning Policy for Data Processing, Analysis, and Data Retrieval.")

### C. Conclusions

The above findings lead the Committee to four conclusions:

1. That Food and Drug Administration programs and processes, such as the new drug approval process, the food additives, pesticides, and color additives safety tolerances programs, the hazardous substances labeling program, and others, are so dependent on the timely and efficient utilization of valid and current scientific data and information that every effort should be made to systematize the flow and availability of these data.

2. That present efforts to improve the flow, utilization, and dissemination of scientific information will not effectively meet the agency's needs within a reasonable period of time.

3. That FDA lacks the necessary technical and professional skills needed to develop an efficient and timely agency-wide program of its own.

4. That a number of steps designed to bring about improvements are practicable, providing this area is given sufficient priority in terms of leadership and resources.

The Committee's conclusion that present efforts at self-improvement will not produce an efficient agency-wide program within a reasonable period of time stems primarily from two factors:

1. The Committee's belief that the present system places too much reliance on the initiative and ingenuity of individual scientists and units not technically trained to develop data systems and already overburdened by their regular program responsibilities.

2. The Committee's belief that current efforts to design scientific data retrieval projects, at least insofar as computer programs are concerned, do not carry a sufficient priority to permit the development of the necessary new data retrieval systems and procedures.

The Committee's conclusion that FDA lacks the necessary technical skills needed to develop its own agency-wide program within a reasonable time applies to both those skills required to analyze existing paper and work flow procedures,

FDA footnote:

<sup>2</sup> For this purpose, data retrieval is defined as an effort to identify and index information so that it may be stored for later use—possibly, usage that cannot, at the time of storage, be fully anticipated. This is in contrast to efforts to systematize the routine processing and analysis of data.



as well as to the skills of professional program personnel needed for such an effort. The lack of skilled program personnel was brought out clearly during the course of the National Bureau of Standards study. The NBS study group indicated repeatedly that FDA was unable to make knowledgeable professional program personnel available to the extent required. In addition, this problem was alluded to in the NBS report itself. With all the new responsibilities and growing program workloads facing FDA today, the Committee can find no reason to believe that, within existing staff, improvements in the availability of program personnel for this purpose can be made. By the same token, existing shortages, both in Government and industry, of skilled systems analysts and computer programmers are such as to make it difficult for the Committee to conclude that FDA will be able to obtain, within a short period of time, the necessary technical personnel needed in this area.

#### *D. Recommendations*

As indicated above, the Committee believes that FDA should take immediate steps to improve the flow and utilization of scientific information. A number of steps appear to be practicable, and following are the steps which the Committee recommends be taken now to effect necessary improvements:

1. *Staff assignments.*—The Committee recommends that a number of staff assignments be made immediately, including the establishment of certain new positions. The recommended staff assignments are:

(a) The designation of the Assistant Commissioner for Science as the key FDA official responsible for the development and coordination of an FDA-wide science information program. It is also suggested that the Assistant Commissioner for Science be given specific responsibility for representing FDA in this area with outside organizations. This latter point is discussed in detail in section III of this report.

In making this recommendation, the Committee emphasizes that its intent is to identify and pinpoint responsibility and not to encumber this position with a significant workload. For this reason, it is further recommended ((c), below) that a specific position be established to assist the Assistant Commissioner in this area.

(b) The designation of the Chief Chemist of the Bureau of Field Administration as the FDA official responsible for identifying scientific data requirements for FDA field activities.

(c) The immediate establishment of three new positions, as follows:

(1) A special assistant to the Director of the Bureau of Biological and Physical Sciences for scientific information coordination;

(2) A special assistant to the Director of the Bureau of Medicine for scientific information coordination; and

(3) A staff scientist to be assigned to the Assistant Commissioner for Science to carry out the details of the responsibilities recommended for assignment to the Assistant Commissioner for Science under recommendation 1(a), above.

2. *Establishment of higher priority for data retrieval projects.*—As reported, the Committee found that the policy order of priority followed by the Data Automation Branch in the initiation of data automation and systems improvement projects does not rank advanced data retrieval projects above routine laboratory computations and regular data processing efforts. While the Committee recognizes that the limited resources available in this area make priorities necessary, it, nevertheless, recommends that the current practice for computer operation be revised to place first priority on scientific data handling, including data retrieval systems.

3. *Proposal to contract for development of scientific data handling system.*—Having reached the conclusion that FDA lacks the skills to establish an effective system within a reasonable period of time, the Committee recommends that the agency enter into a contract with a commercial organization competent in the field of systems design and development to:

(a) Study the basic work processes enumerated in this report and, if appropriate, other operations of the agency, to determine what kind of agency-wide system(s) might be feasible and might produce improvements in the utilization, dissemination and exchange of valid scientific information and data;

(b) Develop plans for specific systems (including, if practicable, automated systems); and

(c) Install and make such systems operational.



*Phasing and cost.*—It is recommended that the above contract be entered into during the current fiscal year and that it be phased over a 2-year period. It would appear that a contract of the type proposed concentrates the cost of such an undertaking within a limited period of time, whereas an effort to make improvements on a process-by-process basis would stretch out the total cost. However, it has the significant advantage of minimizing the burden which such an undertaking will have on the limited FDA manpower and skills that would be needed to participate in such an undertaking. This plan places the major manpower and skills burden on the contractor. It also represents, in the opinion of the Committee, the most efficient method of bringing the necessary technical skills to bear on a problem which FDA is not prepared to solve for itself.

The Committee suggests that the contract be phased as follows:

*Fiscal year 1963*

1. Reconnaissance study to determine feasibility and to identify program requirements.

*Fiscal year 1964*

1. Planning and analysis.
2. Systems design, equipment procurement, installation, and testing.

Attempts by the Committee to develop detailed cost estimates for such a contract were generally unsuccessful. However, it is believed that a contract would cost between \$250,000 to \$300,000. Phased over a 2-year period, this would result in an annual budget of \$125,000 to \$150,000 a year.

The Committee recommends that the 1964 budget, now pending before the Bureau of the Budget, be modified to include specific funds to finance the 1964 portion of the proposed contract. It is further suggested that the necessary funds for reconnaissance during 1963 be funded by reprogramming regular 1963 appropriations for this purpose.

*Potential contractors.*—The Committee believes that the development of such a contract is possible and practical. A number of potential contractors with experience which would qualify them for this assignment appear to be available.

*E. Basis for Recommendations—NBS Study*

The above recommendations are based on the conclusions enumerated earlier in the report and also take into consideration the fact that the National Bureau of Standards study indicated that it would be possible to systematize much of FDA's scientific data processing. As indicated, the recommendations having to do with personnel assignments also take into account the experiences of the National Bureau of Standards. However, the recommendations depart somewhat from the suggestions of the National Bureau of Standards in that the FDA Committee is recommending that the total problem be attacked on an agency-wide basis rather than on a process-by-process basis. It is suggested that the views of the National Bureau of Standards be solicited in the development of the proposed contract.

### III. EXCHANGE OF SCIENTIFIC INFORMATION WITH OUTSIDE ORGANIZATIONS

#### *A. FDA Participation in the Program of Science Information Exchange, (Smithsonian Institution)*

Based on recommendations of this Committee, on November 6, 1962, Deputy Commissioner Harvey addressed a letter to Dr. Monroe E. Freeman, Director of the Science Information Exchange, indicating that FDA will begin on or about January 1, 1963, to register individual FDA research projects with the Exchange [see appendix B]. The FDA proposal calls for the registration of food, food ingredient, nutritional, chemical and biological research projects conducted by the Bureau of Biological and Physical Sciences. Deputy Commissioner Harvey also made a commitment in the November 6 letter to expand, at a later date, FDA registration to include human and veterinary drug studies conducted by the Bureau of Biological and Physical Sciences and the Bureau of Medicine. The letter designated Dr. Daniel Banes, Deputy Director of the Bureau of Biological and Physical Sciences to represent FDA and to work with the Science Information Exchange to complete arrangements for FDA participation.

The Science Information Exchange has acknowledged FDA's offer to participate and Dr. Banes has had followup discussions with representatives of the



Exchange. Dr. Banes is now taking steps to assure that the various BPS projects are screened preparatory to actual reporting.

The Committee believes that every effort should be made to insure that the present arrangement is carried out in good order. It is recommended that the Assistant Commissioner for Science review the status of the agreement at the end of the first 6 months and that he be designated to follow up on the commitment to register medical and drug studies. The latter commitment will require some effort on the part of the Bureau of Medicine. The duties of the special position proposed earlier in the report for assignment to the Bureau of Medicine to deal with science information handling problems should include responsibility for developing participation by the Bureau of Medicine in the program of the Science Information Exchange.

#### *B. Cooperation with Other Outside Organizations*

In addition to the question of FDA participation in the Science Information Exchange program, the Committee gave special attention to the question of FDA cooperation in this area with other outside organizations, including international organizations. Specific steps taken thus far by the Committee include:

1. *Discussions with representatives of the National Institutes of Health to determine ways and means of improving cooperative information exchange efforts.*—The Committee, working with Dr. Thomas J. Kennedy, Jr., Special Assistant to the Director, NIH, for Scientific and Technical Communications, has drafted a memorandum of understanding outlining a number of worthwhile steps which the two organizations could take (some of the steps have already been inaugurated) to exchange medical and scientific information. These include the transmission by NIH to FDA of the following:

(a) A monthly report on adverse reactions to drugs encountered in the patient and normal control populations under observation in the Clinical Center at Bethesda and in other clinical investigational projects conducted elsewhere by members of the staff of the National Institutes of Health. With respect to investigational or recently released drugs, adverse reactions will be reported to the FDA immediately as well as in the routine monthly report.

(b) Pertinent information, generated by the activities of the Cancer-Chemotherapy National Service Center. This will include the transmittal, upon publication, of Cancer Chemotherapy Reports and Cancer Chemotherapy Abstracts.

(c) Pertinent information generated by the activities of the Psychopharmacology Service Center of the NIMH.

(d) An annual report of those NIH grants and awards which are directed at the investigation of drugs. NIH will increase as rapidly as possible the frequency at which FDA is notified of awards made by the NIH in this field of endeavor.

As proposed, FDA would, in addition to naming the Assistant Commissioner for Science as special liaison with NIH in this area, provide NIH with the following:

(a) A monthly summary of all adverse reaction information reported to FDA by private and public organizations.

(b) From time to time, special reports of unusual experiences developed during the course of FDA inspections, investigations, or reviews of particular drugs or drug products, wherever such drugs might be expected to be of interest to NIH.

In addition, the draft proposal calls for attendance of FDA personnel at meetings of the NIH Committee on the Management of Drug Information and the series of joint NIH-FDA meetings to identify FDA activities and programs which might be able to furnish further information of interest to NIH.

Under consideration is a draft proposal calling for jointly sponsored seminar-type meetings to be held periodically and to be attended by NIH and FDA scientists to promote better dissemination and utilization of medical and scientific information.

The Committee recommends that a formal memorandum of understanding between FDA and NIH be consummated as quickly as possible. January 1, 1963, is suggested as a possible target date.

2. *Discussions with other officials of PHS.*—During the course of its study, representatives of the FDA Committee on Scientific Information discussed with



Dr. F. Ellis Kelsey, Special Assistant to the Surgeon General, various aspects of the overall problem of scientific information exchange. As a result of these discussions, arrangements were made for two representatives of the Food and Drug Administration (Dr. John W. Nesbitt and Dr. Bert J. Vos) to attend the November 5 and 8, 1962, sessions of a special Public Health Service sponsored Conference on Health Communications. The purpose of this conference was to consider the growing problems of medical and scientific communications and how PHS and other units of Government might contribute to their solution.

The Committee is of the opinion that both PHS and FDA have a number of common objectives in this area and that a basis for further cooperative effort already exists.

It is recommended that FDA, through the Assistant Commissioner for Science, take the steps necessary to develop a formal memorandum of understanding between FDA and the various units of PHS, in addition to NIH, as a means of improving the exchange of medical and scientific information.

In addition, it is recommended that FDA also take the initiative to develop formal agreements in this area with other units of Government, particularly:

1. The Department of Agriculture.
2. The Veterans' Administration.
3. The Patent Office.
4. The National Bureau of Standards.
5. The National Library of Medicine.

In each of the above cases it is believed that a sufficient common ground already exists to warrant such agreements and understandings. It is suggested that the Assistant Commissioner for Science continue to identify other Government agencies where more formalized exchanges and agreements might be advantageous.

#### *C. State and Local Agencies*

It is recommended that the Division of Federal-State Relations give special emphasis to science information requirements in its programs to improve Federal-State cooperations.

#### *D. Participation in International Science Information Programs*

The Committee gave this aspect of the total problem special consideration.

Dr. F. O. Kelsey, representing the FDA Committee on Scientific Information, together with a representative of the Public Health Service, attended a meeting sponsored by the Federal Council for Science and Technology to discuss ways by which the international exchange of drug information might be improved. Much of the discussion centered on a tentative plan which the World Health Organization<sup>3</sup> has under consideration calling for the development of an international exchange of information concerning the safety and efficacy of drugs. As a result of the discussions held during this meeting, the FDA Committee concludes that FDA has a vital interest in promotion of an international movement to improve the exchange of medical and other scientific information. The Federal Council for Science and Technology has offered to arrange meetings between FDA and other organizations having an interest in this subject. In addition, the Federal Council plans to meet with FDA in the future to develop concrete methods by which it might assist FDA to obtain information from international sources.

It is recommended that steps be taken to follow up with the Federal Council for Science and Technology in this area.

Although the exact role of FDA in any international movement to improve the exchange of scientific information is not yet clear, in the opinion of the Committee, the development of a sound intra-agency effort is appropriate at this time. Such an effort will put FDA in a position to participate in any future international program.

The Committee recommends that FDA actively pursue the possibility of participating with the World Health Organization and other agencies in any effort to effect an international exchange of medical and scientific information.

#### *FDA footnote:*

<sup>3</sup> At the Fifteenth World Health Assembly, held in May 1962, a resolution was passed calling for the development of a program to (1) establish minimum basic requirements and standard methods for clinical and pharmacological evaluation of new drugs, (2) secure regular exchange of information on the safety and efficacy of new drugs, and (3) secure prompt transmission to national health authorities of new information on serious side effects of such drugs.



## APPENDIX A

## SUMMARY OF SCIENTIFIC DATA IMPROVEMENT PROJECTS

December, 1962

*1. Projects that are now operational:*

(a) *Vitamin D data analysis.*—All vitamin D assays conducted by FDA now routinely undergo statistical analysis on a computer. Such analysis rapidly determines, on the basis of U.S. Pharmacopoeia standards, whether vitamin D content is within acceptable limits. In addition, this computer program assures that all analyses are objectively and uniformly evaluated. Prior to this, such statistical analyses were made only on a selected basis because of their laborious nature. Now all of the data are stored in machinable form and are available for future use and references within and without the Food and Drug Administration.

(b) *Manometric computations.*—Manometric devices are used by FDA to determine the effects of various chemicals on living tissue. The data obtained from these experiments are now entered into a computer and analyses are made in conformity with the wishes of individual scientists conducting particular experiments. All such information is stored and is made available for future reference and analysis.

(c) *McBee Keysort for New Drug Applications.*—Selected chemical information found in New Drug Applications and important to FDA scientists evaluating such applications are now entered onto a McBee Keysort card file system. This makes the data quickly available to the individual scientist evaluating the NDA.

(d) *Statistical analysis system.*—FDA now has available commonly used statistical systems that can be applied to particular scientific or other mathematical-type problems. These routine statistical systems have been entered on magnetic tapes and can be quickly applied to the solution of any problem for which they are appropriate.

*2. Projects about to become operational:*

(a) *Manometric computations.*—Since experiments making use of manometric techniques differ from one scientist to another, and since the results sought are different, FDA has been developing computer programs that can meet the individual needs of its scientists. The availability of such programs will save much manpower and will mean that sources outside of FDA could make use of the data should they need them.

(b) *Processing of data for pharmacological chronic and subacute toxicity studies.*—An important function of FDA is to determine the chronic and subacute toxicity of various ingredients. One way to do this is to develop experiments with small test animals, making use of the calculations of averages, standard deviations, and variances over periodic intervals. The weight gain, the feed intake, and the feed efficiency ratios of each animal must then be recorded. All this information is now being fed into computers and weekly print-outs of the accumulated data will soon be prepared. The information is placed on magnetic tape for future use and analysis. The print-outs are legible and can be made available to interested scientific groups outside of FDA.

(c) *Indexing system for the retrieval of spectrophotometric curves of chemical computations.*—FDA makes use of spectrophotometers to identify chemical compounds. This apparatus accomplishes this by means of graphical curves, the peculiar characteristics of which identify specific chemicals. FDA is now coding these characteristics and entering them into a Termatrix system (sometimes referred to as a peekaboo system) and on magnetic tape. The peekaboo system is being made available to FDA's district offices and to its scientific divisions at headquarters. This means that in each case a readily available indexing system for chemical compound identification is at hand. The magnetic tape information will be produced in handbook form with all the information contained in the system. Also, it will provide a basis for modifying or expanding the system and it permits the information to become readily available to groups outside of FDA.

*3. Projects in initial stages:*

(a) Study to develop and implement a system for automating the analytical procedures used in certifying antibiotics.

(b) The development of a computer-oriented indexing system for retrieval of veterinary drug product labels to be stored on microfilm.

(c) The development of an indexing system for the retrieval of spectrophotometric curves of several different classes of chemical compounds.



## APPENDIX B

## DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

## FOOD AND DRUG ADMINISTRATION,

Washington, D.C., November 6, 1962.

Dr. MONROE E. FREEMAN,  
*Director, Science Information Exchange,*  
1825 Connecticut Avenue NW.,  
Washington, D.C.

DEAR DR. FREEMAN: On August 7, 1962, representatives from the Food and Drug Administration met with Dr. David F. Hersey and Dr. W. R. Foster of the Science Information Exchange to discuss the possibility of registering research projects of the Food and Drug Administration with the Exchange.

The Food and Drug Administration would appreciate the opportunity of participating in the program. We are prepared to take the steps necessary to register, wherever practicable, various research projects beginning on or about January 1, 1963, or any time thereafter convenient to the Science Information Exchange. As a beginning, we propose to register food, food ingredient, nutritional, chemical, and biological projects underway in our Bureau of Biological and Physical Sciences. As soon as feasible, we propose to expand reporting to include human and veterinary drug studies conducted by our Bureau of Medicine.

Steps are now being taken to screen the various projects, to establish a coding procedure and to develop a systematic reporting method.

We are asking Dr. Daniel Banes, Deputy Director of our Bureau of Biological and Physical Sciences, to represent the Food and Drug Administration and to work with you to complete arrangements for FDA participation.

We would like to express our appreciation for your cooperation.

Sincerely yours,

JOHN L. HARVEY, *Deputy Commissioner.*

## EXHIBIT 172

## MISCELLANEOUS CORRESPONDENCE ON DRUG ISSUES

This exhibit consists of letters received by the subcommittee from physicians and laymen on diverse drug issues. Some of these letters came in response to inquiries by Senator Humphrey; others were received spontaneously. In instances where there may be uncertainty as to whether or not the incoming letter may have been intended for private as distinguished from public use, the name of the correspondent is withheld.

In cases where letters received by the subcommittee were vital to various chronologies which are published elsewhere within this volume, the letters are reprinted therein.<sup>33</sup>

DUBUQUE, IOWA, March 19, 1963.

DEAR SENATOR HUMPHREY: I have been following the progress of your Senate Government Operations Subcommittee in the Des Moines Register and hope that in some manner the FDA will be encouraged (perhaps a stronger word is advisable) to heed advice of its staff doctors rather than be so swayed by the influential drug companies.

Surely it took courage for such a doctor as Dr. John Nestor to testify so frankly before your subcommittee and I just hope it won't result in his being castigated by his superiors.

We have much to thank the drug companies for but by the same token, they are dealing with a very precious commodity too, the human life.

<sup>33</sup> Elsewhere in this volume appear additional letters, grouped under major subjects, together with other documentation, e.g., letters on vitamin K<sub>3</sub>, exhibit 133, p. 962, on MER/29, exhibit 127, p. 919, ff., and on adverse drug reactions, exhibit 157, p. 1129. Some letters on the two last-named subjects will also be found on the present exhibit.



Our [child] was born shortly after the thalidomide scare and we have been so thankful that she is a normal, healthy 6-month old baby. Due to difficulties in pregnancy I was given different preparations but, thanks to Dr. Frances Kelsey, no thalidomide.

I wish you well in your investigation and hope that much good will result.

Sincerely,

[Name withheld.]

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CANADIAN PHARMACEUTICAL MANUFACTURERS ASSOCIATION,  
*Ottawa, March 15, 1963.*

DEAR SENATOR HUMPHREY: Many thanks for sending us part one of the hearings of your subcommittee.

Your cordial invitation to submit to your subcommittee our recommendations concerning international drug cooperation is much appreciated. I will bring your kind offer to the attention of our board of directors for consideration.

Thanks again and kindest regards.

Yours very truly,

STANLEY N. CONDER, *General Manager.*

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CANOGA PARK, CALIF., *March 21, 1963.*

DEAR SENATOR HUMPHREY: On a news broadcast this morning, I heard an item that your subcommittee on "Drugs" had received testimony concerning the use, over-use and abuse of antibiotic and tranquilizing medications.

I wish to add my humble opinion to the validity of these testimonies. The frequent use of these medications by the physician without proper diagnosis and without proper regard to indications is to be deplored. The constant demand by the patient for these drugs is also to be deplored—and the patient would often be better served if these demands were curtailed. The use of antibiotic drugs in cough drops, deodorants, washing products, etc., is an abomination.

These medications are regarded by the public with the awe and respect of gum-drops—and, unfortunately, also by many physicians. These medications are as dangerous as T.N.T., and I would be pleased to support legislation which could control these abuses.

Very truly yours,

DAVID MISHKIN, M.D.

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CHARLESTON, S.C., *March 22, 1963.*

DEAR SENATOR HUMPHREY: May I commend you on the stand you have taken against the Food and Drug Administration's procedure in testing the safety of drugs.

I am so grateful to you for trying to do something about this condition which played a very horrible part in my life 3 summers ago. The drug, Altafur, one of the furadantins, came very close to killing me and I still 3 years later have various symptoms and partial limitation of motion because of it.

A Charleston doctor was also one of its victims the same summer.

I shall be watching the news media for the results of your crusade and wish you all the success possible.

With all good wishes, I am,

Gratefully,

[Name withheld.]

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TAMPA, FLA., *March 25, 1963.*

DEAR SENATOR HUMPHREY: An AP release in the Tampa Tribune, Tampa, Fla., states that your subcommittee, investigating unsafe drugs, uncovered the fact that although FDA Deputy Commissioner John L. Harvey upheld a hearing examiner's recommendation for suspension of a New Drug Application for Altafur, this drug was allowed to be marketed and continued to be marketed after the risks were known.

I would like to know the dates of when the manufacturer submitted the application, when the risks were known by the manufacturer and the FDA and all other pertinent facts about the drug Altafur.

The reason why I want these facts is that in September 1959, I was a patient in Tampa General Hospital with an antibiotic resistant staphylococcus infec-



tion, and a low grade osteomyelitis infection in my right foot. I was given Altafur because the manufacturer's brochure stated that Altafur was developed as a potent agent against just these types of infection. Almost immediately my blood level became depressed to such a low point that the osteo became very active and within a short time the only way to save my life was to amputate my right leg.

These hospital records are available to your committee and I would gladly testify before your committee.

Thanking you in advance for the facts that I have requested, I am

Respectfully yours,

[Name withheld.]

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NEW JERSEY, March 26, 1963.

The physicians of the present decade who have available such a powerful and varied armamentarium of drugs usually feel grateful to the manufacturers who have made these preparations available to us. Since the development of the various chemotherapeutic and antibiotic agents, many illnesses are no longer seen in their full-blown, classical, clinical picture and others, for all practical purposes, have disappeared from the scene entirely. Although innumerable new preparations have appeared on the market in the 15 years I have been in practice and although the efficacy of some of these was not as great as may have been claimed by the initial presentation of the manufacturer's representative, I recall few, or, if any, instances in which a potentially dangerous preparation was sold to us because of a lack of previous laboratory testing by the manufacturer.

Although, as I stated above, physicians are grateful to drug manufacturers for the excellent tools which they provide us, we maintain a healthy skepticism regarding salesmen's claims for these preparations. We are more likely to wait for reports in our established journals before beginning to use the newer agents. It has been our observation that when widespread use of a new agent begins to produce in the literature scattered reports of untoward effects, the drug companies seem to be very prompt in notifying the physicians of the country of these facts; to advise caution in the use of the preparation and, if necessary, to voluntarily withdraw the drug from the market.

Although I believe that the people who manufacture these agents are men with a conscience who do not wish to do their fellow men a wrong, the chief factor in their eagerness to detect unexpected dangers in the use of the drugs is the threat of a civil action by a patient who feels that he has been injured by such a preparation. I believe Mr. Belli of California, who has been called "The King of the Torts," has been a far greater influence on the conscience of drug manufacturers than Mr. Kefauver. The whole country should be grateful to Dr. Kelsey for delaying the introduction of thalidomide to the United States. If more stringent Government regulation of testing of pharmacologicals will protect us from such a tragedy as occurred in certain of the European countries, we certainly must be in favor of such regulation. One cannot discount, however, the American public's desire to decide for itself what may be good for it. For many years, the public has completely disregarded all conclusive scientific evidence reported by the Federal Government, private medicine, and learned scientists throughout the country and has insisted upon using such agents as the Hoxey treatment for cancer, Krebiozen, another worthless treatment for cancer, chiropractic and "naturopathic" treatment involving the use of complicated and ineffective machines, plus literally millions of gallons of attractively packaged and worthless proprietary remedies.

To summarize, I would say that the physicians whom I represent are grateful to the drug manufacturers for the fine products with which they supply us despite occasional overenthusiasm on their part, an occasional mistake, and some flagrant examples of overpricing. If some judicious policing by Federal agencies without undue interference in the competitive nature of the drug industry can elevate the standards of this industry even higher, such an effort is certainly to be encouraged. We are well pleased with things the way they are and if they are going to be better, we shall be even happier.

Thank you very much for the opportunity to state this opinion.

[M.D.'s name withheld.]

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MARCH 28, 1963.

DEAR SENATOR: The [name of newspaper] has been carrying daily reports on your commendable investigation into the marketing of dangerous drugs. I enclose two clippings.



I am a victim of one of these drugs. I recently underwent surgery for cataracts on both eyes as the result of taking MER/29, and am now forced to wear heavy cataract glasses and have no peripheral vision. As you know, doctors and pharmacists were not warned of the possible dangerous side effects of MER/29 until December of 1961, but the drug was not taken off the market until several months later—I believe in March or April. I had been taking MER/29 since June 1960.

Thanks—and keep up the good work.

Very truly yours,

[Name withheld.]

BOZEMAN, MONT., *March 28, 1963.*

DEAR SENATOR HUMPHREY: I have just finished reading Morton Mintz' article "New Drugs: Is Government Supervision Adequate?" in the March 28 Reporter and I want to express to you my gratitude for what you are trying to do. Eight years ago my doctor prescribed the tranquilizing drug Thorazine, manufactured by Smith Kline and French. Within less than two weeks it had caused hepatitis. My doctor, who has since died, never did tell me what had caused my hepatitis, and I might easily have returned to the drug in ignorance, except that I read an article in Newsweek that told of Thorazine's possible side effects. Fortunately, the experience does not seem to have left any ill effects behind, but that does not excuse such a drug being placed on the market.

It seems to me that if the Commissioner of the FDA will not carry out the law he should step down and let someone who will take over. Certainly it seems to me that the head of this department should be trained in some phase of medical science.

My best wishes to you, and I hope you can help to tighten up at least enforcement, if not the law itself.

Sincerely yours,

[Name withheld.]

SANTA MONICA, *March 29, 1963.*

DEAR SIR: You are now investigating dangerous drugs that have been on the market only 6 months. This is my recent experience with a dangerous drug that has been on the market for years.

A Santa Monica physician prescribed Compazine, a drug for stomach upset and nausea, for my 10-year-old son.

Symptoms began to appear after my son had taken the medicine. His eyes became fixed in his head. He couldn't move them. His facial muscles became rigid. His body began to twist and pull until he had no control whatever. He was rushed by ambulance to the Los Angeles County Hospital (March 8, 1963) where eight doctors diagnosed the correct cause as Compazine. They gave him a shot to counteract the medicine and saved his life.

I assumed that my son was that 1 person in 1,000 allergic to the medicine. But now I find that Time magazine warned against Compazine and other ataxics built around phenothiazine molecule as long ago as October 27, 1958. Time said that these tranquilizers (Thorazine, Compazine, Sparine, Pacatal) are so potent that they may cause undesired side effects of which one of the commonest is Parkinsonism with rigidity, tremor, pill-rolling motion of the hand, disturbances of all movements, and drooling, and symptoms may persist 2 or 3 months after medicine is stopped. Thorazine can also cause severe liver damage—sometimes fatal.

I ask you to help make this fact known so that parents may become aware of the harmful effects of these drugs. An investigation should be made and if possible these dangerous drugs removed from the market.

Sincerely,

[Name withheld.]



BEVERLY HILLS, CALIF., March 30, 1963.

DEAR SENATOR HUMPHREY: I wish to congratulate you, among others, who have taken such effective action regarding the FDA's handling of new and experimental drugs.

I wish to make one brief suggestion which concerns the free distribution (to physicians) of both experimental as well as accepted drugs, which is as follows: That no drug company may distribute any drug, whether acceptable or experimental, to any physician as a sample or for experimental trial, without that physician's prior written permission.

The problem I am addressing myself to may be obvious to you. Our physicians' offices are flooded with an unbelievable amount of drugs of all kinds, designated as "physician's samples," unrequested by the physician, which tend to promote an unwise usage of drugs with which the particular physician is unfamiliar. In addition, these drugs often find their way, via the wastebasket, to medical building janitorial help, and thence to other hands. But the particular deleterious effect, to which I would like to call your attention, is the promotion of a loose, undisciplined attitude in physicians about drugs in general.

I can see no justification, I can see no purpose served in the indiscriminate distribution of unrequested drugs. No physician can adequately acquaint himself with the particular effects and dangers of the literally hundreds of thousands of drugs on the American market. And no physician should provide to a patient any drug with which he is not well acquainted. That they should be encouraged to do so, even if the drug is "approved," can be most dangerous. FDA "approval" cannot substitute for the physician's own knowledge of a drug. Both are essential.

Thank you for your consideration for this suggestion.

Very truly yours,

D. F. RENDINELL, M.D.

LONG ISLAND, N.Y., April 1, 1963.

DEAR SENATOR HUMPHREY: It is most edifying to note your conscientious appraisal of the drug situation. It has been too long delayed. As a registered nurse and wife of a pharmacist, we have felt the slings and arrows of indiscriminate marketing of drugs, particularly since my husband had been on MER/29 for many months, during which time he had recurring corneal ulcerations. I had written to Merrell repeatedly asking if this drug could be the causative agent. They wrote reassuring, mollifying letters. Needless to say, this condition remains and has brought much heartache and pain to the breadwinner in our home. The drug profession today, as you must be acutely aware, is an all-consuming, pitiful business, made increasingly difficult through duplication, and the many aspects of pharmacy which make it very hard to stay in a solvent state.

The purpose of this letter is to inquire if there is a national clearinghouse for users of certain drugs which would help the medical profession determine the usefulness or danger in the use of certain drugs. We have recently become aware of a number of drug-induced cataracts in people on the drugs [names withheld], both appetite depressants. There is no mention of this in the literature. Similarly, we have noted a small incidence of carcinoma of the stomach in the users of [name withheld]. Possibly this is coincidence, but all attempts to find if there has been a survey on a national level in this area have been futile. Perhaps the physicians are not correlating these facts and presenting them to the authorities. Would it be presumptuous of me to ask if a determination could be possible with the cooperation of all members of the medical profession. We are in an era of massively produced drugs, some of which may be used wide-scale and might be potentially most harmful to constant users, as in the case of [name withheld].

Senator, I would be most appreciative of any information you might have for me. We are anxious to have an appraisal of [name withheld], particularly, and would feel it is our good fortune to have you reassure us that this drug is not breaking down the tissue in the stomachs of its users.

Thank you so very much for all your efforts in behalf of the drug profession.

Sincerely,

[Name withheld.]



VETERANS' ADMINISTRATION CENTER,  
*Martinsburg, W. Va., April 17, 1963.*

DEAR SENATOR HUMPHREY: I have much appreciated your progress reports regarding the problems of drugs. I have been much impressed by your sincere and earnest and thorough-going efforts to assure to the American public safe and effective drugs.

Throughout my own medical career and particularly as Professor of Clinical Medicine at the New York Medical College for 21 years, I have been much concerned with and interested in the appraisal of therapeutic agents. So much so that twice since I came to West Virginia 6 years ago I have been requested to consider the position as Chief of the Medical Bureau of the Food and Drug Administration.

I mention the above to let you know that I too have given considerable thought to the problems of our most important Food and Drug Administration agency. In both of my visits to the Medical Bureau in Washington I was much impressed by the very small, hardworking corps of dedicated people trying to do a job far beyond the capacity of the Bureau's physical size and equipment. It seems to me there is no dearth of laws and rules on the books to insure safe and effective drugs. There is, however, a tragic dearth of facilities for implementing these laws.

In the first place, I was informed that the Chief of the Medical Bureau could have, in no way, any opportunity to discuss his problems with those primarily concerned with the creation of laws and regulations. This is a field which is constantly changing. I cannot imagine anyone with initiative and a major interest in the field who would assume the tremendous responsibilities of this position without feeling that he might from time to time play a guiding role in shaping policies designed to increase continuously the safety and effectiveness of drugs released for use to the American public.

In the second place, the entire budget and the individual salaries of the Bureau are tragically pitiable. I found that those who had held this position had found it well nigh impossible to obtain full time physicians and to hold those who did become available. As a rule such physicians were young men just graduated, who spent half their time with the Bureau while building a practice.

All of the low salaried clerical help you can make available for investigating drug houses' investigators is going to offer very little to the American public, unless it is buttressed by a strong control bureau. Moreover, were there a strong control bureau, such fishing expeditions as can be carried out by lay clerks will be of very little use. Some of the directives which have appeared in the last several months seem to me merely to be beclouding the issues. Moreover, the money which will be spent to implement them could be better used for the creation of a proper central medical bureau of the Food and Drug Administration.

It seems rather ridiculous that this Bureau should be directly and solely responsible to a lay Commissioner, who can in no way directly help the primary work of the Bureau. I make this statement despite my personal respect for and the esteem in which I know the present Commissioner is held by all who have had any serious contacts with him. Despite this, I think the situation remains an anomalous one.

Earnestly and sincerely,

THOMAS H. MCGAVACK, M.D.

VETERANS' ADMINISTRATION,  
MEDICAL TEACHING GROUP HOSPITAL,  
*Memphis, Tenn., April 18, 1963.*

DEAR SENATOR: I have recently read a reprint of:

- (a) A Statement on Drug Policy which I made in the Senate on April 2, 1963, and of
- (b) pertinent exhibit materials.

I was highly impressed with this document and have taken the liberty to disseminate this information to physicians in this hospital and in private practice. I feel the average professional individual has a very limited knowledge in this field and the proposal of a National Drug Information Clearinghouse would make great strides in the dissemination on non-slanted pharmaceutical information in this country.

I would be very appreciative if my name could be added to your mailing list enabling me to receive automatically further reports as stated in "Progress Report on Helping To Assure Safe, Effective Drugs."



As a citizen and a pharmacist in a large teaching hospital, I would like to commend you on the stand and action you are taking in this field.

Sincerely yours,

JOEL D. LOHR, *Chief, Pharmacy Service.*

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[NOTE.—At the request of the subcommittee, Dr. Nestor made available certain correspondence from his personal files, pertinent to fields of interest to the present review. The following letters appear with the permission of Gilbert R. Clark, M.D. See also page 1256.]

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WATERLOO, IOWA, April 18, 1963.

DEAR DR. NESTOR: \* \* \*

A recent paper "Reversible Fanconi Syndrome by Degraded Tetracycline," JAMA 184: 111-113, 143-144, April 13, 1963, brought to mind my one encounter with the FDA.

My son was admitted to Children's Hospital, D.C., in August 1959, on the service of Dr. William S. Anderson with symptoms and laboratory findings described in the above paper. We were fraught for a diagnosis while the child gradually deteriorated with little or no response to the adequate supportive care he received.

I recalled, during his hospitalization, that the only medication he had received prior to admission was Achromycin for a pharyngitis. I opened the capsules and found that the powder had deteriorated to a gummy red-brown material.

This deteriorated material was taken to Dr. Donald Grove, Antibiotics Division, FDA. He was given the history of the illness and the expressed belief that the tetracycline may be the cause. He professed that he had never seen tetracycline that looked like the material I submitted to him but stated that he did not think this could be the cause of the child's trouble.

Dr. Grove's people did do an assay for me which showed marked decrease in antibiotic potency. They then administered the material to several mice with resultant convulsions and death of some of the test animals. I requested a qualitative analysis and was told that this was something which they were not prepared to do and that they could be of no further help in the matter. I returned this original material to my desk in the Washington Hospital Center. It was "taken" from my desk by the local Lederle representative and that was the last I ever saw of it.

At that time, August 1959, Dr. Grove gave me Achromycin of known lot number and expiration date with the understanding that I would store the material in a pill box under the same conditions as the suspected material. If any change did occur I was to return it to him for analysis.

The material did indeed deteriorate to a gummy red-brown substance and I returned it to Dr. Grove.

Dr. Grove promptly returned the deteriorated tetracycline to me with an accompanying letter to the effect that he had no further interest in the subject.

I sincerely sympathize with you in your efforts to have tighter controls over medications released for public consumption. If I had been able to stimulate some interest in the FDA people 4 years ago to investigate the material submitted to them, further cases may have been prevented. Storage procedures and possibly expiration dates should be modified. These two points were stressed to Dr. Grove but he was not interested. We will never know how many cases of toxicity due to deteriorated tetracycline may have had a fatal outcome and were signed out as "nephrosis."

My own brief, futile and frustrating experience with the FDA was indeed disheartening.

If you are interested in further information and documentation of this case, please feel free to contact me.

With best wishes, I am,

Sincerely yours,

GILBERT R. CLARK, M.D., *Pathologist.*



(Copy of letter sent by Dr. Clark to Dr. Nestor)

WATERLOO, IOWA, May 27, 1963.

MR. DANIEL BANES,

Acting Director, Division of Antibiotics, Bureau of Biological and Physical Sciences, Food and Drug Administration, Washington, D.C.

DEAR MR. BANES: Thank you for your letter of May 7, 1963, on which I offer the following comments.

Your department did do antibiotic assay studies in September 1959 on tetracycline material I submitted to them and I have that report. Maleic acid has been shown to be nephrotoxic and it was at my request that studies to identify this compound were carried out. None was found.

The disturbing thing to me was the complete lack of interest in members of your department's staff to identify a demonstrated toxic material in the decomposed tetracycline—a situation which has gone unreported in the medical literature until April 1963.

Although, in 1959, Dr. Grove stated that he had never seen tetracycline in the state of deterioration as the material I submitted to him, he rejected the possibility that it may be nephrotoxic and the entire matter was dropped.

In November 1959, Lederle Laboratories reported a tetracycline assay on this material of 38 milligrams per capsule and anhydrotetracycline at 204 milligrams per capsule. Dr. Hugh Macdonald of Lederle states, "We can only assume the reactions observed were due to degradation products which accumulated during the period of loose storage."

This information was forwarded to your department at that time. No interest in pursuing the matter was shown.

The tetracycline given me by Dr. Grove was of known lot number and expiration date. It was stored in an unsealed pill box to be observed for deterioration. The material did deteriorate and as requested, I returned it to Dr. Grove for study. He promptly returned it to me and stated the FDA had no further interest.

This seems like an unusual and unfortunate attitude for a regulatory branch of our Government charged with the responsibility of "safe" medications for our people.

I personally believe that tetracycline is an excellent antibiotic for which there is a real need. I agree with you that it is well packaged by the producers and under these ideal circumstances can be expected to maintain its stability well past the expiration date.

To assume that the pharmacist usually uses the original bottle or transfers the capsules to another tightly stoppered bottle may be fallacious thinking. Many pharmacies still dispense in pill envelopes or pill boxes and most rural physicians who dispense their own drugs use this form of packaging. Possibly individual hermetically sealed capsules are the only realistic solution to this problem.

It is erroneous to believe that antibiotics are used by the patient without prolonged exposure to adverse environmental conditions. Usually the patient receives a 4- to 6-day supply.

All too often the capsules are taken regularly at first. The patient feels better in 2 or 3 days and the balance of the capsules is "saved" for his next illness or that of a member of the family. What happens to these capsules so stored?

I have no criticism of the method in which tetracycline is originally packaged. On several occasions since 1959. I have made known to your department my feelings that it should be required that tetracycline be packaged in airtight containers at all times.

I will appreciate being informed of any action taken in this matter.

Sincerely yours,

GILBERT R. CLARK, M.D., *Pathologist.*

IRWIN, NEISLER & Co.

Decatur, Ill., May 3, 1963.

DEAR SENATOR HUMPHREY: I have appreciated continuing to receive for a number of years the printed and interim reports of your Subcommittee on Reorganization and International Organizations of the Senate Committee on Government Operations.

I have read with considerable interest your recent memorandum entitled, "Progress Report on Helping to Assure Safe, Effective Drugs," which com-



prised a statement on drug policy which you made in the Senate on April 2, 1963. Since you invite interested citizens to comment or make suggestions, I am availing myself of the opportunity to do so.

These comments are offered informally as those of an individual and not as a spokesman for any organization. Of some 25 years in research, I have spent more than 21 of these in the pharmaceutical industry and for the past 12 have been concerned with conducting or supervising research in one of the smaller pharmaceutical companies with an active research program. The various matters touched on in your April 2 presentation are of interest to me including those relating to Food and Drug Administration problems and those pertaining to the drug literature. As a reading and practicing scientist I am very much interested in the literature problems. As a Director of Research for a small to medium-size pharmaceutical company, I am also concerned about the implementation of Food and Drug Administration regulations and it is with regard to this aspect of your contribution that I would like to comment at this time.

Among my responsibilities during the past 12 years has been that of communication with the Food and Drug Administration in Washington in relation to new drug matters. During this time I have had an opportunity to observe individuals who range from career professionals to more transient, "accelerated" experts. The Food and Drug Administration contains some experienced professional scientists such as Dr. Ralph Smith (medical), Dr. Arnold Lehman (pharmacology), Dr. Earl Meyers (chemistry), just to name a few among those who have earned the respect of their fellow scientists and are also considered as gentlemen of integrity.

Of particular concern have been some of the problems of the Bureau of Medicine of the FDA. This is not surprising when one considers that the definitiveness of the bases for drawing conclusions generally decreases as one proceeds from chemical to laboratory-biological to human problems of evaluation. This places the Medical Officer in a particularly difficult position to arrive at error-free decisions. To operate effectively within this framework would require well-trained, experienced, medical officers with good judgment and an understanding of the significance as well as limitations of research. For a variety of reasons, not the least of which is inadequate compensation and recognition, it appears to have been extremely difficult for the FDA to attract and hold such medical officers.

In any endeavor as large and complex as the pharmaceutical industry and its relationship with the Food and Drug Administration, any positive action is inevitably fraught with calculated risks. Errors of commission on the part of medical officers of the FDA can be rather readily implied particularly in areas in which there can be real and honest differences among the opinions of experts. Experts vary not only with regard to knowledgeability of the subject matter, but also in their motivations and relative immunity or freedom from retribution for positions which are assumed or opinions rendered. There is a real problem in selecting objective experts and the damage to individuals and organizations that can be produced by a single intemperate witness can be appalling.

The intensity of criticism leveled at the FDA with regard to implied laxity in clearing new drugs is also in danger of being overdone and could have an equally serious effect of further inhibiting release of valuable new drugs. In retrospect, during the past year our Government branches have tended to place a premium on lack of positive action. If one places himself in the position of a Medical Officer of the FDA, what incentive is there for him to act on, let alone expedite clearance of, a potentially valuable drug? How many people has our Government seen fit to honor for prompt acts of commission? The safest position to assume is one of inaction—thus avoiding possible errors of commission. In the present atmosphere, how many individuals with the necessary ability and courage to act, can the FDA attract? To those of us with responsibilities and motivation to get things accomplished, the present premium placed on inaction and delay is frustrating and disturbing. If this situation were to continue or worsen, then advances in medicine can be seriously impeded.

Hopefully, the FDA will act wisely and within the statutory intent of Congress. There is, of course, an apprehension that the regulations may be injudiciously implemented. Unreasonable delays in processing NDA's or unrealistic and arbitrary demands would be serious enough problems for the larger pharmaceutical firms; for the smaller firm, such actions by a regulatory agency could be disastrous. Those of us with responsibilities in industry are quite cognizant of this



and, as a result, are particularly concerned with avoiding any circumstances which might allure a punitive action. The increased complexity of regulations markedly enhances the opportunity for unintentional infraction of unclear rules.

One of the original goals alleged for promulgation of the 1962 drug regulations was that of lowering drug prices and increasing competition. Already the cost of developing new drugs has significantly *increased*, and it would be further ironical (yet unfortunately quite possible) if the smaller, ethical pharmaceutical firms will be eliminated as creative, competitive components in the industry. This could easily come to pass if overly restrictive regulations are injudiciously implemented by frightened individuals. It is encouraging that you do recognize this in your statement before the U.S. Senate on April 2, 1963, in which you remark, "I may say that I would be particularly interested in reasonable treatment to the smaller drug enterprises which, in this highly competitive industry, inevitably face particularly difficult problems."

Respectfully yours,

C. J. CAVALLITO,  
*Director of Research.*

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PETER BENT BRIGHAM HOSPITAL,  
*Boston, Mass., May 8, 1963.*

DEAR SENATOR HUMPHREY: The studies you are carrying out on interagency coordination on drug research and regulations seem to me to be of high order, and I have followed them with a great deal of interest. In the end, I think that something very good will come out of the type of study you are conducting.

As I see information developed as a result of your work, it seems to me that the problem is one that goes back to something much deeper than appears on the surface at the present time. I believe that the American people do not realize what an extensive revolution has taken place in therapeutic research in the past two decades. Unquestionably, the greatest number of our most useful drugs have been developed during this time. There are now literally hundreds of highly potent and effective new synthetics. It is, therefore, no wonder that difficulties in control, avoidance of harmful effects, and improper dissemination of information concerning these agents has occurred. The machinery which had been established in a much more leisure era to handle the problems that existed then could not hope to cope with the sudden tremendous pressures created by this modern development in medicine. The physicians carrying on the administrative work in various Government bureaus as well as scientific people in research institutes, universities, and pharmaceutical company laboratories have all been caught in this sudden explosive development. It is time now for all of us to develop a much better scientific and administrative approach in order to not only adequately meet the present demands but to cope with future developments which I feel sure will continue to accelerate.

On the whole, I have had very little dealings with various Government agencies although I have met individual members from various agencies from time to time. I must say, I have been distinctly impressed by the forthrightness, honesty, and sincere efforts on the part of the members of the Food and Drug Administration whom I have had the opportunity to meet. They readily admitted there were tremendous problems facing them and that there was very little in the way of guidelines. Often they had to make decisions in fields in which they had very little previous training and experience. Unquestionably, mistakes have been made both of omission and commission, but I must say, on the whole, I am surprised that there has not been much more difficulty than has already been seen.

Some time ago, I wrote Secretary Celebrezze a letter proposing that national consultant panels be established to aid officers of the Food and Drug Administration, similar to the consultant panels that are available to members of the Committee on Scope of the U.S. Pharmacopeia. These panels would operate in this manner. A drug comes in to the Food and Drug Administration which, for example, is in the cardiovascular field. It might exhibit unusual properties which would require special skill and knowledge in some particular field of cardiovascular development to understand properly. It would be too much to hope that an ordinary member of the medical profession serving the Food and Drug Administration would have comprehensive knowledge about some special field of development in cardiovascular research. However, if the officer handling the drug had available a national consultant panel, he could immediately send information concerning this drug to members of the panel, who would have means available



to secure the most recent and accurate information concerning this subject and inform the officer as to the merit or lack of merit of the agent in question. I believe the scientific community at large would be delighted to help the Food and Drug Administration in making these decisions. Furthermore, the use of such consultant panels in various categories of medicine would enable officers of the Food and Drug Administration to be constantly abreast of the developments. They would thus quickly learn of any possible undesirable effect of drugs that are already in use, and be able to act much more quickly in recalling toxic agents.

I realize that many scientists have recommended that such consultant panels be established, but as yet, I do not believe much has been done about it. There are at least three ways such consultant panels could be established.

First, the U.S. Pharmacopeia could be asked to help the Food and Drug Administration. The U.S. Pharmacopeia already has consultant panels who advise the members on drug efficacy. This operation could be extended to include new drugs. The U.S. Pharmacopeia is already a semi-official body and through the efforts of members and consultants represents the best thinking concerning drugs.

Secondly, the National Academy of Sciences could be requested by the President to appoint groups of subcommittees from their own major committees to serve the specific function as consultant to the Food and Drug Administration.

Finally, the Food and Drug Administration might be reorganized into a new institute or division of the National Institutes of Health, parallel to the Division of Biologics Standards, to pass on new drugs, conduct research into methods of drug identification, standardization and evaluation. Such an institute should have an extramural grant program to support clinical pharmacology and drug evaluation.

You, as a pharmacist, I am sure well-recognize that it is impossible to legislate absolute protection against the possible harmful effect of new chemical agents, made available for use in therapy. However, we must all of us be much more alert to detect toxic drugs. As you no doubt know, the Council on Drugs of the American Medical Association has set up an Adverse Drug Reaction Committee. They are now contacting hospitals throughout the country in an endeavor to get a reporting system on adverse drug reactions operating on a wide scale. In this way, it is hoped that information concerning toxic effects will quickly be accumulated and give leads to what possible untoward effects an agent may have, whether it is a new one or one that has been in use for many years. I think such a committee working closely with officers of the Food and Drug Administration would expedite early recognition, and where indicated, much more prompt removal of toxic drugs from medical use.

There needs to be much improvement in medical communications. Information concerning toxic effects of drugs often is known to a few individuals in medical centers long before it is made generally available. This is because of the slow method employed in medical communications. Physicians wait to see such information in medical journals or to hear it at meetings. This usually means a delay of from a few weeks to perhaps a year or more.

Some time ago, a few of us banded together to act as consultants without remuneration to assist Dr. Cortez Enloe launch a most modern and effective method of rapid medical communication called "Mediphone." This program which was to be supported by private enterprise consisted of a huge central body of drug information, continually kept up to date and available to any physicians who wished it by a telephone call to Washington, D.C., at any time night or day. In case there were unusual problems, the consultants would be contacted to help the subscribers with their problems. Working with a highly intelligent physician in a distant hospital, I had the satisfaction in at least one situation of probably helping to save a life. Unquestionably, such rapid medical communications as "Mediphone" is going to be more important in the future and some central readily available source of information should be maintained and made available to all persons dealing with drugs and drug therapy.

Finally, I think there must be much more education about the hazards of drug therapy not only to physicians but also to the lay public who unfortunately through over-the-counter sales are participating in self-medication to a far greater extent than was ever possible in the past. Unquestionably, there is definite danger in such self-medication particularly when it is sold by persuasive advertising programs and agents are secured in supermarkets and restaurants where the restraining wisdom of the pharmacist or the physician's prescription is not operating.

I am sorry there has been some delay in writing you. This was occasioned partially by the recent scientific meetings which necessitated my being away



and partially because I took time to consult with several of my scientific colleagues as to what suggestions they might have. They all agreed you are doing important work and are hopeful your committee will be able to improve the communication system between agencies, physicians, and the public. The expressions in my letter represent our composite views.

Sincerely yours,

DALE G. FRIEND, M.D.

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THE CITY OF NEW YORK DEPARTMENT OF HEALTH,

New York, N.Y., May 21, 1963.

DEAR SENATOR HUMPHREY: Thank you very much for your letter relating to the safety of drugs and side reactions.

I will be most happy to have you reprint my letter of May 10 as an exhibit in your next volume. We will also continue to share with your subcommittee any information which we feel may be helpful to you.

I am enclosing a copy of the letter which I sent to the editor of the *Journal of the American Medical Association* and to the various editors of pediatric journals.

Sincerely yours,

HAROLD JACOBZINER, M.D.,  
Assistant Commissioner.

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(Enclosure)

MAY 17, 1963.

Dr. JOHN H. TALBOTT,  
Editor, *The Journal of the American Medical Association*,  
535 North Dearborn Street, Chicago, Ill.

DEAR DR. TALBOTT: In these days of disclosive labeling, the U.S. Food and Drug Administration will require bracketing of generic and trade names in drug advertising.

However, those same journals which would carry this dual disclosure in advertising as a Federal requirement are at the same time violating this concept by using only the generic name in the titles of papers. This is especially true when some objectionable facet of a drug is discussed. This sensitivity of editors to name names may arise from the reluctance to endanger advertising which supports the journals. The obvious and trade name in the title (and index) and, of course, the advertisement.

The experience of the New York City Poison Control Center has been that at the present time, doctors frequently do not recognize generic names. When skimming through the index page, as a busy doctor does, he would not recognize the subject discussed which might be of especial importance to him.

This situation will improve with time as the new regulations are implemented in practice. Meanwhile this divergence in advertising and editorial practice poses a professional as well as a moral issue. What is good for the advertising goose, is good for the editorial gander.

Sincerely yours,

HAROLD JACOBZINER, M.D.,  
Assistant Commissioner.

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NEW YORK, N.Y., May 21 1963.

DEAR SENATOR HUMPHREY: Many thanks to you for your letter of April 19, 1963, enclosing your statement relating to certain problems arising in connection with the Food and Drug Administration.

Your presentation was fearless, effective and in the tradition in which you, throughout the past years, have met all problems.

It would be a blessing to all of us if the various individuals in public life approached our domestic as well as our international problems in the same effective manner as you have done and are still doing.

With best wishes,

Sincerely yours,

WILLIAM A. HYMAN, Attorney at Law.



WHITTIER, CALIF., May 27, 1963.

DEAR SENATOR HUMPHREY: I wish to thank you for sending me volume 2 of the hearings on Interagency Coordination in Drug Research and Regulation in which one of my statements has been reprinted on pages 498-501. Mr. Elfstrom, Editor of the Daily News Tribune in Fullerton, has written me of your committee's efforts to solve the massive drug problem. I am sure that great numbers of doctors and hospitals in the United States will welcome legislation tending to correct some of the evils of drug manufacture, distribution and promotion that will lead to better consumer protection. Your outstanding record as a public figure and legislator will have great influence on the entire drug and medical care problem.

We feel that here in California progress has been made by the recent passage of Senator Murdy's Resolutions 150 and 151. If similar resolutions could be introduced into the U.S. Senate it would tend to alert the drug manufacturers and the American Medical Association as to their real duty. The excessive commercialism and advertising of some drug firms during the past 12 years rather than protecting the public and impressing the medical profession have now on the other hand tended toward a loss of public confidence.

Very sincerely yours,

FRANKLIN FARMAN, M.D.

CORNELL UNIVERSITY MEDICAL COLLEGE,  
New York, N.Y., June 17, 1963.

MY DEAR SENATOR HUMPHREY: Thank you for your letter of June 7th and for part 2 of your subcommittee's drug hearing series. I have followed the hearings with great interest. Indeed, it is the evidence assembled by your subcommittee along with problems raised by the new drug laws which led to the founding of the American College of Clinical Pharmacology and Chemotherapy.

Until the present time there has been no group which adequately represented clinical pharmacology. It is hoped that when we are fully organized we may be able to contribute to various aspects of the general area you have under review. Our objectives are listed on the enclosed sheet.

We look forward to the time when the college may represent an authoritative voice of those engaged in clinical pharmacology and the testing of drugs. I believe we will then be in position to assist in forwarding our common objective of providing the public with safe and effective drugs.

Sincerely yours,

McKEEN CATTELL, M.D.

AMERICAN COLLEGE OF CLINICAL PHARMACOLOGY AND CHEMOTHERAPY

OBJECTIVES

1. To promote scholarly achievement in clinical pharmacology and chemotherapy and to establish and maintain standards of qualification of the physicians engaged in this science.

2. To develop an educational program to exchange information on new developments in medicinal chemistry and therapy and to promote research leading to the development of the safest and most reliable methods of evaluating the actions of drugs clinically.

3. To edit a publication in clinical pharmacology and chemotherapy to describe new developments in therapy and drug evaluation, including studies of the toxic and side effects of drugs.

4. To provide a means of communication between the clinical investigators, the pharmaceutical industry, and the Food and Drug Administration for the purpose of promoting the science and practice of therapeutics so that the safety and best interests of the public will be maintained at all times.

THE JOHNS HOPKINS HOSPITAL,  
Baltimore, Md., June 19, 1963.

DEAR SENATOR HUMPHREY: Thank you for your letter of June 5 and the enclosures. If I am in Washington in the near future, I shall try to visit with your staff.



I was particularly struck by the sections in your published hearings dealing with the abundant documentation, dating back at least 4 years, as to what needs changing in the Food and Drug Administration. It is appalling to see the same recommendations made over and over again by distinguished scientists or citizens committees, only to have those recommendations ignored so far as implementation is concerned. There is an urgent need for a strong man to be appointed as head of the Bureau of Medicine in the Food and Drug Administration and for him to be given sufficient backing and authority to reorganize the group. With the responsibilities of the Food and Drug Administration heavier than they have ever been, the right people, both in terms of quality and quantity, must be found at the earliest opportunity, lest the American public suffer grievously from inept handling of the problems in drug introduction and control.

Sincerely,

LOUIS LASAGNA, M.D.,  
Division of Clinical Pharmacology.

(Copy of Published Letter Sent to Subcommittee)

EDITOR,  
Washington Daily News,  
Washington, D.C.

AUGUST 27, 1963.

DEAR SIR: Recently the newspapers have reported that the FDA has proposed a ban on common cold preparations which contain bacteria-killing drugs. This decision is said to have been based on the report of a panel of experts who stated: "There is no acceptable evidence that any antimicrobial agent is of any value in the treatment of the common cold or of any other upper respiratory viral agent."

One newspaper reported: "The FDA first permitted antibiotics to be combined with other drugs for use against colds in 1952. The agency's only basis for the decision under the law then in effect was whether the drug would be safe or not."

It was a well known and widely accepted fact in 1952 that an antibiotic, which was not efficacious and could cause serious reactions, was not safe. It was also a well known and accepted fact at that time that antibiotics were not effective against the virus of the common cold. The 11 years which have passed since 1952 have not altered that fact.

One wonders who made the original decision in 1952 and why a panel of experts was not consulted at that time before Pandora's box was opened? One wonders who was asleep at the switch, so to speak, then and played Rip Van Winkle for the next 11 years, a period during which the decision could have been reversed on the basis of lack of safety at any time?<sup>1</sup> One further wonders whether the same individuals are still in the position to make similar, bad decisions?

Very sincerely,

(Name of physician withheld.)

#### EXHIBIT 173

#### POSSIBLE SIGNIFICANCE OF SOME EXHIBITS WITHIN THIS VOLUME:

##### BACKGROUND MEMORANDUM BY SENATOR HUBERT H. HUMPHREY

Senator Humphrey has provided the following concluding memorandum to the volume.

#### OBSERVATIONS ON CERTAIN OF THE CONTENTS IN THIS VOLUME

##### PURPOSE OF MEMORANDUM

The purpose of this memorandum is to serve as a reference tool. It is designed to help set in perspective a few of the many phases which are covered within the 52 exhibits of the volume.

<sup>1</sup> Editor's note: The same point (as to alleged excessive delays in FDA's issuance of a regulation on OTC antibiotics), was made in a news interpretation in the magazine Science, published by the American Association for the Advancement of Science, August 30, 1963, p. 791. Subcommittee records, based on internal FDA files, reveal that the proposed "new" FDA policy has been "under study" within the agency for years. An FDA internal memo of June 12, 1961, from William H. Kessenich, M.D., to the Division of Medical Review, stated, for example: "the jacket has shuttled about for some months now. . . . The AMA has not specifically responded . . . except to object (to use of OTC antibiotics—ed.) in general terms. . . . We may . . . have to consider calling a conference with outside consultants."



## HELPING THE READER

It is hoped that by means of this memorandum, the reader may be helped in his efforts and the efforts of all interested sources in strengthening the vital role of the pharmaceutical sciences.

This memorandum lists what are regarded to be some of the significant points within the volume. In addition, it poses questions whose answers may be helpful in the public interest.

Since this volume is almost 500 pages long, the reader, may inevitably face a problem in trying to sift out important phases—if only because so much time for reading may be necessary. Whatever can be done, therefore, to assist the reader is gladly done. It may be noted in this connection that the subcommittee's efforts to help the fact-finder have been commended in hundreds of letters which we have received from all over the Nation, as well as from other countries.

This memorandum urges, however, that the reader use the facts, the tentative observations and the questions herein as a "tool." Thereby, the reader may proceed to search out many more facts and opinions from still other sources. The reader can then arrive at his own conclusions in his own way.

## BOTH SIDES PRESENTED IN VARIED CONTENTS

It will be recalled that the exhibits within this volume are varied. They present views on both sides of many issues. In the open literature, which is quoted extensively, every effort has been made to draw upon the most highly regarded sources, such as the Journal of the American Medical Association.

A wide variety of other sources are also used, including sources, which, by their nature, may be presumed to be favorable to industry. Thus, drug trade publications are quoted at length. In addition, letters both favorable and unfavorable to views presented to the subcommittee at the hearing are reprinted.

## READERS' DIFFERING INTERPRETATIONS

Each reader will tend to come to his own conclusions, depending, perhaps, upon his own background, interests, and the views with which he approaches the volume.

Some may find in the exhibits confirmation that the Food and Drug Administration "has, by and large, been doing a satisfactory job"; some may conclude that the exhibits "confirm that this is not the case."

Some readers may find herein proof that FDA evaluation of new drugs has been "too tough" on industry; or that it has been "too soft"; or some will feel that the agency has tended to go "right down the middle of the line."

Insofar as I am concerned, one conclusion which I would personally urge is that "still more facts are needed" in order to arrive at a fair evaluation. That, indeed, is why the subcommittee has devoted so much effort toward bringing to light facts which heretofore have been unavailable. I have confidence that when the Congress and the people are given adequate facts, a consensus will be possible which up until now has been difficult, if not impossible to achieve.

In any event, some readers may conclude that, as the agency states in various exhibits, major improvements now become possible through the new law and the new regulations. Others may see in the exhibits what they believe to be "proof" that FDA still confronts deep-seated problems which no mere law or regulation or appropriation may change.

## EXHIBITS INDICATE DILIGENCE OF SCIENCE

On some points, there may be a wider area of agreement. I believe, for example, that one cannot read the exhibits in this volume without being impressed anew with the awesomely difficult and complex tasks faced by the Food and Drug Administration; nor can one fail to appreciate the immense research and development activity of the pharmaceutical industry, nor the heavy burdens which confront it.

Many exhibits in the volume confirm, I believe, brilliant private and public research on drugs, e.g., at the National Institutes of Health (exhibit 128), or outstanding private clinical work, e.g., at the Mayo Clinic (exhibit 129), or impressive technical analysis within the Food and Drug Administration (pp. 840 ff.).

Each interested reader will tend to find some aspect of the contents which appears of specialized interest.



## DRUG COMPANY PROBLEMS

Some readers will find of particular interest the helpful observations by the director of research of a pharmaceutical company, pointing out the exceedingly difficult problems faced by drug companies under the new laws and regulations, particularly in the instance of smaller enterprises.

This scientist noted, for example, with concern: "During the past year our Government branches have tended to place a premium on lack of positive action [on New Drug Applications]" (p. 1247).

## UNDERESTIMATE OF ADVERSE REACTIONS

Many readers may find significant the extensive information as to adverse reactions. Some readers may, for example, wish to read in detail the statement by the Public Health Service on the considerable number of "therapeutic misadventures": "We believe this [official—ed.] figure of 1,368,000 is probably an underestimate" (p. 1124).

## COMPLEX ISSUE AS TO ALLEGED MALPRACTICE

Some readers may note the unsolicited observation by a physician on the (controversial) effects of widespread lawsuits on alleged medical malpractice:<sup>1</sup> "I believe Mr. Belli, of California, who has been called 'the King of Torts' has been a far greater influence on the conscience of drug manufacturers than Mr. Kefauver" (p. 1241).

## A PRINCIPAL PROBLEM—FEDERAL EXCELLENCE

To a committee such as ours, the Senate Committee on Government Operations, a major question is: "Do the exhibits in this volume indicate that, by and large, Federal scientific and regulatory programs in the Food and Drug Administration have been characterized by general excellence? Or, do these hearing exhibits indicate that the caliber has been lower than it should have been?"

The answer to this question will be provided in the subcommittee's final report.

A fair and tentative conclusion would, I believe, be that the exhibits do indicate that "all has not been well" within the Food and Drug Administration and that to say the least, excellence has not uniformly prevailed. This assertion, in itself, is not conclusive; when it is proved (as I believe will be the case), one must understand the reasons for the lack of excellence; one must determine whether the reasons were or were not within the agency's whole or partial control.

For example, some of the exhibits reflect the chronic handicaps under which the agency has had to work, unfortunately. I have often stated that FDA has, regrettably, "been under-staffed, under-paid, under-equipped, under-appreciated, and under-supported."

The question is, however, "are these the only reasons for weaknesses?" The answer, I believe, is "no." One must look to deeper causes for the answer.

In any event, whatever may be the reasons which may have contributed to weaknesses, the fact is that weaknesses have existed within the agency.

A further question is:

"How significant are the weaknesses?"

An additional question is:

"Are the instances of weaknesses which are cited relatively rare or are they frequent; i.e., are they the exception or are they the rule?"

This memorandum does not, of course, attempt to answer these broad and crucial questions. The subcommittee's final report will endeavor to do so.

<sup>1</sup> As indicated in the exhibits, the subcommittee has received many messages from attorneys. The subcommittee has uniformly informed them as a matter of policy that (a) as regards input, the subcommittee is interested in receiving solely such information as might prove pertinent to its factfinding efforts on matters directly involving agencies of the U.S. Government; (b) as regards output—the facts which the subcommittee finds are made available to the Congress as part of its legislative duties and to the Nation as part of the Nation's right to be informed on Federal issues. How these facts—once published—may ultimately be used is beyond our control or purview; (c) an exhibit in vol. 4 will contain a letter received by the subcommittee from the U.S. Department of Justice as regards the Federal issue of some lawsuits, filed against the U.S. Government because of alleged malpractice with drugs in Federal clinical programs.



## WEAKNESSES REVEALED BY HERETOFORE CONFIDENTIAL MATERIAL

The memorandum does, however, note at this point and in the table which follows some of the weaknesses which the exhibits, quoting various professional sources, would appear to illustrate.

Some of these weaknesses are in the internal operations of the Food and Drug Administration; others may be within at least some segments of industry.

For purposes of brevity, only exhibit material which has heretofore been unknown to the public will be highlighted. Thus, the memorandum will not attempt to analyze what articles in the open literature, long available to the public, may show; it will cite what internal agency files or what letters to the subcommittee may state. The subcommittee, it is felt, can render its most useful service by bringing within the public view information not otherwise obtainable.

Some of this information speaks for itself, e.g., the quotations from professional sources state—without equivocation—that weaknesses exist or the exhibits inherently point to weaknesses; other materials indicate weakness, only by implication.

## FRANK ADMISSIONS BY FDA

Weaknesses are explicitly stated in FDA's commendable (although belated) effort to appraise its adverse reaction reporting system. An internal FDA study stated frankly:

(P. 1121) "The FDA Adverse Reaction Reporting Program should be either improved or abandoned."

(P. 1113) The FDA program "apparently suffers from the lack of an efficient administrative system to receive, utilize, and disseminate needed information on a volume basis."

(P. 1233) The FDA study "finds little coordination among the various efforts to improve the processing, dissemination, and utilization of scientific information within FDA."

## IMPLIED SHORTCOMINGS

Sometimes in internal memorandums reprinted within this volume, agency employees have, by implication, raised serious issues of agency weakness. After studying a New Drug Application file, for example, Dr. John O. Nestor noted in an internal memorandum:

"There is no evidence that the New Drug Application was sent to pharmacology for review" (p. 1118).

"Why not?" one wonders.

The same memorandum noted that the entire original New Drug Application contained a letter from only one investigator—that he administered a drug intravenously to 34 newborn infants without observing a reaction. Is one letter from one clinical investigator, tabulating 34 cases, "sufficient" evidence for a company to present in an application? (This is wholly aside from whether FDA should regard such a submission as "complete"; reference is made here to a company's own internal standard as to "completeness.") (Later, the company followed up with additional cases from the same single investigator.)

## NONREPORTING OF ADVERSE REACTIONS BY SOME COMPANIES

The contents of some exhibits are inherently disturbing. One example is in the nonreporting of adverse drug reactions by some companies in some instances—even when (under the limited provisions of the old law) they were legally, not merely morally, bound to do so. For example, the following facts were already known through the open literature: Commissioner Larrick stated on one company and one drug (which was withdrawn from the market):

"We later learned the firm had accumulated reports of jaundice and deaths associated with the drug's use for a period of over 5 years before it reported them to us" (p. 1099).

However, what has not heretofore been known publicly are facts mentioned in an internal FDA memorandum (p. 1095); nor has it been known that in addition to the 54 known cases of hepatitis and jaundice (including 15 deaths), 30 additional reactions were later reported (p. 1098) *after* the drug was removed from the market.

In any event, a question arises (in the light of this exhibit as well as other material not yet published by the subcommittee): "What did FDA actually ever do about what might have been flagrant violations of this nature—both as to the spirit and the letter of the law?"



## QUESTIONS AS TO TIMING

Many of the exhibits raise questions as to timing of regulatory decisions. As indicated earlier (p. 819), timing is crucial. A regulatory agency should be neither too fast (i.e., premature and rash), nor too slow. Evidence from professional sources has been that FDA has, at times, been too slow in protecting the public health. (See p. 1252, for example, as to alleged delay on a regulation on over-the-counter antibiotics.)

ADDITIONAL EXAMPLE: DANGER IN IMPROPER STORAGE—4 YEARS BEFORE  
PRECAUTIONARY LETTER AND ACTION

In 1959 (pp. 1245-1246) a physician wrote to a drug company and to the Food and Drug Administration with regard to the need for careful storage procedures so as to protect a potent useful drug, tetracycline, from decomposing into a dangerous product. In April 1963, after the issue was raised in the open literature,<sup>2</sup> the physician wrote to FDA expressing dissatisfaction with the way the agency had handled the case originally.

Four years after the physician's original comment to FDA, Lederle Laboratories sent out (on August 23, 1963) a "Dear Doctor" Letter.<sup>3</sup> It cautioned, in effect, as to effects of improper storage under "extreme conditions of heat and humidity" on tetracycline antibiotic capsules in developing "certain degradation products."

Is 4 years the shortest period of time within which the need for such a warning could have been studied and the warning sent?

ANOTHER EXAMPLE—VITAMIN K—10 MONTHS' DELAY

On May 24, 1962, the Bureau of Medicine of the Food and Drug Administration concluded (pp. 956, 959) that a drug, Vitamin K<sub>3</sub>, should not be on the over-the-counter market in prenatal vitamin capsules because proof of safety did not exist. On March 22, 1963, there was finally published in the Federal Register (p. 958) the order denying further use of the drug in prenatal vitamin capsules on an over-the-counter basis. Was 10 months the shortest period of time that might reasonably have been expected under the circumstances?

KONAKION—9 MONTHS' DELAY

FDA noted with pride (p. 1112) that on July 27, 1962, an alert physician telephoned it with regard to adverse reaction from Konakion.

On October 18, 1962, the company submitted revised labeling, mentioning the fatal reaction which had been reported.

Nine months later, in July 1963, the company sent out a "Dear Doctor" Warning Letter (p. 1130) concerning the danger. Is this the shortest period of time within which such a warning letter could and should have been sent?

No one would, of course, attempt to answer any of the above questions "off the cuff." Each case must be studied in detail in order to arrive at a fair answer.

MER-29—SERIOUS IMPLICATIONS FOR EVALUATION

Many of the exhibits are inherently highly technical. That is particularly true of the MER/29 exhibits. Only a scientist can properly evaluate them. The evaluation is urgently necessary. For example, one scientist (outside FDA) who commented on exhibit 128, in particular, has stated this view to the subcommittee: During the drug's active usage, the company's brochure to practicing physicians allegedly failed to inform adequately of the potential implications of the desmosterol problem. He said:

"The whole clinical chemistry method gave a falsely low [indication] for total sterol levels. The practicing physician should have [been informed] that he [could not] rely on ordinary laboratory help for evaluation of his therapy."

On another phase of MER/29, weaving throughout its entire history is the significant thread of possible effect of the drug in producing cataracts. The reader will wish to examine each such reference carefully in the interest of

<sup>2</sup> See article referred to by the doctor, as well as a subsequent letter to the editor of the Journal of the American Medical Association, by Frimpter, George W., M.D.; Timpanelli, Alphonse E., M.D.; Eisenmenger, William J., M.D.; Stein, Howard S., M.D.; Ehrlich, Leonard I., M.D., New York, Aug. 3, 1963, vol. 185, No. 5, p. 414.

<sup>3</sup> The principal element of the letter was announcement of an "important change" in the capsules to Lactose U.S.P. "for the better protection of your patients." The letter stated that new laboratory studies confirmed that "in the presence of Lactose U.S.P., tetracycline shows little or no degradation even under the most severe test conditions" (in contrast to the possibility, formerly, with citric acid).



fairness. The reader will wish, for example, to study (p. 840) what the FDA Division of Pharmacology stated in February 1960, 2 months before the Bureau of Medicine approved the New Drug Application. Then, the reader will note that as late as May 1963 a significant paper presented by a distinguished NIH scientist stated that:

"Recent reports \* \* \* of cataract development in patients treated with Triparanol (MER/29) for prolonged periods indicated that experimental work on the possible cataractogenic effect of the drug is needed" (p. 916).

Fortunately, the expert study was made. It found "34 of the 38 rats developed cataractous changes within 10 weeks after Triparanol feeding was started" (p. 917).

But the question emerges: Why is it that, as late as May 1963, "experimental work on the possible cataractogenic effect of the drug was 'still needed'?" Was not definitive work on this subject strongly indicated years and years earlier? After all, we are dealing here with conserving the priceless blessing of human vision.

#### SHORTCOMINGS IN VARIOUS SOURCES

Most of the exhibits relate, as the title of this volume indicates, to the Food and Drug Administration. Many relate to practices which may have been rare or common within the drug industry. Some relate to conditions within other Federal agencies. The reader will find, for example, that only in June 1963, 9 months after the subcommittee first raised the issue, did the Veterans' Administration, which runs the world's largest clinical program, finally get around to establishing a coordinated system of reporting adverse reactions within its own agency (p. 1129) (much less attempting to exchange such information with the Food and Drug Administration—a task still to come).

#### TABLE CITING A FEW INSTANCES OF ALLEGED, IMPLIED, OR CONCEDED WEAKNESSES

There is listed below in alphabetic order a series of weaknesses which are alleged, and/or which are implied, or, in a few instances, conceded within the sources quoted by the various exhibits. This table is submitted for illustrative purposes as a reference aid to the reader in coming to his own careful evaluation. The table refers solely to those exhibits containing heretofore confidential material; it does not attempt to include the numerous weaknesses which are alleged in the open literature as reprinted herein, nor within the testimony by the two witnesses on March 20, 1963.

##### Adverse reactions—

companies, alleged under-reporting or failure to report promptly, pp. 893, 1095-1097, 1098

weaknesses conceded in FDA system, pp. 1114, 1121, 1122, 1128

weaknesses in nationwide estimates, p. 1124

Consultants, inadequate FDA use of, pp. 985, 1249, 1252

Information system, FDA, shortcomings of, pp. 996, 1233

Labeling claims, excessive, pp. 877-879, 889-890, 936-937, 1093

Records, FDA, inadequate hand written notes in, p. 869

Release, company, to lay press, allegedly inaccurate, p. 904

Testing, alleged frauds in, pp. 815, 907-908, 975

alleged inadequate, pp. 841-842, 1117-1118

Warning letter, alleged delays in sending to physicians, pp. 1245-1246

#### PRAISEWORTHY STRENGTHS IN THE AGENCY, IN SCIENCE, AND IN INDUSTRY

Let it be clearly noted that the exhibits, as indicated earlier, do confirm many strengths within FDA and within the pharmaceutical sciences. The subcommittee wishes to see these strengths capitalized and expanded upon to the greatest possible extent. On many occasions, in comments at our hearings, we have rightly praised the dedicated work of drug researchers and regulators; we will continue to do so in the future. But we will also seek to call a "spade a spade," to be frank and constructive in building for a still more valuable drug agency, drug industry, and drug science in serving the health of our people.

This Nation enjoys the most advanced healing arts in the world; much of our preeminence is due to the pharmaceutical sciences. The further excellence of these outstanding and crucial sciences is a goal worthy of our best efforts.

Drug standards in the United States are the highest in the world; American drug companies have rightly prided themselves on their hard-earned, world-esteemed reputation. But lapses do occur and have occurred, sometimes even on the part of some otherwise outstanding firms. And some companies' standards, according to what the subcommittee has been told, may leave much room for improvement, to say the least.



## RAISING THE AVERAGE LEVEL OF PERFORMANCE

A statistician might define the problem as "raising the norm"—the average level of performance. Thus, great progress could be achieved if the average caliber of FDA activity in drug regulation could be raised closer to the outstanding caliber which already prevails in some FDA drug activities. Similarly, mankind would be greatly benefited if the average quality of New Drug Applications, as submitted by drug companies, could be raised closer to the superb caliber which is attained by some companies, in numerous instances.

Qualities of human and of company performance will always vary. No one expects the impossible. But the poor level at the "bottom" of performance should not be allowed to drag down the overall level. Moreover, science should not be apathetic in the face of what observers have characterized as, frequently, unimpressive activity among the "middle" mass of performers. The "norm" should be improved inside and outside FDA. This can be done. It must be done. There are excellent men within industry and FDA who are striving to do it; their hands should be strengthened.

## STANDARDS OCCASIONALLY SHOCKINGLY LOW

The plain fact is this (as revealed in public testimony, in the open literature, and in the heretofore confidential exhibits within this volume): In some instances, standards both in FDA's Bureau of Medicine and in some drug companies have been distressingly, even shockingly, low, relatively speaking. Needless human suffering has resulted.

No one, at this point, knows how rare or how common have been such instances of inferior standards; even a few such instances are, however, intolerable. (A single instance can and does influence the lives of thousands of people.) The low standards which have prevailed in certain instances do not represent what either the agency or the industry or the individual companies would themselves wish. To the contrary, I do not have the slightest doubt that the drug industry deplures, for example, the numerous inexcusable failures by some personnel in some companies to report to FDA promptly and completely on adverse reactions, particularly on fatalities (even if, under the old law, reporting was not mandatory because an NDA had already been approved). So, too, I have no reason to doubt that FDA's dedicated personnel do want to perform and have always wanted to perform the best possible job in the public interest.

The Congress' job and the still more basic job of the medical, pharmaceutical, dental, nursing, and allied professions is to help them to do so. But FDA and industry must also help themselves; they must not cover up departures from their own high ideals. They must not tie their own hands in relative inactivity and then complain, "our hands are tied." And they must not be content with mere pro forma gestures toward improvement.

Exhibits in subsequent volumes will elaborate on the points mentioned above and on many other points which are mentioned only briefly within this volume.

## AGREEMENT ON STRENGTHENING FDA

For the present, I would conclude with this sound quotation (p. 1023) from the Commissioner of Food and Drugs. In it, Commissioner Larrick well summarized my comments to him in a personal meeting and in writing, following the March 20, 1963, hearing:

"DEAR SENATOR HUMPHREY: \* \* \*

"It was very reassuring to find in your letter a statement of views which we already understood you hold with respect to our operations—that by and large our agency has served the Nation faithfully, and that it is your intention to strengthen the agency and enable it to do the best possible job in the public interest. I am sure you know that it is our sincere desire to continue to discharge our trust faithfully and effectively. \* \* \*

The Nation has a new drug law and new regulations. This subcommittee looks forward hopefully to the finest possible implementation of the law and the regulations. The subcommittee hopes to be of further assistance in this process. It will examine evidence which has been compiled as to the strengths and weaknesses of the past. It will then file its own report, looking ahead to still more effective Federal and private drug policy and action.



# INDEX OF NAMES OF INDIVIDUALS AND OF DRUGS<sup>1</sup>

## SECTION 1. INDEX OF NAMES OF INDIVIDUALS

Included herein are the names of witnesses, of authors of professional papers whose views are quoted within exhibits, agency and company employees mentioned therein, correspondents, as well as other individuals referred to in this volume.

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<sup>1</sup> This index is published in order to facilitate rapid access to the contents. A detailed subject index, listing organizations, activities, etc., will appear in a later volume. The contents of several volumes will be covered in that subject index.



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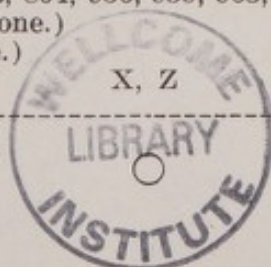
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