COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

HEARINGS

BEFORE THE

SUBCOMMITTEE ON MONOPOLY

OF THE

SELECT COMMITTEE ON SMALL BUSINESS

UNITED STATES SENATE

NINETIETH CONGRESS—SECOND SESSION

AND

NINETY-FIRST CONGRESS—FIRST SESSION

ON

PRESENT STATUS OF COMPETITION IN THE PHARMACEUTICAL INDUSTRY

PART 10

DECEMBER 11, 17, 18, 19, 1968, AND JANUARY 23, 1969

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COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

WEDNESDAY, DECEMBER 11, 1968

U.S. SENATE,
MONOPOLY SUBCOMMITTEE OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to call, at 10:20 a.m., in room 318, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; and Elaine C. Dye, research assistant.

Senator NELSON. The hearings of the Monopoly Subcommittee of the Senate Small Business Committee will come to order.

After a brief statement by the chairman, we will hear from the distinguished Dr. William B. Bean.

There is growing concern, as reflected in medical literature as well as in testimony before our subcommittee, that the medical profession has forfeited too much responsibility for the continuing education of physicians to the pharmaceutical industry and that the increasingly close financial relationship between the industry and the medical profession may be contrary to the best interests of the profession and the public.

The purpose of the series of hearings we are undertaking this week and next is to explore further the questions raised in this regard; particularly as they involve the ethical implications, possible conflicts of interest, and professional responsibility, as, for example, in some of the following situations:

When many physicians base their prescribing practices, to a large extent—I don't think anybody knows exactly to what extent—on information supplied them by industry salesmen—detail men—and other commercial sources.

When many physicians prescribe dangerous drugs for nonindicated purposes. For example, during the past year a highly dangerous drug was prescribed by doctors—this was chloramphenicol—for 3.5 to 4 million people in the United States. Yet, testimony from eminent medical authorities who appeared before the subcommittee indicated that no more than 10 percent—at the most—should have received it.

When many doctors prescribe drugs without adequate knowledge of the costs of these drugs relative to other drugs which have the same action.

When many medical organizations and publications—national, local, and student—are substantially dependent on income derived from industry advertising.

When many doctors lend their names for articles and letters written by members of the pharmaceutical industry.

The implications for the medical profession and the public when the so-called independent giveaway sheets and journals—which are easy to read and subsist entirely on drug advertising—are becoming a factor of some importance in the physicians' education.

When influential doctors or pharmacy educators, particularly in high academic positions, are stockholders and/or serve as policy-setting members of boards of drug corporations. Since these men are in a position to mold the attitudes of other doctors and to make policy decisions in key medical and pharmaceutical organizations, might there not be a conflict of interest here? What are the ethical implications when doctors and pharmacy educators do not make known their industry affiliations?

As long ago as January of 1961, Dr. Charles D. May, of the Department of Pediatrics of Columbia University, in an article in the Journal of Medical Education entitled "Selling Drugs by 'Educating' Physicians," [1] asked:

> Is the public likely to benefit if practicing physicians and medical educators must perform their duties amidst the clamor and striving of merchants seeking to increase the sale of drugs by conscripting "education" in the service of promotion?
>
> Is it prudent for physicians to become greatly dependent upon pharmaceutical manufacturers for support of scientific journals and medical societies, for entertainment, and now also for a large part of their education?
>
> Do all concerned realize the hazard of arousing the wrath of the people by an unwholesome entanglement of doctors with the makers and sellers of drugs?

In an article in Ethical Issues in Medicine,[2] Dr. William Bean, our witness today, of the University of Iowa Medical Center, stated that:

> The physician who is in the pay of pharmaceutical manufacturers is in no position to keep public confidence in his objectivity. The editors and owners of medical journals which depend so heavily upon advertising are vulnerable and not only must be above taint but, like Caesar's wife, above suspicion.

In its efforts to study the far-reaching implications of these and related problems, the Monopoly Subcommittee of the Senate Small Business Committee has invited several highly respected senior physicians—whose integrity and courage to be forthright are well known to their peers—to present their views on these and other matters concerning these questions.

We are pleased to welcome this morning Dr. William Bean, who is a widely known medical authority and is the former chairman of the section on Internal Medicine of the American Medical Association.

Doctor, do you have for the record a biographical sketch?

Dr. BEAN. I didn't bring one with me. I can get one for you and send it if you want.

Senator NELSON. If you would, please. We would simply like to have it in the record at the beginning of your testimony for the reference of those who read the record.

(A biographical sketch was subsequently received and follows:)

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[1] See article beginning at p. 3938, infra.
[2] See article beginning at p. 3957, infra.

BIOGRAPHIC DATA—WILLIAM BENNETT BEAN, M.D.

PERSONAL

Professor of Medicine and Head of Department of Internal Medicine, University of Iowa, College of Medicine, Iowa City, Iowa, 1948–
Residence: 723 Bayard Street, Iowa City, Iowa.
Date of Birth: 8 November 1909 at Manila, Philippine Islands. Son of Robert Bennett Bean, M.D., and Adelaide L. Martin. (Biography of father was in Who's Who in America, American Men of Science, Who's Important in Medicine.)
Married: Abigail Shepard, 17 June 1939.
Children: R. Bennett, 25 March 1941; Margaret Harvey, 9 July 1944; John Perrin, 25 April 1946.

DEGREES

B.A., University of Virginia, 1932; M.D., University of Virginia, 1935.
Diplomate, American Board of Internal Medicine, 1947.
Diplomate, American Board of Nutrition, 1951.

ACADEMIC AND HOSPITAL APPOINTMENTS

Student Instructor in Anatomy, University of Virginia School of Medicine 1932–1933, 1933–1934, and 1934–1935.
Intern, Medical Service, Johns Hopkins Hospital, 1935–1936.
Assistant Resident Physician, Boston City Hospital, 1936–1937.
Teaching Fellow, Thorndike Memorial Laboratory, Boston, 1936–1937.
Teaching Fellow in Medicine, Harvard University, 1936–1937.
Senior Medical Resident, Cincinnati General Hospital, 1937–1938.
Instructor in Medicine, Cincinnati Medical College, 1938–1940.
Fellow in Nutrition, Cincinnati Medical College, 1938–1940.
Assistant Professor of Medicine, University of Cincinnati Medical College, 1940–1947.
Medical Examiner for Draft Boards, 1941–1942.
Assistant Attending Physician, Cincinnati General Hospital, 1941–1946.
Assistant Visiting Physician, Hillman Hospital, Birmingham, Alabama, 1940–1942.
Clinician, Out-patient Department, Cincinnati General Hospital, 1946–1948.
Attending Physician, Cincinnati General Hospital, 1946–1948.
Associate Professor of Medicine, University of Cincinnati College of Medicine, 1947–1948.
Senior Medical Consultant, Veterans Administration, 1947–
Physician-in-Chief, University Hospitals, Iowa City, Iowa, 1948–
Special Consultant, Iowa Selective Service, 1949–
Special Consultant, Iowa Heart Disease Control Board, 1949–

HONORS

John Horsley Memorial Prize, University of Virginia, 1944.
Groedel Medal, American College of Cardiology, May 1961.
American Medical Writers' Association, Award for Distinguished Service in Medical Journalism as Editor-in-Chief of the Archives of Internal Medicine, October 1962.
Gold-Headed Cane, University of California, June 1964.
Citation, Boston City Hospital, Seventy-Fifth Anniversary, June 1964.
University of Sydney Medal for Lambie-Dew Oration, March 1966.

U.S. ARMY

Director, Hot Room Research, Armored Medical Research Laboratory, Fort Knox, Kentucky, 1942–1943.
Director, Medical Research, Amored Medical Research Laboratory, 1943–1945.
Director, Nutrition Research Team, Pacific Theater, 1945.
Commanding Officer, Armored Medical Research Laboratory, 1945–1946.
Captain, MC AUS 8 August 1942; Major 30 March 1944; Lt Colonel 26 February 1946; discharged 28 May 1946.
Commendation Ribbon, 1946.

Special Consultant to Surgeon General, US. Army, 1954–.
Consultant to the Surgeon General, US Army, Advisory Committee to the Surgeon General of the Army on Nutrition, 1959.

EDITORSHIPS

Assistant Editor, Nutrition Reviews, 1945–1946.
Editorial Board, Book Review Editor, Cincinnati Journal of Medicine, 1946–1948.
Associate Editor, Journal of Clinical Investigation, 1947–1952.
Editorial Board, Journal of Laboratory and Clinical Medicine, 1948–1954.
Associate Editor, Diseases of the Chest, 1951–1961.
Editor-in-Chief, Monographs in Medicine, Williams & Wilkins Co., 1951–1952.
Editorial Board, The Journal of Medical Education, 1953–1956.
Editorial Board, Archives of Internal Medicine, 1953–.
Editorial Board, Medicine, 1953–.
Advisory Board, American Journal of Clinical Nutrition, 1955–1959.
Editorial Board, Pharos, 1955–1962.
Advisory Board, Resident Physician, 1955–1962.
Book Review Editor, AMA Archives of Internal Medicine, 1955–1962.
Editorial Board, Perspectives in Biology and Medicine, 1957–.
Contributing Editor, Encyclopedia Britannica.
Medical Editor, Stedman's Medical Dictionary, 1958–.
Editorial Board, American Journal of Clinical Nutrition, 1960–1961.
Editor-in-Chief, Archives of Internal Medicine, 1962–1967.
Editorial Consultant, Modern Medicine, 1964–1967.
Editorial Board, Familiar Medical Quotations, Little, Brown & Co., 1964–.
Editorial Consultant, Dictionary of American Portraits, 1964.
Consulting Editor, Stedman's Medical Dictionary, 20th Ed. (1961); 21st Ed. (1966), Williams & Wilkins Co., Baltimore.
University of Iowa Editorial Board, reappointed, June 1966–.
Editor-in-Chief, CMD (Current Medical Digest), 1967–.
Consulting Editor in Medicine for Medical Aspects of Human Sexuality, 1967–.

COMMITTEES AND BOARDS

Scientific Board of Directors, The National Vitamin Foundation, 1950–1953.
Associate Member, Commission on Liver Disease of the US Army Respiratory Disease Commission, 1949–1952.
Executive Committee on Scientific Council, American Heart Association, Inc., 1951–1954.
Committee on Borden Award, 1953–1955.
Committee on Abraham Flexner Award, 1958; Chairman, 1959.
Association of American Medical Colleges; Section of Clinical Cardiology, American Heart Association, 1954–1958.
Study Section, General Medicine, National Institutes of Health, 1957; Chairman, 1958–1961.
National Advisory Committee, Grand Rounds Television Programs, 1957–1963.
Board of Regents, National Library of Medicine, 1958–1961; Chairman, 1960–1961; reappointed to the National Library of Medicine, 1965–.
International Committee on Clinical Cardiovascular Disease, American College of Chest Physicians, 1960–.
Judging Committee, Theobald Smith Award, AAAS (Amer. Assoc. Advancement of Science), 1960–1962.
Inter-Study Section Committee on Influenza Research, National Institutes of Health, 1960–1961.
Governor for the state of Iowa of the American College of Cardiology, 1962–1968.
Member, Pan American Medical Association Council on Cardiovascular Diseases, 1965–.
Regional Representative, University of Virginia Alumni Fund, Inc., Oct. 1966.

VISITING PROFESSORSHIPS

Providence Hospital, Providence, RI, 1955.
Ohio State University School of Medicine, Columbus, Apr 1955.
Georgetown University School of Medicine, Washington, DC, Nov 1955.

Mt. Sinai Hospital, Miami Beach, Fla, Sept 1956.
Visiting Professor and Acting Chief of Department, Bowman Gray School of Medicine, Winston-Salem, NC, Apr 1958.
Visiting Professor and Acting Head of Department of Medicine, University of Georgetown College of Medicine, Washington, DC, Apr 1958.
Visiting Professor and Acting Head, Washington University School of Medicine, St. Louis, Mo, Nov 1958.
Visiting Professor of Internal Medicine, Head of Department of Medicine pro tem, Washington Medical Center, Washington, DC, May 1959.
Lackland Air Force Base Hospital, Department of Medicine, Texas, Apr 1959.
University of Utah School of Medicine, Salt Lake City, Utah, Dec 1959.
Baylor Medical School, Houston, Tex, Mar 1960.
University of Mississippi School of Medicine, Jackson, Mar 1960.
University of Oregon, Portland, Apr 1950.
University of Oklahoma College of Medicine, Oklahoma City, Nov 1960.
Johns Hopkins School of Medicine, Baltimore, Md, 1963.
Sir Norman Paul Visiting Professor, University of Sydney Medical School and Sydney Hospital, Sydney, Australia, Mar 1966.
Visiting Professor, Tampa General Hospital, Fla, Oct 1966.
Second Master Teachers Course, San Diego, Calif, Feb 1967.
Visiting Professor of History of Medicine and Internal Medicine, University of Virginia, School of Medicine, Charlottesville (Grant from the Univ Va and Josiah Macy Foundation) Feb 1, 1968/July 31, 1968.
Visiting Professor of Medicine, Medical College of Georgia, Augusta, May 22–23, 1968.

SOCIETIES

Raven Society, University of Virginia, 1932; Alpha Omega Alpha, 1934; Central Society for Clinical Research, 1938, Council 1947–49, Vice President 1950, President 1950–51; American Society of Tropical Medicine, 1938; Sigma Xi, 1939.
American Heart Association, 1940; American Association for the Advancement of Science, 1940, Fellow 1952, Vice President and Chairman of Section N, 1957; American Medical Association, Fellow 1941, Chairman, Section of Internal Medicine, 1958–59; Ohio State Medical Society, 1941; American Society for Clinical Investigation, 1942, Council 1949–51; Association of Military Surgeons, 1943; Charter Member Medical and Jockey Society of the Interior Valley of North America, 1946; Association of American Medical Colleges, 1948; American College of Physicians, Fellow 1948. Ex-Gov; Iowa State Medical Society, 1948. Chairman of Section of Internal Medicine, 1958–59; Iowa Heart Association, 1948, President 1951; Tuberculosis and Health Association, 1948; Central Interurban Clinical Club, 1948, President 1958–59, Archaeology Institute of America, Iowa Chapter, 1948, President 1955–57; Iowa Clinical Medical Society, 1949; World Medical Association, 1949.
Association of American Physicians, 1950; Society of Experimental Biology and Medicine, 1950; Research Club, University of Iowa, 1950; American Association for the Study of Liver Diseases, 1950 (Charter Member); American Clinical and Climatological Association, 1951, Council 1956–59, Vice-President 1963, President 1967, Council 1968–71; American Association of Medical History, 1952; American College of Chest Physicians, Fellow 1954. Ex-Gov. Ia; The Horse Shoe Club, Regional President, 1954; Consultant in Internal Medicine to Surgeon General, US Army, 1954; American Medical Writers Association, Fellow 1958; Dallas Southern Clinical Society, Honorary Member, 1954; Society of Medical Consultants to the Armed Forces, 1954; American College of Sports Medicine, 1954, Charter Member; New York Academy of Sciences, Fellow 1956; American Academy of Political and Social Science, 1955; Royal Society of Medicine, Fellow, London, 1958; Consultant on Advisory Committee to the Surgeon General of the US Army on Nutrition, 1959; The Nockian Society, 1959.
American Society for Clinical Nutrition, Council 1960, President 1962–63; Consultant in the Survey of Medical Research in VA Hospitals, Division of Medical Sciences, National Academy of Sciences, 1960; History of Science Society, 1960; American Institute of Nutrition, 1960; The Honorable Order of Kentucky Colonels (rank of Colonel), 1963; Stuart and Tudor Club, Johns Hopkins University, 1963; The John Fulton Society, 1963; Hobart Hare Society, Jefferson Medical School, 1964; Board of Directors, National Association for Standard Medical Vocabulary, 1964; Sydney Hospitallers, 1966; American College Cardiology, Fellow 1967. Ex-Gov; Fellow, Council on Clinical Cardiology, American

Heart Association, 1963; The Osler Club of London, 1967; Member, History of Medicine Section Richmond Academy of Medicine, Virginia, 1968; Honorary member, Milton Anthony Medical Society, Univ Georgia Medical College, 1968.

BOOKS

Osler Aphorisms: Collected by Robert Bennett Bean, M.D. Edited by William Bennett Bean, M.D. Schuman, Inc, NYC, September 1951.
Osler Aphorisms: Reprinted by Charles C. Thomas, Springfield, Ill., September 1961.
Osler Aphorisms: Third printing by Charles C. Thomas, Springfield, Ill., June 1968.
Monographs in Medicine, Series I: Edited by William Bennett Bean, M.D., Williams & Wilkins Co, Baltimore, Md., November 1952.
Omphalosophy and Worse Verse: William B. Bean, M.D., privately printed, Iowa City, January 1955.
Vascular Spiders and Related Lesions of the Skin: Edited by William Bennett Bean, M.D., Charles C. Thomas, Springfield, Ill., December 1958.
Aphorisms From Latham: Collected and edited by William B. Bean, M.D. The Prairie Press, Iowa City, October 1962.
Rare Diseases and Lesions—Their Contributions to Clinical Medicine: William B. Bean, M.D. Charles C. Thomas, Springfield, Ill., 1967.

Senator NELSON. Dr. Bean, we are very pleased to have you appear here today. You are free to present your testimony in any way you wish, and in any event, all of it will be printed in the record, and if you desire to elaborate or extemporize on anything that you have in your printed presentation, feel free to do so.[1]

I assume that as questions occur to the chairman you would have no objection to interruptions.

Dr. BEAN. Very well.

Senator NELSON. Thank you very much, Doctor.

STATEMENT OF DR. WILLIAM B. BEAN, PROFESSOR OF MEDICINE, AND HEAD, DEPARTMENT OF INTERNAL MEDICINE, UNIVERSITY OF IOWA COLLEGE OF MEDICINE

Dr. BEAN. Senator Nelson, ladies, and gentlemen, I am here as an individual, and although I have many connections and affiliations, as a teacher, as a physician who is in a consulting practice, as a former editor of a number of journals, and as a member of the editorial board of four or five still today, and as someone who has done a certain amount of research and investigation, I have a broad background of interest in the problems presented.

As I commented in my first paragraph, this sort of testifying I find extremely difficult and distasteful, simply because it puts one in the position of perhaps thinking he is a little better than others or being a critic of your family if you will. Nonetheless, I think that someone must take responsibility in these matters, and I have done so in the past, and I suppose I shall do so in the future, even though I find it difficult.

Some 18 years ago I was president of the Central Society for Clinical Research, and addressed myself to a number of problems that I thought were important in American medicine. These had to do with medical education, with licensing, with specialty boards.

[1] See prepared statement beginning at p. 3927, infra.

I included a paragraph on the moral responsibility to be intelligible, which I think is not always adhered to by people in various positions in the world where they should be intelligible, and I had the following to say about the role which more or less willy-nilly detail men from drug firms had come to take in the postgraduate education of physicians in the country. I said as follows:

What is the most effective general teaching today at the postgraduate level? In sorrow we must admit that the artistic and artful brochures of wealthy pharmaceutical houses, sped on by a crusading band of detail men, have effectively taken over graduate teaching. The blandishments of advertising, siren song of the purveyor of pills, now that there really is a multitude of specifics, puts professional judgment in a sorry place. Harnessed to the lightning strokes of lay publicity, the demand for new miracle drugs often comes from radio or newspaper coaching, and the practitioner, fearing to "be not the first by whom the new drug is tried" because party to a conspiracy of ignorance, fraud, and twisted idealism which has run the gamut from vitamin craze to spurious cold cures and Hadacol. After all, we have some responsibility in this mess, and must provide leadership to protect the public and embellish the name of medicine. Certainly many pharmaceutical houses are advancing the cause of medicine. More power to them. I do not grudge the honest dollar to the shareholders in drug enterprises, but when their advertising budgets exceed the total outlay for teaching and research provided by all our medical schools concern is justified, "for where your treasure is there will your heart be also." [1]

Senator NELSON. May I interrupt just a moment, Doctor. Would this statement still stand today in your judgment?

Dr. BEAN. I certainly think the problem exists, and I would imagine that the scope is pretty much the same.

But real advances are being made in continuing education. For instance, the group interested in general practice, the American Academy of General Practice, has insisted that its members have a certain amount of formal postgraduate training every year. They are probably going to have a specialty board in which a renewal of the specialty certificate will require a re-examination perhaps at 5-year intervals.

This will require formal continuing education of the kind which has not been required by law, and is not in any sense uniformly followed by the individual drive incentive of the practicing physican.

One of the great problems is time. Obviously if somebody is going to go back in school freshening up, he won't be treating the sick in his community, and this I think has been a real deterrent. So the problem is there. Certain formal and productive efforts are being made to upgrade the role of teaching at the postgraduate level in continuing education. This I think is a real advance.

Many postgraduate courses of all sorts have existed for a very long time. These tend as a rule to be attended by those who are well abreast of what is going on anyhow. The people who should come do not, their function is very fine but it doesn't always reach the doctors who need it most.

Senator NELSON. Thank you.

Dr. BEAN. Ten years ago I addressed myself to the broad problem of the relationship of physicians to the pharmaceutical industry in an essay, entitled "Joint Responsibility," published in the Archives of Internal Medicine in May 1959. The main substance of my comments

[1] J. Lab. Clin. Med., 39 : 7, January 1952.

was that a team of physicians and representatives of the pharmaceutical industry should work out, voluntarily, means of evaluating claims for drugs, evaluating the therapeutic effect of drugs, and then seeing that advertising, sales, detailing, and retailing were managed according to regulations developed by joint action. Thus the manufacturers of drugs and the physician prescribers might best serve their collaborative purpose in preventing, palliating, or curing disease. This plea had very little effect. No formal study, joint effort, or confrontation of producer, distributor, dispenser, and user ever came about. Later the substance of my comments was recorded in presentations 10 years ago before the Kefauver committee, in this room.

Recently in an essay, entitled "The Medical Profession and the Drug Industry," published in Ethical Issues in Medicine, a book recently released by Little, Brown & Co. in Boston, I dealt with the present situation in regard to the ancient confrontation and sometimes antagonism of apothecaries and physicians, and this as you know has a long and fascinating history. Among the comments made were the following:

> At a time when scientific advance was slow and new drugs, such as they were, were likely to be found by painstaking evaluation of herbs and their essences, the introduction of new drugs was uncommon. Therapy, not very effective, was about at a standstill. There was no incentive to go into the mass production of new compounds, for there simply were not enough new compounds. When advances began to develop explosively, the traditional function of ethical pharmaceutical houses was magnified and multiplied, and to some extent the directing forces were removed from individual or family enterprises into the large realm of big business.
>
> At the same time, there was not at first a comparable awareness or alertness to deal with the increasingly complex problem of drug testing. In any society when problems which are new in kind, as well as new in dimension, arise, its institutions are tested. Unfortunately it turns out often enough that the institutions and organizations, well geared for a slower pace and a simpler set of problems, may prove not only insufficient but dangerous. The evolution of medical practice and medical science as it relates to therapy and the employment of powerful drugs is moving fast but uncertainly. Institutions rarely have a built-in autoanalyzer, a central controlling monitor, to examine and provide a dispassionate critique of purposes, functions, and the capacity to fulfill them. This is why institutions change, or fail and are replaced.
>
> Human nature being what it is, things may go along until some disaster appears. Some threat becomes ominously evident. Or a general quickening of the moral pulse of the community leads to an investigation or an intervention. Often a crash program of poorly thought out schemes results in passing laws to achieve ends which would be managed much better if collaborative but voluntary arrangements and agreements could be worked out by those concerned. The two parties involved here are pharmaceutical manufacturers on the one hand and the body of medical practitioners, teachers, and investigators, those who must be responsible preservers and protectors of the public, on the other.
>
> The great majority of pharmaceutical manufacturers have a just concern for their good name and are wary lest this be sullied by entrepreneurs who have come into the field without the traditional background accumulated during the more leisurely days. They have a steady sense of responsibility and wish it to permeate the drug industry. While many of the problems which are of concern to us now have, more or less by default, gone into the hands of external agents or agencies, it is still wise for physicians and those who produce pharmaceutical agents to review jointly their common material problems.[1]

Senator NELSON. May I interrupt for a moment, Doctor?

Dr. BEAN. Yes, sir.

[1] Pp. 231–232, 1968.

Senator NELSON. You referred to drug testing. As you know, when a company develops a new drug, the control of the testing is exclusively within the jurisdiction of the owner or the discoverer of the compound, and the testing is done at the direction of the company and the New Drug Application includes whatever testing is done, all of it under the control of the company.

The question has been raised in the medical literature and testimony before this committee as to whether that is a satisfactory method of presenting the evidence for review; that is, should a person having a financial interest in marketing a drug also supply all the information about the drug.

Do you have any observation about this method of developing a New Drug Application?

Dr. BEAN. Senator Nelson, I think everyone would agree that the better and certainly more nearly idea way to deal with this problem would be to have a neutral judging body professionally competent, and quite independent of any extraneous force of financial support or any hint of obligation or connection with the promulgators—the inventors—the promoters of the drug.

I think anybody would realize it is human nature to react to information one has in some relationship to those who will review it, those who support it, and the auspices under which studies are done. For example, somebody working for a very autocratic department head will fine that some of his own work, at least work that he thinks is his own, may be taken over in part by somebody whose name is on the paper, but who in fact had nothing more than a slight relationship, but was not in fact actually engaged in the work.

Likewise, if a series of tests is supported, as it commonly is, though not invariably, by the people who invent it and have the copyright or patent or control of a particular drug, and if this support comes to be important in the general academic progress perhaps of the person doing the studies, it is human nature for one to accentuate the positive and to report things which a certain amount of human observer parallax, a little body english that creeps into interpretations.

This is, I think, inevitable in the order of most of the relationships that people are in. It would be better if it were done in medical schools and in departments of clinical pharmacology. If a series of testing panels could be established, without any necessity for continuing support from a particular group whose products are being tested, I think that the truth would have a better chance of being reached than under the present system.

I think it is overidealistic to suppose that there will be a sudden, instant, radical change. I would hope that in the long run this is the direction in which we aim—to have totally independent, and we hope unbiased observers—testing under conditions in which they have no academic, scientific, financial, or personal equity the various drugs that come along.

The real difficulty is that this is a very expensive, very time-consuming and very difficult thing to do. The actual testing of the effectiveness of a drug which would seem to be pretty cut and dried to the average laymen, is indeed a very complicated thing, ranging all the way from variation in individual batches of a particular compound

to the enormous effect of the placebo. This is the effect that the mere giving of a drug, without regard to its pharmaceutical power at all, may have in influencing somebody who gets it, whether you test it out on medical students and tell them you are giving them a drug which will prevent nausea and vomiting when in fact it usually induces them. You will find that some respond appropriately to the pharmaceutical power of the drug; some respond to the power of suggestion. This is a complicated problem that I don't need to get into further.

It is evident that if testing is done with financial support of those who obviously wouldn't be spending money if they didn't think they had a good and effective drug, and who want the test to come out favorably, a bias is introduced that it would be better to get rid of, if we could.

Senator NELSON. Is there any reason why you think it wouldn't be feasible to have a national or independent national institute of drug testing, which supervised testing with qualified people and delegated testing to, as you suggest, medical schools?

Dr. BEAN. Some such central panel would be the kind of thing that I would certainly hope would come in and what its relationship should be to existing medical bodies, what its relationship to the Government I am not in any position to say.

As you are aware, many years ago there was a seal of approval given by the American Medical Association to drugs that were tested under its auspices. This was an independent panel. They would not accept advertising from those drugs which did not pass this panel. Its cost was said to have become far too extensive and expensive. It was given up. Whether that in fact was the reason I am in no position to say, but I do know that any testing of that kind does become tremendously expensive in manpower, in dollars, and in actual clocktime.

Senator NELSON. With respect to the question of expense, would you see any reason why the companies couldn't be charged by the independent institute for the testing that was done, so long as the institute was totally responsible for how it was done?

Dr. BEAN. This it seems to me is the proper direction. As you may know, there are such things as the National Vitamin Foundation and the Nutrition Foundation, and life insurance companies all over the world have gotten together and supply money to do research which is quite independent of any particular company that supports this, and this is the sort of thing.

We have good precedent for it in the ones that I have mentioned. I should think that direction would be wise to go in.

Senator NELSON. Thank you very much.

Mr. GORDON. May I ask a question at this point? Coming back to your previous statement about the tendency of someone who has a financial stake to try to accentuate the positive—a very good example, incidentally, is a letter which is taken from our own record on indomethacin. This is a letter from Dr. Paul from the University of Iowa, in which he starts out:

To Merck Sharp & Dohme:

DEAR DR. CANTWELL: I received your letter this morning and want to thank you for suggesting a grant for the Rheumatology Section at the University of Iowa.

Then he talks about tests with indomethacin:

This is a method we will follow for the time being, with our fingers crossed.

Apparently he has a desire to show that it is a good drug.

Now doesn't it seem reasonable that a person who is thanking a company for giving a grant to his department would be very reluctant to put in the next paragraph, "I am sorry your drug is a very poor one"?

Dr. BEAN. I agree that you have stated it admirably. I think it would be asking too much of human nature to reckon that somebody could be absolutely fair under these circumstances, and though this comes from Iowa, I don't condone it and I don't think it is the way one should operate.

Senator NELSON. Thank you, Doctor.

Mr. GORDON. We have many letters like this, by the way.[1]

Dr. BEAN. I am sorry to hear it. I hope no more from Iowa.

Senator NELSON. Go ahead, Doctor.

Dr. BEAN. The Medical Letter, which is a newcomer on the scene in the past dozen years or 10 years or so has provided a service which makes an effort to give an independent critique of both published work dealing with drugs, drug costs, drug efficacy, the relative merit of similiar drugs used for the same thing, and they have operated a clearinghouse, collecting, reviewing, and evaluating, because they do not maintain any drug testing program of their own. There is a real effort to get authoritative information in a readily digestible, easily managed form as promptly as possible. To do this a certain amount of the material in Medical Letter is presented as preliminary appraisals. Naturally it is impossible for the accumulation of experience gathered from the periodical literature to be ready shortly after the introduction of a new drug. Alternations in positions taken in Medical Letters, though uncommon, have occurred, which indicates that they have no claim to infallibility and are giving their considered and studied opinion, but it may be wrong.[2]

"Medical Letter helps the physician judge the accuracy and significance of what may be reported as medical discoveries in the breathless tempo of newspaper and magazine. This may be very valuable in dealing with the insistent but perhaps confused patient who comes in with high expectations waving his clipping and calling for action. In this day of the mass media, we have not found a way to protect the average person, naive in his knowledge of science, biology, and medicine, from the booby traps of his own ignorance.

"Cost and potency of comparable or identical compounds have been brought out from time to time. The lag in getting information about newly reported toxic reactions has been reduced. Recurring audits keep the physician up to date. An evaluation of over-the-counter drug products helps evaluate preparations widely advertised in extensive campaigns and provides a check on the hard face of reality. Thus sturdily realistic and impartial appraisals of drugs are available and can be referred to as a reasonable help in making decisions." [3]

[1] See full text of this letter and other letters included in Competitive Problems in the Drug Industry, Part 8, beginning at p. 3452.

[2] "The Medical Profession and the Drug Industry," Ethical Issues in Medicine. Little, Brown & Co., p. 236, 1968.

[3] "The Medical Profession and the Drug Industry," Ethical Issues in Medicine, Little, Brown & Co., p. 237, 1968.

Senator NELSON. May I interrupt again a moment, Doctor?

Dr. BEAN. Yes, sir.

Senator NELSON. A number of witnesses before the committee, physicians and pharmacologists, as well as representatives of the drug industry, have expressed praise of the Medical Letter as being a very good source of information on drugs and other problems. I am glad to note that you concur.

We also have had testimony on the question of the availability of an adequate objective source of information about all drugs. Representatives of the FDA as well as others have commented on this before the committee. During the last session of the Congress I introduced a bill to create a national compendium of drugs. The Food and Drug Administration has endorsed this bill, so has the President.

The HEW task force did a survey and announced some preliminary results—something like 70 percent of their sampling indicated support for the idea. Have you given any thought to the idea of a national compendium which would list all drugs with indications for use, the precautions and so forth that would be available to all physicians?

Dr. BEAN. As you know, there exist certain books brought out or brought up to date every year. There are two or three books on therapy which are private. They are printed as private ventures by publishing houses quite independent of anything but the usual hope for sales that will take care of them, "Current Therapy" being just an example. It is a sort of a sampling of how several different physicians treat different conditions.

I would agree that an annual that was fairly well up to date would be eminently desirable if this could be kept current in actual fact. Inertia is built into any publishing and distributing venture, even something like the National Library of Medicine's current Index Medicus, which may be anywhere from 3 to 10 months behind in actual appearing when you get it in terms of what is the most recent journal that you refer to.

If a forum or panel or group could do this across the board, so that all available drugs were cataloged in an up-to-date manner in the way you describe, it would be quite advantageous. I have not thought under whose auspices this should be done or how it might be supported financially, but again I think it might be supported like the Drug Index and the Desk References supported by the various manufacturers of drugs to identify their product, to tell the indications, the doses, the forms in which the medicine is available, the methods, whether it needs to be injected and if so how, or can be taken by mouth and so on.

An annual or even more frequently updated document could be made available to all practicing physicians and could be used in teaching, could be used in residents in training, could be used particularly by the doctor in practice, who is writing most of the prescriptions today. This would be much better than the way things are now.

Senator NELSON. Some months ago we had testimony, I believe from Dr. Goddard and others of the FDA, on the question of a compendium. It was their testimony, if my memory is correct, that it would be important to send out inserts on a quarterly basis or at least several times a year in order that the compendium would be kept current.

Dr. BEAN. Some looseleaf format or something else would be desirable, I suppose or essential.

Senator NELSON. Yes. Go ahead, Doctor.

Dr. BEAN. "In a competitive, capitalistic society," and I am quoting again from the book on Medical Ethics, "those who gain the advantage by patenting discoveries have a clearly legitimate claim to profits. In the long run, however, when the pharmaceutical industry devotes so much of its talents to developing minor but patentable variations to deal with the competitive market rather than exploring unexplored territory, the major result is likely to be seen in conspicuous new allotments for advertising rather than a new boom for the sick man or the physician trying to take care of him.

"A company with skill enough to make an original discovery in this field obviously should be rewarded for its effort. If the legal situation to insure this award were clearer, at least some of the troubles would disappear. Even the contemplated revision of the patent laws, however, gives no clear evidence that the ends desired would be achieved. As far as trade names are concerned, if the company making the original discovery were granted the patent, only a single trade name would be needed to be used by licensee as well as discoverer. If a sufficiently different new way were discovered for making the drug, the new discoverer would market it under the generic, or nonproprietary, name, thus at once easing the job of the patient, the pharmacist, and the physician. By reducing the retailer's overhead of multiple duplicating stocks, the same drug with different names, the cost to the consumer would be reduced. The battle of generic names has gone on furiously and there seems to be very little hope that it will abate." [1]

The concept of generic equivalence is not a cut and dried one as we may be led to think since what one really wishes to be able to identify is therapeutic equivalence rather than generic equivalence. In the November 18, 1968, issue of the Journal of the American Medical Association, Dr. Alan B. Varley of the clinical pharmacology department of Upjohn Co. discussed "The Generic Inequivalence of Drugs," differentiating very sharply between chemical equivalence, availability equivalence, that is to say, the amount actually taken into any patient's body which may vary absorption from the digestive tract as well as absorption from injections made under the skin. One would suppose that injections made into the bloodstream would insure any desired level of effective drug. This may not be true if the drug is sequestered in some storage place where it is rendered inactive, is excreted, or changed to an inert form by the body's own mechanisms. If a drug produces an easily measurable effect such as the lowering of blood sugar under the influence of the agent tolbutamide (Orinase), the availability of the drug to the patient may not be directly related to the actual quantity taken if there is a significant effect of the material in which the substance is packed or dispensed.

It was Varley's contention that the data in his study helped establish the point that differences between generically equivalent drugs were not rare or unimportant.

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[1] "The Medical Profession and the Drug Industry," Ethical Issues in Medicine. Little, Brown & Co., pp. 241–242, 1968.

Mr. GORDON. May I interrupt here, Doctor? When I read the article yesterday, I immediately got in touch with the USP and got a letter from Dr. Lloyd Miller,[1] its director. He says the following:

> The data Dr. Varley presents are not at all surprising or particularly new. For years the drug firms have been making and testing experimentally drug dosage forms that have been less than fully satisfactory in comparison with other very similar products. Only comparatively recently have good methods become available to make such tests fruitful. There is very little evidence that such products get out on the market, but we can all agree that then even the risk of their doing so should be minimized.

Let me ask this, Doctor. Is the data sufficient for an objective scientist to determine the validity of the results presented in this article?

Dr. BEAN. All the figures are not given, although many of them are. Much of the information is presented in line graphs and drawings which indicate the averages in a stated number of tests.

This is a field in which I do not claim any special competence. It is not one in which I have done investigation or in which I have spent much time. I did not study the article the way an editor would read to see whether it was acceptable in terms of the security of the data presented and the relationship of the conclusions as far as they agreed with a presumably adequate base of the material presented. I am not evading the issue, I simply am not qualified to make a statement in this particular circumstance. It is something I should have gotten advice on before I came. Taking what he said as he said it impressed me, this again probably should be looked upon as testimony rather than evidence.

Mr. GORDON. Dr. Bean, may I refer to your article, the "Medical Professional Drug Industry," in which you state:

> The physician who is in the pay of pharmaceutical manufacturers is in no position to keep public confidence in his objectivity.

Now, Dr. Varley is in the employ of the Upjohn Co. Do you think that if his results showed the opposite, this would have been published?

Dr. BEAN. Well, I think by the way that you frame the question you have given the answer. It seems to me that it would be not impossible but of the highest order of improbability that such things would turn out against the product; or the man who did it would be turned out. So I think you have answered your own question.[2]

Senator NELSON. I note that the drug firms through the Pharmaceutical Manufacturers Association argue the issue, as they put it, of generic equivalence. I think what they are trying to say is that brand names are better than generic name drugs, although a good many of them, of course, buy generic drugs themselves from such distinguished manufacturers as Strong, Cobb & Arner and then put their own labels on them. It seems to me that that isn't really the issue at all. The industry testified before the subcommittee on several occasions. Not once did they present specific cases of instances where two drugs met USP standards or U.S. Formulary standards, and were not therapeutically equivalent. The testimony of the U.S. Pharmacopeia and the National Formulary representatives is that there are, at most, half

[1] See letter, p. 3966, infra.
[2] Other correspondence related to this matter is on p. 3967, infra.

a dozen instances where it has been proven two drugs meeting the USP standards, had a different therapeutic result.

I think this kind of article by Dr. Varley, as well as continuous publicity by the industry, is an attempt to convince doctors that they should never use anything but brand names and to convince them that drugs that meet the USP standards do not necessarily have the same results. If the USP discovers that a brand name drug does not have the same result as a generic drug and that its standard is not adequate, then the standard is changed. I think the industry knows that pretty well, but I note this in all their advertising. In my judgment it is intended to confuse the medical profession and the public, rather than to inform it.

Mr. GORDON. Doctor, the USP does not have a dissolution rate. Apparently up until this time they have not had a satisfactory test for it. Now, if the Upjohn Co. has developed a method for determining the dissolution rate, isn't it a public and moral responsibility on its part to give it to the USP and the National Formulary?

Dr. BEAN. The question you ask is a very logical and very difficult one to answer. The question in effect is at what stage altruism should take over and at what stage the capitalistic tendency of anybody with an equity in the discovery, the manufacture, the sale of drugs should have that be the determining factor.

This is a little different from the drug industry coming up with a new invention or a patentable variation on a well-known or well-established molecular configuration which is therapeutically effective in one or another of the various circumstances. I don't know what the situation is from the legal point of view at all. I have no notion as to what legal requirement there might be.

From the moral and ethical point of view, it would depend I should think on some judgment as to what was in the long run altruistic and thus better for the patient and to what degree making such a gesture would conflict by providing evidence for not only the Federal testing group but for competitors in this particular field.

Do you know of any precedent in this situation where the problem has come to a solution one way or the other?

The point I suppose is that the majority of such circumstances would not be made known outside of a company which had the particular skill involved, and at what stage they have an obligation to turn that over to the FDA or to those who do the work on the National Formulary. I know how I feel about it, but I don't know that I know enough to tell you to what extent they ought to do this or should not do that.

Mr. GORDON. You have stated Varley's contention, and I assume it is Varley's contention, that "The data in his study helped establish the point that differences between generically equivalent drugs were not rare or unimportant." I don't see how you can come to that conclusion. The only thing he shows is that it is possible for Upjohn Co., to manufacture a tablet which is not as good as another tablet they manufacture, of tolbutamide, which is highly insoluble. It is a compound, as I understand it, which is almost insoluble in water. Now how did he jump from that to his grand conclusion, when there is no such thing as a generic tolbutamide anyhow?

Dr. BEAN. Well, I think you have said it. He jumped, whether he landed upright or not.

Senator NELSON. Thank you, Doctor.

Dr. BEAN. Well, the last two paragraphs in that particular quotation from his article you have dealt with in your question so I think we needn't go further with that. Then I say thus: "There seems to be no doubt that we need more, rather than less, and more careful, rather than less careful, testing of drugs. Limited facilities in medical school or hospital centers, an already overburdened staff in clinical pharmacology might not shift satisfactorily into new lines of work. In medical education, in medical care, in medical ethics, in the extraordinarily complicated problems of precisely what and when death occurs, our institutions and our people seem overwhelmed by complexity. It behooves us then to see what can be done to correct the situation, repair the damage, and make all possible realistic efforts to plan more wisely for the future. It seems unlikely that anyone would condone doctors owning stock in drug companies whose products they are evaluating; special efforts to support special drugs for prescriptions; or doctors paid directly by a drug firm to evaluate its products rather than having it done by a testing panel or a team is certainly questionable. When influential physicians have important academic and administrative posts as drug promoters, the conflict of interest is automatic rather than merely possible. Retainer fees, control of publication, drug advertising, the teaching function of the detail man, each has the special problems of responsibility and honesty.

"It is impossible even to touch many other vitally important aspects of the situation; for instance, the vast industry of quackery, fraud, nostrum, and poison which is so profitable and so hard to control. The use of psychedelic drugs, so widely used, so poorly understood, and so little tested, may have effects that could range all the way from those of an innocuous and banal holiday from reality to one in which psychosis, suicide, or genetic calamity are serious risks. The fact is that these things have simply not been studied. And I think it ultimately comes down to a paragraph in what I wrote back in 1959 about what is the professional responsibility of physicians, and particularly those who are teachers and those who are in the position of testing drugs, those who are doing research, be it basic or applied.

"In 'Ecclesiasticus,' a book which was relegated to the Apocrypha rather than put in the Bible as a result of a curious ecclesiastical popularity contest, we find these words, 'For a man's soul is sometimes want to tell him more than the seven watchmen that sit above in a high tower.' Is our collective conscience too dependent on others at a time when the very word controversial has become anathema? Physicians and responsible members of the pharmaceutical industry have an obligation to examine controversial matters in order that, collaborating effectively, apothecaries and physicians change their ancient traditions of antagonism. Only thus will the best interest of society be served." [1]

That concludes my formal testimony.

Senator NELSON. Thank you, Doctor.

(The complete prepared statement of Dr. Bean follows:)

[1] "Joint Responsibility," Arch. Intern. Med. 103: 685, May 1959.

STATEMENT OF DR. WILLIAM B. BEAN

Assuming public responsibility in matters of drug use, advertising, testing, and control, though critical to the proper function of medicine and the welfare of persons using drugs, is inherently distasteful. It is especially so to physicians. No doubt this is why we neglect it. Seventeen years ago in an address before the Central Society for Clinical Research, entitled "A Testament of Duty: Some Strictures on Moral Responsibilities in Clinical Research," I had this to say about postgraduate teaching.

"What is the most effective general teaching today at the postgraduate level? In sorrow we must admit that the artistic and artful brochures of wealthy pharmaceutical houses, sped on by a crusading band of detail men, have effectively taken over graduate teaching. The blandishments of advertising, siren song of the purveyor of pills, now that there really is a multitude of specifics, puts professional judgment in a sorry place. Harnessed to the lightning strokes of lay publicity, the demand for new miracle drugs often comes from radio or newspaper coaching, and the practitioner, fearing to 'be not the first by whom the new is tried' becomes party to a conspiracy of ignorance, fraud, and twisted idealism which has run the gamut from vitamin craze to spurious cold cures and Hadacol. After all, we have some responsibility in this mess, and must provide leadership to protect the public and embellish the name of medicine. Certainly many pharmaceutical houses are advancing the cause of medicine. More power to them. I do not grudge the honest dollar to the shareholders in drug enterprises, but when their advertising budgets exceed the total outlay for teaching and research provided by all our medical schools concern is justified, 'for where your treasure is there will your heart be also'." (J. Lab. Clin Med., 39:7, Jan. 1952.)

Ten years ago I addressed myself to the broad problem of the relationship of physicians to the pharmaceutical industry in an essay, entitled "Joint Responsibility," published in the *Archives of Internal Medicine* in May, 1959. The main substance of my comments was that a team of physicians and representatives of the pharmaceutical industry should work out voluntarily means of evaluating claims for drugs, evaluating the therapeutic effect of drugs, and then seeing that advertising, sales, detailing, and retailing were managed according to regulations developed by joint action. Thus the manufacturers of drugs and the physician prescribers might best serve their collaborative purpose in preventing, palliating, or curing disease. This plea had very little effect. No formal study, joint effort, or confrontation of producer, distributor, dispenser, and user ever came about. Later the substance of my comments was recorded in presentations before the Kefauver Committee.

Recently in an essay, entitled "The Medical Profession and the Drug Industry," published in *Ethical Issues in Medicine*, Little, Brown and Company, I dealt with the present situation in regard to the ancient confrontation and sometimes antagonism of apothecaries and physicians. Among the comments made were the following:

"At a time when scientific advance was slow and new drugs, such as they were, were likely to be found by painstaking evaluation of herbs and their essences, the introduction of new drugs was uncommon. Therapy, not very effective, was about at a standstill. There was no incentive to go into the mass production of new compounds, for there simply were not enough new compounds. When advances began to develop explosively, the traditional function of ethical pharmaceutical houses was magnified and multiplied, and to some extent the directing forces were removed from individual or family enterprises into the large realm of big business.

"At the same time, there was not at first a comparable awareness or alertness to deal with the increasingly complex problem of drug testing. In any society when problems which are new in kind, as well as new in dimension, arise, its institutions are tested. Unfortunately it turns out often enough that the institutions and organizations, well geared for a slower pace and a simpler set of problems, may prove not only insufficient but dangerous. The evolution of medical practice and medical science as it relates to therapy and the employment of powerful drugs is moving fast but uncertainly. Institutions rarely have a built-in autoanalyzer, a central controlling monitor, to examine and provide a dispassionate critique of purposes, functions, and the capacity to fulfill them. This is why institutions change, or fail and are replaced.

"Human nature being what it is, things may go along until some disaster appears. Some threat becomes ominously evident. Or a general quickening of the moral pulse of the community leads to an investigation or an intervention. Often a crash program of poorly thought out schemes results in passing laws to achieve ends which would be managed much better if collaborative but voluntary arrangements and agreements could be worked out by those concerned. The two parties involved here are pharmaceutical manufacturers on the one hand and the body of medical practitioners, teachers, and investigators, those who must be responsible preservers and protectors of the public, on the other.

"The great majority of pharmaceutical manufacturers have a just concern for their good name and are wary lest this be sullied by entrepreneurs who have come into the field without the traditional background accumulated during the more leisurely days. They have a steady sense of responsibility and wish it to permeate the drug industry. While many of the problems which are of concern to us now have, more or less by default, gone into the hands of external agents or agencies, it is still wise for physicians and those who produce pharmaceutical agents to review jointly their common material problems" (pp. 231–232).

"*Medical Letter* operates as a clearing house, collecting, reviewing, and evaluating, since it does not maintain its own drug-testing program. It has no equity in a compound, but in the truth. There is a real effort made to get authoritative information in a readily digestible, easily managed form as promptly as possible. To do this, a certain amount of material in *Medical Letter* has to be presented in the form of preliminary appraisals. Naturally it is impossible for the accumulation of experience gathered in periodical literature to be ready shortly after the introduction of a new drug. Alterations in positions taken in *Medical Letter*, though uncommon, have occurred. This indicates that they have no proprietary interest in pontification but try to let the facts speak for themselves." (p. 236)

"*Medical Letter* helps the physician judge the accuracy and significance of what may be reported as medical discoveries in the breathless tempo of newspaper and magazine. This may be very valuable in dealing with the insistent but perhaps confused patient who comes in with high expectations waving his clipping and calling for action. In this day of the mass media, we have not found a way to protect the average person, naive in his knowledge of science, biology, and medicine, from the booby traps of his own ignorance.

"Cost and potency of comparable or identical compounds have been brought out from time to time. The lag in getting information about newly reported toxic reactions has been reduced. Recurring audits keep the physician up to date. An evaluation of over-the-counter drug products helps evaluate preparations widely advertised in extensive campaigns and provides a check on the hard face of reality. Thus sturdily realistic and impartial appraisals of drugs are available and can be referred to as a reasonable help in making decisions." (p. 237)

"In a competitive, capitalistic society, those who gain the advantage by patenting discoveries have a clearly legitimate claim to profits. In the long run, however, when the pharmaceutical industry devotes so much of its talents to developing minor but patentable variations to deal with the competitive market rather than exploring unexplored territory, the major result is likely to be seen in conspicuous new allotments for advertising rather than a new boon for the sick man or the physician trying to take care of him.

"A company with skill enough to make an original discovery in this field obviously should be rewarded for its effort. If the legal situation to ensure this award were clearer, at least some of the troubles would disappear. Even the contemplated revision of the patent laws, however, gives no clear evidence that the ends desired would be achieved. As far as trade names are concerned, if the company making the original discovery were granted the patent, only a single trade name would be needed to be used by licensee as well as discoverer. If a sufficiently different new way were discovered for making the drug, the new discoverer would market it under the generic, or nonproprietary name, thus at once easing the job of the patient, the pharmacist, and the physician. By reducing the retailer's overhead of multiple duplicating stocks, the same drug with different names, the cost to the consumer would be reduced. The battle of generic names has gone on furiously and there seems to be very little hope that it will abate." ("The Medical Profession and the Drug Industry," *Ethical Issues in Medicine.* Little, Brown and Company, pp. 241–242, 1968.)

The concept of generic equivalence is not a cut and dried one as we may be led to think since what one really wishes to be able to identify is therapeutic equivalence rather than generic equivalence. In the November 18, 1968 issue of the *Journal of the American Medical Association*, Dr. Alan B. Varley of the Clinical Pharmacology Department of Upjohn Company discussed "The Generic Inequivalence of Drugs," differentiating very sharply between chemical equivalence, availability equivalence, that is to say, the amount actually taken into any patient's body which may vary absorption from the digestive tract as well as absorption from injections made under the skin. One would suppose that injections made into the blood stream would insure any desired level of effective drug. This may not be true if the drug is sequestered in some storage place where it is rendered inactive, is excreted, or changed to an inert form by the body's own mechanisms. If a drug produces an easily measurable effect such as the lowering of blood sugar under the influence of the agent tolbutamide (Orinase), the availability of the drug to the patient may not be directly related to the actual quantity taken if there is a significant effect of the material in which the substance is packed or dispensed.

It was Varley's contention that the data in his study helped establish the point that differences between generically equivalence drugs were not rare or unimportant. The evidence that he presented indicated that it was "possible to produce considerable differences in both availability of drug to human patient and in eventual therapeutic usefulness by making tiny changes in the formulation which are clearly within present USP chemical equivalence standards.

"It is not my contention that generic, therapeutically equivalent drugs cannot be formulated. Quite to the contrary. It is my contention that criteria for establishment of equivalence cannot be made by chemical and physical standards as they are now established in the USP, unless one is not interested in the patient's therapeutic response which concerns most physicians.

"Without question, the ideal criterion for establishment of therapeutic equivalence is trial of comparative efficacy in appropriately disease-afflicted patients. While not within the scope of data presented in this communication, this is a concept probably not feasible in the context of today's clinical research methodology and standards of ethical medical research. Inasmuch as chemical or USP-type specifications are clearly not a satisfactory answer, the medical world is left with drug availability as the present most sensible and feasible way of establishing generic equivalence of drugs" (JAMA, 206:1748, No. 1968).

Thus there seems to be no doubt that we need more, rather than less, and more careful, rather than less careful, testing of drugs. Limited facilities in medical school or hospital centers, an already overburdened staff in Clinical Pharmacology might not shift satisfactorily into new lines of work. In medical education, in medical care, in medical ethics, in the extraordinarily complicated problems of precisely what and when death occurs, our institutions and our people seem overwhelmed by complexity. It behooves us then to see what can be done to correct the situation, repair the damage, and make all possible realistic efforts to plan more wisely for the future. It seems unlikely that anyone would condone doctors owning stock in drug companies whose products they are evaluating; special efforts to support special drugs for prescriptions; or doctors paid directly by a drug firm to evaluate its products rather than having it done by a testing panel or a team is certainly questionable. When influential physicans have important academic and administrative posts as drug promoters, the conflict of interest is automatic rather than merely possible. Retainer fees, control of publication, drug advertising, the teaching function of the detail man, each has the special problems of responsibility or honesty.

It is impossible even to touch many other vitally important aspects of the situation; for instance, the vast industry of quackery, fraud, nostrum, and poison which is so profitable and so hard to control. The use of psychedelic drugs, so widely used, so fully understood, and so little tested, may have effects that could range all the way from those of an innocuous and banal holiday from reality to one in which psychosis, suicide, or genetic calamity are serious risks. The fact is that these things have simply not been studied.

"In 'Ecclesiasticus,' a book which was relegated to the Apocrypha rather than put in the Bible as a result of a curious ancient ecclesiastical popularity contest, we find these words, 'For a man's soul is sometimes want to tell him more than the seven watchmen that sit above in a hightower.' Is our collective conscience too dependent on others at a time when the very word controversial has become

anathema? Physicians and responsible members of the pharmaceutical industry have an obligation to examine controversial matters in order that, collaborating effectively, apothecaries and physicians change their ancient traditions of antagonism. Only thus will the best interest of society be served" ("Joint Responsibility," *Arch Intern Med*, 103 : 685, May 1959).

Senator NELSON. You have touched upon the question of financial relationship between drug companies and physicians or institutions, medical schools, and so forth.

Many doctors and others have commented on this kind of relationship. We intend to explore the matter in much greater depth than we have thus far. But, for example, many medical journals, including the Journal of the American Medical Association, receive substantial sums of money for advertising from the drug companies. Does this raise, in your judgment, a serious question?

Dr. BEAN. Well, it certainly raises a serious question. The problem may be solved or may be left unsolved in a variety of ways. It depends, I think, to some extent as to who controls the editorial policy and who may veto or select or set the standards for advertising. This has varied with different circumstances.

For instance, if a journal is the property of a medical society, the medical society assumes responsibility through an editorial board and an editor for not only the editorial content but all other features of the journal, including the advertising.

Having been an editor for a good many years of one of the journals published by the American Medical Association, the Archives of Internal Medicine, I was allowed to look ahead of time at all of the copy for advertising, and on only two occasions did I come upon things that I thought were either in such outrageously bad taste or were scientifically invalid that I requested, and this request was acceded to, that the material not be used, or it was changed in an appropriate way.

I was in a position not of setting the policy, and my request of veto might itself have been vetoed in the circumstances of my arrangement with the American Medical Association, since the last say was in the hands of the chief editor of the Journal of the American Medical Association, and the 10 archives specialty journals.

If a journal is owned by a publishing house, and if this is a commercial venture, then the responsibility of the publishing house or of the editor becomes the determining factor in what is accepted and what is not accepted, and as an example of in effect what amounts to an independent journal, the New England Medical Journal, which is one of the very fine ones, the determination and the acceptance of advertising is in part determined in the first place by whether or not the American Medical Association has accepted it, and this, therefore, becomes a kind of a model, not by rule but by custom. They may find other reasons for objecting or refusing advertising, which are determined by a fairly independent editor and the editorial board.

This journal is the effective representative of all of the New England States, although their connection as medical societies with the journal is somewhat diffused, because it isn't one State—one journal, as it is with the majority of State journals. So there is no question but that there is a temptation, and this may operate at the conscious or the unconscious level, of a selection in which articles being unfavorable

to the use of drugs which had been heavily advertised in a journal might present qualms of consciousness, if they were not published freely, even though they might say things that weren't favorable to the promoter of a particular form of drug under those circumstances.

I am not aware of any overt coercion in any of the reputable journals, but I can conceive that this might well happen, that there might be pressures to publish papers that were favorable to the use of a particular drug. I simply haven't run into that as a personal problem. I was dealt with, I think, very liberally by those who were superior to me in the American Medical Association, and who might have objected to my request for deleting a particular thing. I didn't exert the option often. It was not a common problem.

I don't know whether that answers your question or not, but I think the temptation and the risk is there, and it would depend on the scruples of the editor and the pressures which beset him, and whatever adjustment or compromise he might make under those circumstances.

Senator NELSON. As I say, we have not gone into this in depth yet. It does seem to me, however, that if any journal receives a significant amount of its income from a certain advertising source, that the pressure is there, with nothing being said.

The other question that would seem to me to cause some concern is the example we have had, with some extensive testimony before this committee, on chloramphenicol. We had five or six very distinguished and nationally recognized authorities in various fields, including Dr. Dameshek from Mount Sinai, a recognized authority on hematology, who has written on chloramphenicol in the AMA Journal and other professional journals.

Frankly, what concerned me is that chloramphenicol was widely advertised in the AMA Journal. I looked at the number of the ads.

Now, as a person who is not a physician, I thought the ads were quite clever. However, I thought they were misleading, after carefully reading the literature, as to the indications for use of the drug, and looking at the ads. Now, maybe it wouldn't be misleading at all to a qualified physician.

But in testimony before the subcommittee—unrefuted by the company itself—five or six witnesses stated that from 90 to 99 percent of the persons receiving chloramphenicol were receiving it for nonindicated cases. One of the doctors thought 10 percent was for indicated cases, and one of them thought less than 1 percent.

As an example, here we have a drug that is being widely advertised in medical journals, including the Journal of the American Medical Association; 3½ to 4 million people received the drug in 1967. Yet, Dr. Goddard, in testimony before the committee, said that he was at his "wit's end" as to how to stop physicians from prescribing the drug for nonindicated cases. I raised the question that someone in the medical profession must be at fault. It shouldn't take a congressional committee to expose the fact. After wide publicity, as a result of our hearings, and after Dr. Goddard's testimony, FDA sent a "Dear Doctor" letter to 200,000 physicians throughout the country defining and limiting the use of the drug. Following this, batch testing dropped from 23 million grams in the first 6 months of 1967 to

4 million grams in the first 6 months of 1968, down to zero in terms of batch testing in June of 1968. This was a very dramatic drop as you can see.

I raised the question at the time that it seemed to me the medical profession was grossly in default of its responsibilities to allow this situation to go on for years, with distinguished people in the medical profession knowing it, the AMA knowing it, and the journal accepting ads.

I think it raises a serious ethical question and it raises a serious question in the mind of the public, valid or not, as to the objectivity of the AMA for not just screaming to the high heavens, to all the doctors in America, that the drug which is widely advertised and promoted is being vastly overprescribed, to the great detriment of many, many people.

This is the kind of question it raises for me. Do you agree?

Dr. BEAN. I think that is a very legitimate question and I think your interpretation is right. The medical profession is sort of easy to name. Then you begin to name and think of particular doctors. Let me just give you my experience.

In our teaching program in the medical school at Iowa we have a very active hematology section and to the undergraduate and postgraduate courses and in the local State journal and in national journals, and especially in hematology journals, the position that you say has been supported by the consultants who have discussed the matter with your subcommittee here has been sustained and maintained, and on the local scene for many, many years the drug was not used except for that five plus or minus percent of people for whom no other equally good drug was available and where the known risk which is numerically small but in terms of the severity of what happens is formidable, and so the people were taught and told about this. The AMA Journal and some of its subspecialty journals, the Archives of Surgery, the Archives of Internal Medicine, have had a number of articles dealing with the hematological bad effects of the drug.

It is very evident from any rational or any ethical or moral point of view, if you have a drug, excellent as it may be in the great majority of instances, that has a danger, serious danger, though not very often, you have to make a judgment about what level and what kind of disease you would require to occur before you used it, realizing that there is this risk, and that the problem is particularly serious in children. It has certain circumstances where it may be much worse to use it than in others. It is effectually a cure for typhoid fever and some of the other conditions which fortunately we don't have to use it for very often.

So I would agree with you that this is a situation which the medical profession has dealt with on a more or less personal basis, with experts in the field all agreeing, with many papers being available that show this, and it indicates perhaps two things. One is a breakdown in the lines of communication, where simply issuing information and printing it in a journal doesn't tell people, because they don't read it, and the other thing is that when a circumstance of this kind exists, there has been no body in medicine which took responsibility automatically, when such things come up.

Now there is afoot interest in forming what may become a National Academy of Medicine, with analogies or perhaps direct relationship either tandem or in parallel with the National Academy of Science. It might concern itself with many problems upon which the Government, the lay public, the pharmaceutical industry, and the medical profession needs firm and authoritative counsel. It may be able to provide this and thus head off difficulties in the future which otherwise are not likely to be studied because nobody, or very few are willing to spend the time and effort and incur the unfavorable comments of people who think that they are appointing themselves the conscience of American medicine.

This is simply human nature, which on the one hand has a profound built-in inertia, and on the other hand is much more anxious to do something that brings praise or glory than brings blame, no matter how praiseworthy what they do may be in bringing blame or odium of some kind or other.

I don't deny that this is a deficiency. It is a glaring one. It is a sad commentary on the present situation. I hope that we will be able to develop the corporate wisdom in medicine to correct such things as they may appear especially where one could not anticipate them ahead of time, as, for example, the thalidamide situation, unless the drug had been tested in a great many pregnant women it wouldn't be known that it might cause a disaster under these circumstances although it could be taken with impunity otherwise.

I would agree that this is a sore and serious point of neglect. We need to do something about it, and I hope that there will be developed along the lines I have mentioned a group which will automatically assume the monitoring watchdog function. This has not existed except within the individual conscience of individual physicians, and unfortunately this is not strong enough to be an impelling force to make many people speak out forthrightly on various controversial issues, and very obvious situations.

Senator NELSON. One of the experts who testified on this subject stated that of all the cases he had seen of aplastic anemia caused by chloramphenicol, he had never in his career seen a single case in which the drug was administered for a properly indicated case. This gets back to the question of the advertising and promotion.

All this advertising and promotion occurred in medical journals or through detail men or in the direct mailing of brochures to the physician. I am sure there isn't a physician in the United States who, if he really realized the consequences, would administer the drug, as the testimony demonstrated, for cases of acne, sore throat, headache, infected teeth or infected hangnails. But it is pretty clear the advertising and promotion, especially the detail men, convinced the physician that this was a general use, broad spectrum antibiotic.

I looked at the ads myself some months back and can quote several ads which simply said that "When it counts—Chloromycetin," not a word about precautions, contraindications, and side effects, but just a continual pounding of very clever ads, "When it counts—Chloromycetin." It was quite successful in promoting the drug.

It seems to me it raises a very serious ethical question within the profession itself, when doctors responsible for the medical journals

know very well that it is being widely misused, and yet are accepting ads that successfully convince the doctor to prescribe it for nonindicated cases. In fact, the same journals carry articles by doctors such as Dr. Dameshek cautioning against this kind of use, while at the same time they carry the kind of clever ads that end up promoting this kind of use. Doesn't that seem to raise a serious ethical question?

Dr. BEAN. It absolutely does, and I think you have to take into effect human nature again. Man has been defined as the pill-eating animal or the medicine-taking animal, and there seems to be some instinct that exists that is satisfied by the ingestion of medicine which may symbolize the power of the physician or the power of medical knowledge.

The change that has occurred is in part perhaps a reflection of I won't say the decay or decline of morale but a period of change in which responsibility is not perhaps so routinely or regularly assumed by those who should assume it, and there is no question but that under these circumstances in the nature of things, tragedies will occur, and that I think the blame can be laid nowhere but on the medical profession.

The best chance of some effectual monitoring will be a body of, we hope, wise physicians who will get together and, with their corporate power, be able to put things in their proper place, and be able to take the aggressive initiative in seeing that these things are done.

It is when things go bad or when mistakes are made or when duty hasn't been done, it is fairly easy to identify what is wrong, it is not nearly so evident in the problem of how you treat a particular patient. It would be wonderful if all proper physicians included, had perhaps a sterner and more upright moral and ethical outlook. It would be wonderful if this pervaded also those generally older, more conservative men who come to be effectual administrators within medical organizations, particularly the big ones, where the power structure accumulates in those who tend in their nature to be conservative, older, and so on.

I think the best chance of coming to a solution is to have an independent medical body which will take upon itself responsibility in identifying problems and acting upon them and avoiding just such things—one could mention a great many, as Krebiozen, mineral oil being sold under high pressure to people who are in an agitated state because of tragic disease. There is no evidence, only testimonial assertions that it did anything. But even knowing this, the decisions about it have been determined before juries, a popularity contest rather than a scientific evaluation.

Senator NELSON. What scientific value is there in the kind of promotion of drugs we see? I think you comment that more money is spent on drug advertising than on all of medical education. Was that your comment or were you quoting from somebody else?

Dr. BEAN. I made that comment.

Senator NELSON. More than the whole cost of medical education? How necessary and valuable is it to have the kind of full-page ads we see in medical magazines and all the brochures? How useful is that to a physician? Or to put it another way, is it useful to him at all? Or is there another way that he could get the information that would be more reliable and that wouldn't be misleading?

Dr. BEAN. Well, it seems to me the very nature of the question suggests the operational answer, and that much of this is ineffectual in terms of an educational value which is objective. It does have a certain amount of information which gets to people that might not otherwise get there, and even allowing for the fact that it may, in terms of competition for the sale of drugs be somewhat biased, it may still get information to a physician who might not otherwise get it.

I don't think this happens in the majority of instances, and I don't think it should happen, and to some extent this is a reflection of two things, the enormous increase in the actual effectiveness of a multitude of powerful specific drugs to do a lot of things in medicine, and the inevitable parallel circumstance that undesirable effects are more or less in parallel with the desired effectiveness.

For instance, if you have an anticancer drug, this is a drug that kills cells, and it is going to kill some cells that aren't cancer cells. You have to try to devise such a drug with most of the effect that you do want and little of the effect that you don't want. In the nature of the biological situation, we probably will never find a perfect drug.

Under these circumstances the problem of how one gets information to those who are perhaps in many ways reluctant to take it has been the brochure, the detail man, the sample, and the ad in the journals that the physician is supposed to look at.

I think that the answer to your question is almost automatically evident in the fact that you ask it. A very considerable part of advertising is not primarily education, and in many instances is not necessary at all.

Mr. GORDON. Doctor, I have here some documents which are part of the public record in a court case against the William S. Merrell Co. on MER–29; I don't believe these documents have been made public. However, they are part of the case.[1]

Here is a document dated April 19, 1960, an interdepartmental memorandum of the William S. Merrell Co.[1] It is from R. H. McMaster, medical doctor to Dr. R. L. Stormont. It is about Dr. Hyman Engelberg and they say as follows:

> Although it begins to appear that any report from this study may be a negative one, we may find that we are money ahead to keep Dr. Engelberg busy at it for a while longer rather than to take a chance on his reporting negatively on so few patients.

We are talking about MER–29 now. And then in the next paragraph they say:

> My personal recommendation is that the grant-in-aid be approved only to keep Dr. Engelberg occupied for a while longer.

Another document dated August 19, 1959, to Dr. Van Maanen from the medical research department[1] says:

> I am strongly opposed to the discussion of any finding from experimental animals until we have agreed upon our interpretation.

Further on they say:

> In this case, I do agree that we can show the pictures to our investigators in Syracuse, but it is acknowledged that we are taking a calculated risk because

[1] See p. 3970, infra. See also appendix V, "The MER–29 Case," beginning at p. 4202, infra.

of a great moral and ethical problem involved. Because of the careful selection of our investigator in Syracuse, I think that it is a reasonable risk for us to take.

For example, in talking about a fee to Dr. Hollander, of Boston, Dr. Hollander mentioned the matter of his consultation fee,[1] and then at the end they say:

My own feeling is that we can't afford to chance alienation of Hollander just now. Perhaps I shouldn't regard this as blackmail.

In another interoffice memorandum [1] a company officer says:

The objective in contacting the Armed Forces was to lay the groundwork for the eventual sale of the product to the various hospitals serving each branch of the Armed Forces when the product is released.

Now, note this:

We are not thinking here so much of honest clinical work as we were of a pre-marketing softening prior to the introduction of the product.

What do you think of all this?

Dr. BEAN. Well, it is unspeakable. I don't think anybody anywhere would condone that. I don't know why I should say selectively that I disapprove completely of everything that you reported there, but that is the fact.

Mr. GORDON. This was during the development of an investigational new drug, and this is what went on. In addition, the firm got a doctor to sign his name to a letter which was written by the company. The letter was then sent by the doctor to the Medical World News. It was then used as a testimonial to the Food and Drug Administration. The company also sent a copy of the letter to all its detail men, with the caption "Dr. Lisan Speaks Up." [1] So the detail men went to doctors saying: "Here is Dr. Lisan of Philadelphia, who says this," when it was actually the company who was saying it.

Also in another memorandum [1] we have the following quote:

Dr. Becker's paper, prepared for the most part by (Richardson Merrell) was rejected by the American Journal of Cardiology and has now been accepted by the Journal of the Medical Society of New Jersey. We have received permission to purchase reprints.

I ask Mr. Chairman, that these documents be put into the record at the appropriate place.

Dr. Bean, in the chairman's opening statement, his last question is "When influential doctors or pharmacy educators, particularly in high academic positions, are large stockholders and/or serve as policy-setting members of boards or drug corporations, since these men are in a position to mold the attitudes of other doctors and to make policy decisions in key medical and pharmaceutical organizations might there not be a conflict of interest here?"

Would you comment on that?

Dr. BEAN. Well, let me put it in a personal frame of reference. I would find it impossible or perhaps intolerable if I were on a retainer fee from any concern, be it drug firm or book publisher or anything else to be put in a position where I had to offer independent informa-

[1] See pp. 3971–73, infra.

tion, advice, teaching, testimony, or whatever. I don't believe that it is possible, it wouldn't be possible for me to act in an unbiased way under these circumstances.

It seems to me this is quite different from acting under contract on a specific function someone might wish to have a certain subject reviewed or an opinion given to somebody who would then pay you as a consultant for this particular thing, but this is quite different from being in the pay, without any special requirement, but with the inference I think overwhelmingly evident, and with the legal requirement also, I believe that one who is a member of a board of directors or who is in the employment of a different firm rather than, say, an educational, or a medical, or a hospital, or a practice arrangement, I think it is nearly impossible for people not to allow that to influence them. I don't say it is impossible. I guess it is possible, but it would be impossible for me not to be influenced under those circumstances.

Therefore, since I don't keep secrets well, and since I believe that what I know is freely available, and I like to let people share it if I think it is going to help, I would find this personally an intolerable operating scheme for me, but I can reckon that there are people of such powerful goodness and rectitude that they might be able to divorce themselves from this relationship in interpreting, teaching, or doing other things, but this must put them under a great deal of strain. Therefore it seems to me the part of wisdom to avoid not only the suspicion of evil, but the temptation to evil, if you think these things are evil.

Mr. GORDON. I would like to mention to you that an analysis of the responsibility of directors to the stockholders of a corporation is included in a memo from the Library of Congress.[1] One of the sentences reads as follows:

> While directors are not strictly speaking trustees, they do occupy fiduciary, or perhaps more accurately, a quasi-fiduciary relation to the corporation and its stockholders. Each director must exercise his unbiased judgment, influenced only by considerations of what is best for the corporation. Many courts have spoken of the rule as being that a director owes a loyalty that is undivided and an allegiance that is influenced in action by no consideration other than the corporation's welfare.

Now, what do you think of a director of a company, who is also an academician, who writes articles and delivers speeches, and does not disclose his identity as director of the company?

Dr. BEAN. Well, I don't think anybody could say anything good about that situation. It doesn't seem to me to be under any circumstance, the law being what it is—which I was not aware of, although I am not surprised that is true—the difficulty of serving two masters is not a problem, if they are both aiming in the same direction and they have almost superimposable functions. But where they are in conflict and you are aiming in two different directions, you have to make a decision either to do nothing or to go in one direction or the other.

Under these circumstances therefore it seems to me it is not only the part of rectitude but the part of wisdom to identify the hat that you may be wearing under the circumstances of a particular statement, or a particular article, or a particular speech, so that people will know where your bread is being buttered from and on which side.

[1] See p. 3973, infra.

Mr. GORDON. I might bring up a specific case. Here I have a book entitled "The Medicated Society." There is an article in it, "The Contributions of the Pharmaceutical Industry," by Chester S. Keefer, medical doctor, former dean of the Boston University Medical School, and who is also an adviser to government. This particular article is very laudatory of the industry. It was taken from a Lowell Institute lecture. Not once, in the lecture which I read, nor in the article which is in the book, does he mention the fact that he is a director of Merck & Co.

Dr. BEAN. It seems to me to be, if an oversight, a flagrant one. If it is something else, I am greatly surprised that Dr. Keefer, who is a good friend of mine and an admirable man, has put himself into this awkward situation. I don't see how you can deny that it is awkward.

Senator NELSON. Doctor, I want to thank you very much for giving us so much of your time to come here and testify before the committee. We appreciate very much your contribution to these hearings.

Thank you.

Dr. BEAN. Thank you.

(The supplemental information submitted by Mr. Gordon follows:)

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SELLING DRUGS BY "EDUCATING" PHYSICIANS*

(By Charles D. May, M.D.†, Department of Pediatrics, College of Physicians and Surgeons, Columbia University, New York)

The traditional independence of physicians and the welfare of the public are being threatened by the new vogue among drug manufacturers to promote their products by assuming an aggressive role in the "education" of doctors. In the recent Congressional investigation of the cost of drugs it was repeatedly stated by executives of pharmaceutical concerns that a major expenditure in the promotion of drugs was the cost of "educating" physicians to use the products—and they mean doing what has always been expected of medical institutions. Is the public likely to benefit if practicing physicians and medical educators must perform their duties amidst the clamor and striving of merchants seeking to increase the sales of drugs by conscripting "education" in the service of promotion? Is it prudent for physicians to become greatly dependent upon pharmaceutical manufacturers for support of scientific journals and medical societies, for entertainment, and now also for a large part of their education? Do all concerned realize the hazard of arousing the wrath of the people by an unwholesome entanglement of doctors with the makers and sellers of drugs?

That these are grave and pressing questions and not trivial fears should become apparent in the ensuing presentation of problems that surely deserve the serious attention of manufacturers, prescribers, and consumers of drugs. No one can be oblivious to the many fine contributions of both doctors and drug companies that certainly deserve the greatest admiration, but the dark side of things must be fully explored if the origins of the present problems are to be determined. The higher purpose of this analysis is to halt practices which are undermining sound medical care as well as degrading the reputation of the pharmaceutical industry and lowering the prestige of the medical profession—to a degree that has already aroused public concern and the probings of politicians.

*The author submitted this manuscript for critical review to the Physicians' Council—an independent group of eighteen eminent physicians who organized in 1956 "to seek means for maintaining high standards for the material on health that is disseminated through the media of mass communication." The Physicians' Council wishes it to be known that it endorses this essay as an accurate, equitable, and constructive analysis of matters of major importance in relations between the medical profession and the pharmaceutical industry. Reprints will be available from the Physicians' Council, 2 East 63rd Street, New York 21, New York.

†Clinical Professor of Pediatrics.

After a general discussion of the deleterious practices, some specific proposals will be offered for preserving proper relations between physicians and manufacturers of drugs and thus spare them from unfortunate experiences in public investigations.

PROMOTION AS "EDUCATION"

Surely physicians realize that they cannot have faith in all drug promotion, but many assume that at least some reputable firms can be depended upon to consistently disseminate reliable information. The soundness of this assumption can be tested by a look at some current specimens of advertising. These items are from a considerable supply of the same kind, and regular scrutiny of the torrent reaching the physician will satisfy the curious that similar examples are easy to find. It will be seen that well known firms are guilty of sponsoring dubious "education" material on topics of vital importance, and so the physician is left without any assurance of authenticity except from his own wits.

Antibiotics.—Antibiotics are therapeutic agents which no one can deny should be used intelligently and with discrimination. Efforts to influence physicians to prescribe these valuable remedies on an unsound basis would be particularly unfortunate; only clear and accurate information should reach the doctor.

For the past 3 years major pharmaceutical companies have been engaged in a competitive struggle to increase the sales of their particular brands of antibiotics by a confused and misleading barrage of promotion (Figs. 1–3). The exuberant campaign was based on meager and poorly controlled observations on the levels attained in the blood by various preparations of antibiotics; additions of certain agents (phosphate, critic acid, glucosamine) were claimed to enhance the absorption of antibiotics and enable higher levels to be reached in the blood more promptly.

Soon after this hectic campaign was well under way, the premise was challenged (9, 14): actually, the action of these agents was to neutralize the unfortunate effects of fillers used in the capsules of the antibiotics—these were calcium salts that combined with the antibiotics and hindered their absorption. When the various forms of antibiotics are administered to fasting persons without fillers, no advantage is observed from addition of phosphate, citric acid, or glucosamine to the plain parent compounds (10). Furthermore, no sound evidence was ever brought forth that the levels and speed of absorption claimed for the widely heralded derivatives offered any practical clinical advantage or therapeutic superiority.

Pointed criticism from competent authorities did not check the eagerness with which the promoters undertook to "educate" the physicians with inadequate and irrelevant data and misleading claims in material distributed for the drug companies. Note the triumphant tone in the examples of promotional material from this campaign—this is the sort of inconsequential contribution the industry sometimes refers to proudly as the result of great investment in research in the companies' own laboratories. This achievement consisted of getting rid of the inhibiting effects of filler the manufacturer customarily used in the capsules of such products.

The "educational" effect on doctors was to confuse them and lead them to believe wonderful new drugs were available and that minor differences in blood levels and the rate of absorption are significant therapeutic advantages.

Similar tactics are now being applied to a derivative of penicilin (Fig. 4). The same substance is put forth under at least six brand names as if it were the discovery of each distributor. It is also slyly touted as synthetic penicilin while it is only a chemical modification of a fermentation product that is not isolated in pure form (15). The same chatter about higher levels being attained faster, without proof of clinical advantages, characterizes this latest "educational" material reaching the doctor. Once again evidence is lacking to prove the clinical superiority of the new derivative; the old penicilin V can be absorbed about as well if administered on an empty stomach (13).

No amount of pleading (7) has discouraged the pharmaceutical industry from marketing and pushing products made up of mixtures of antibiotics. An example of low regard for the intellect of the average doctor is the promotion of Panalba by Upjohn (Fig. 5), where one is asked to believe an *in vitro* sensitivity test is a demonstration of clinical "performance in pneumonia" (no references to clinical

NOTE.—Numbered references at end of article.


"...an improvement
and an ultimate replacement
for the older tetracycline
hydrochloride"[1]
Tetrex
THE ORIGINAL TETRACYCLINE PHOSPHATE COMPLEX
Clinically proven—It has been determined that "blood concentrations correlate well with clinical response."[4] In clinical studies, the assurance that TETREX "would be more effective [than tetracycline HCl] in treating infections due to susceptible organisms"[11] has been fully confirmed.
Typically, when TETREX was administered to 686 patients in two studies, "all patients infected with tetracycline-sensitive organisms responded satisfactorily to therapy."
A "remarkably low incidence of side reactions" has been reported. In four studies involving 480 patients, for instance, side effects were so negligible as to require withdrawal of therapy in only 2 cases.
BRISTOL LABORATORIES INC., SYRACUSE, NEW YORK
TETREX Capsules
TETREX Pediatric Capsules
TETREX Intramuscular '250' with Xylocaine
TETREX Intramuscular '100' with Xylocaine
TETREX Syrup
TETREX Pediatric Drops
TETREX-APC with BRISTAMIN Capsules
References:

FIGURE 1

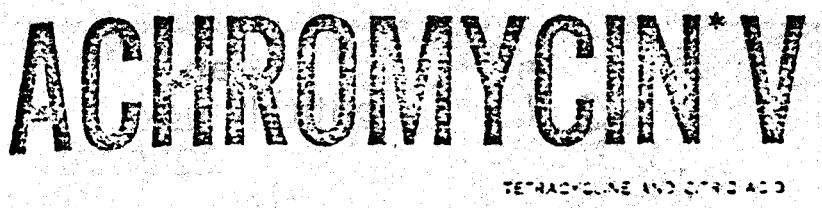

FIGURE 2

trials). The nature of this combination is kept obscure by giving the company's brand names of the ingredients. What will this kind of "education" do to the physician after a few years of domination of his habits and beliefs?

How can one gain confidence in promoters as educators or believe in their sincerity in view of these typical disclosures? There is an astonishing disregard for expert opinion and the complaints of responsible physicians even in the present trend to repeat the tactics that characterized the promotion of "potentiated" tetracyclines in the current advertising of "synthetic" penicilin.

The untrustworthiness of "educational" material employed to promote basic products is not peculiar to antibiotics. Similar disregard for the available evidence and for authoritative opinion can be seen frequently in the advertisements used by leading ethical pharmaceutical firms to instruct doctors.

REVEALING ECONOMICS

It has been estimated (1) that drug companies selling their products through doctors' prescriptions spent $750,00,000 in 1959 on promotional activities. How much of this sum was truly directed to "education" is a moot question. Advertising in medical journals and by direct mail to physicians amounted to $125,000,000. The expense of maintaining the army of 15,000 detail men busily engaged in spreading "education" must account for a huge portion. The remainder went for exhibits, films, trade publications, lectures, televised clinics, samples, etc. All this huge sum was in the last analysis devoted to one prime purpose—to get the physician to prescribe products of particular firms by brand names.

FIGURE 3

Whether various aspects of this immense promotional campaign are labeled as advertising or education, the medical profession and the public cannot safely ignore its effects on either the cost or the physician's use of drugs. The success of the promotional activities depends on gaining an influence over the habits and beliefs of the prescribing physician ("the funnel through which all ethical drug sales must pass"). Two-thirds of the spending for drugs and medications is attributed to items prescribed or recommended by a physician or a dentist, and these absorb 20 per cent of the funds spent by the public for personal health care. Between 1952–53 and 1957–58 the expenditures for drugs and medications increased 120 per cent (1.5–3.3 billion dollars), but the spending for physicians' services rose much less, or 42 per cent (3.8–5.4 billion dollars) (18). The item of interest here is in the share of the health dollar absorbed by expenditures for drugs (an increase from 15 to 20 per cent in 5 years) compared with the portion spent for physicians' services (a decrease from 37 to 34 per cent in 5 years).

Another way of appreciating the factors involved is to note the changing picture revealed by estimates of the increase in the *use* of drugs (in contrast to merely a

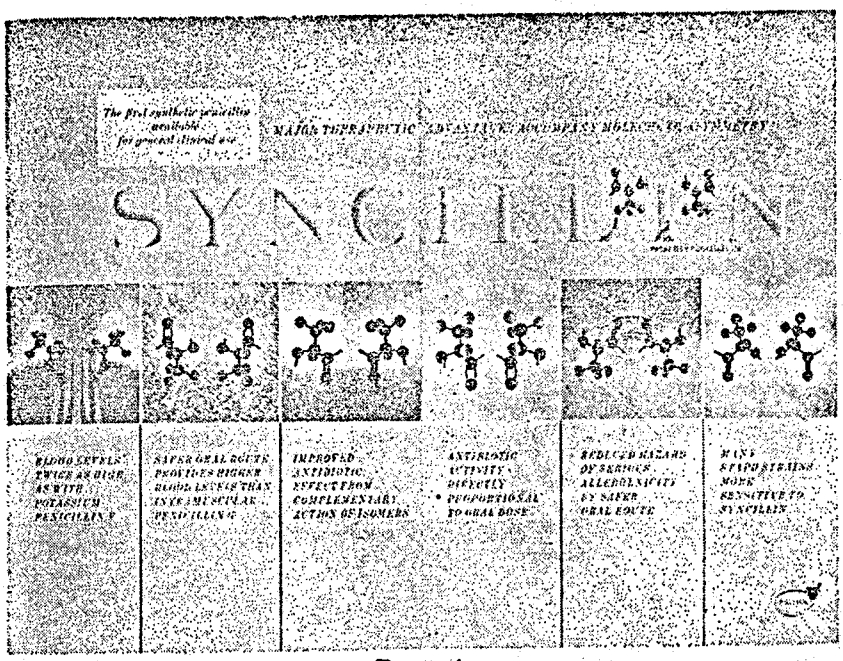

FIGURE 4

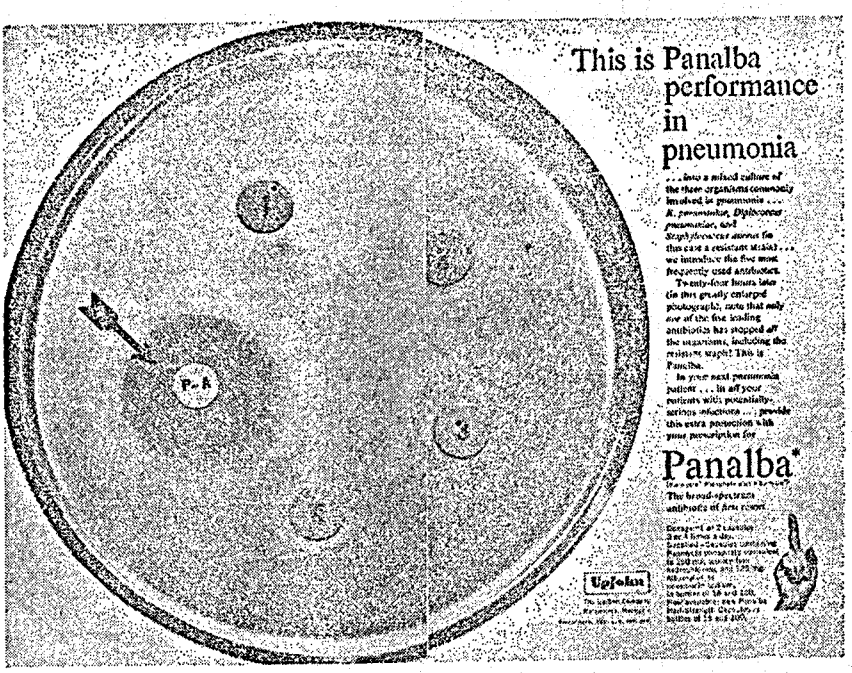

FIGURE 5

rise in the price of drugs). In the 5-year period bteween 1952–53 and 1957–58 there was an increase of expenditures due to rising costs of drugs of only 9.5 per cent, but there was a 73.5 per cent increase in the use of drugs (18). Consider these figures in relation to the outlay for drug promotion in the same period: Between 1953 and 1958 expenditures just for advertising in medical journals and by direct mail to physicians increased by 219 per cent to reach the all-time high of $125,000,000 (1). By contrast, the total funds available to all medical schools in the United States for their educational programs in 1957 was only slightly greater, $200,000,000.

THE QUESTION

There is no way of ascertaining the extent to which improvement in the health of the population is due to a contribution of the medical profession, the achievements of drug manufacturers, public health measures, or socioeconomic conditions. It is evident to everyone that the pharmaceutical industry has made an important contribution to the public health and to the treatment that can be administered by physicians. The pharmaceutical industry and the medical profession have come to occupy prominent places in our society, and we must deal with them as permanent and useful enterprises.

The principal subject under consideration here is the possible impact of promotion tactics aimed at "educating" the physician on the character of medical practice and on the extent and manner of use of drugs, and perhaps on an unnecessary high cost of pharmaceuticals. Of equally fundamental concern is the need to examine the appropriate prerogative of each of the parties engaged in meeting the needs of the people for medical care. Only by a clear definition of their separate roles can the public be safeguarded from evil consequences of unsuitable entanglements between the manufacturers and prescribers of drugs.

The essential purpose of this inquiry is to search out the principles which will bring the trade and the profession into proper alignment in fulfilling their obligations to the people. The objective should be to cultivate cooperation without drifting unconsciously into a collaboration that could undermine the independence of the physician, the free enterprise system of trade, and be deleterious to the medical care of the public.

There is sufficient talent and idealism in industry and the profession to formulate a wholesome partnership, but unfortunately the best intentions of any group are liable to serious dislocation by the machinations of some eager specialists in promotion who may be oblivious to anything but personal gain. Undoubtedly some of the present problems stem from inadequacies in the profession, and these must be dealt with forthrightly.

TO EACH HIS OWN

A wise division.—The right to practice medicine granted to a physician by his license and the privilege given to others to manufacture and sell drugs are each derived through laws adopted by the people dependent upon their services. There is a vital division of responsibility and at the same time a joint obligation inherent in those arrangements. This must always be clearly recognized by the parties to whom the people have assigned a share in the guardianship of their health.

The working relations between the medical profession and the pharmaceutical industry were not formed easily, as though it were a natural and inevitable means of meeting the health needs of the people. There was a bitter struggle for several centuries between apothecaries and physicians for dominant control of both the privilege to manufacture and sell drugs and the right to prescribe treatment. The conflict was not resolved until late in the nineteeth century when the people, through the law of the land, segregated the right to prescribe from the privilege to trade in manufacture and sale of drugs. This safeguard was found necessary to protect the people from exploitation by any one group that might stand to profit by prescribing remedies of their own manufacture.

Do not disturb.—The people would not tolerate for long any tendency to burdensome expenditures traceable to excessive influence of the manufacturer over selection of treatment or to uncritical use of costly drugs on the part of physicians. *Life* magazine (February 15, 1960) concluded a report of the recent Congressional investigations of ethical drug concerns by stating: ". . . in the long run it is up to better informed consumers to insist on being less captive and to pressure the doctors into using a finer discrimination." Neither the medi-

cal profession nor the pharmaceutical industry wishes to feel undue "pressure" from the public, and thus both have every reason to maintain wholesome working relations and a sense of joint responsibility in strict compliance with the welfare and wishes of the people who granted them their privileges. The division of responsibility must be truly respected and not disregarded through any subtle entanglement that may arouse the indignation of the people.

SOURCES OF CONFUSION AND CONFLICT

Legal loopholes.—A typical state law on medical licensure (New York) states that "a person practices medicine . . . who shall either offer or undertake by any means or method to diagnose, treat, operate or prescribe for any human disease . . ." Further, "No person shall practice medicine unless licensed . . ." The legal position of the physician is the basis of operation of the Federal Food and Drug Administration as set forth in the Food, Drug and Cosmetics Act as amended in 1952 which states that a prescription is required for "any drug which because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary for its use, is not safe for use except under the supervision of a practitioner licensed by law to administer the drug."

This places the practitioner squarely in the path of the manufacturer and distributor of drugs which require a prescription; he must therefore be persuaded to use the drug if it is to be commercially successful. The physician becomes the prime target of promotional tactics and exposed to the craftiness of any unidealistic pursuers of profit.

It is not generally appreciated that the Food and Drug Administration is not empowered to control the claims made in the advertising of drugs regarding the usefulness of a product, but must restrict its concern to the safety and proper labeling of drugs distributed in interstate commerce. The Federal Trade Commission is assigned a responsibility in respect to false advertisements of pharmaceutical products distributed in interstate commerce, but somehow an interesting clause gained its way into the Act of 1914 outlining the powers of the FTC and has remained there to this day: "No advertisement of a drug shall be deemed to be false if it is disseminated only to members of the medical profession, contains no false representation of a material fact, and includes, or is accompanied in each instance by truthful disclosure of, the formula showing quantitatively each ingredient of such drug."

Thus it is evident the promoter has a remarkably free hand in seeking to influence the physician. In essence the attitude behind these Federal Acts is that the physician should be able to look out for himself in selecting drugs for treating patients and needs little protection from the law or regulatory agencies. This might be true if he did not have to contend with subtle overpowering promotion and the complexities of modern medicine, especially if he is to be "educated" by the very purveyors of products which require his prescriptions.

Semantic smog.—The companies selling drugs through doctors' prescriptions have enjoyed the distinction of being referred to as in the "ethical" drug trade in contrast to the proprietary firms engaged in sale of drugs direct to the public ("over-the-counter"). Ethical as here used refers only to the channel of distribution and not to the manner and morals of promotion. The distinction becomes even less meaningful when companies deal in both routes of sale; many large "ethical" companies sell products in both categories or have subsidiaries in the proprietary field, and some proprietary firms have acquired control of ethical companies (6). A recent trend has been to expand the market for so-called "over-the-counter ethicals," i.e., products sold directly to the public but not generally advertised as yet in lay media. The Food and Drug Administration permits a product to be sold without a doctor's prescription when it is deemed safe to do so, and no objection comes from the profession after customary notification in the Federal Register. An increasing number of products are making this transition from the ethical to the proprietary realm each year (2). This should be of greater concern to the physician who may become by-passed excessively and the people urged to drug themselves directly by the manufacturer. The movement in this direction may be a considerable factor in the greatly increased use of drugs in the past 5 years, already mentioned. It is easy to see that the retail druggist can also be drawn into the struggle to influence the physician and the public to use particular brands of drugs.

DRUGS FOR MERCHANDISE OR FOR HEALING?

Temptations of bigness.—The difficulties in maintaining proper independence of physicians from the sellers of drugs have been aggravated by the growth of the pharmaceutical industry to a "big business"—drug sales climbed to about 3.3 billion dollars in 1958. It has been predicted that this volume will triple within the coming 15 years (16). It is inevitable that such a promising market, unless carefully watched, will be the prey of fierce competition and the hard-hitting promotional tactics of the commodities market. This may be within the legitimate functioning of our free enterprise system of economy, but there are special considerations calling for restraint in seizing upon the public health as a commercial plum. Certainly the medical profession would be well advised to take care that the public does not come to believe doctors are too entangled with the hustling in the market place.

Manufactured complexity.—One result of the eagerness to share in the profitable business of making and selling drugs is an energetic effort to launch new products. At present about 400 new products are introduced by pharmaceutical companies each year (4). Actually, not more than forty of these are new chemical entities, most being slight modifications or different preparations and mixtures of established agents put forth with claims of advantages such as flavor or absorbability, etc. As a matter of fact, the really new drugs of material assistance in treatment, and requiring advancement in the knowledge of the physician for their use, probably amount to less than six compounds a year. Thus the task of keeping abreast of significant new therapeutic agents is complicated for the physician by the difficulty of identifying these among the avalanche of minor variations, often heralded in the promotional material as striking achievements. The physician might not need so much "education" if there was not so much duplication in brands produced for profit rather than to meet real needs of patients.

It is commonly believed that catchy brand names are better chosen for easy remembrance than proper or generic names for drugs, but see if the following list is familiar or informative.

UNREVEALING BRAND NAMES

Madribon	Medrol	Miradon
Marsalid	Mephyton	Moderil
Maredox	Meprolone	Monodral
Mebaral	Methium	Mulvidren
Medomin	Midicel	Mysoline

Any potential advantage of a catchy name is lost when one is faced with new trade names for 400 products a year for perhaps a tenth this number of different specific agents. One wonders whether the few generic names that actually should be learned could not be even better mastered than the numerous variants in brand names for a single drug, if comparable promotion ("education") were devoted to implanting the fewer generic names in the mind of the physician, for example:

SINGLE GENERIC NAMES FOR DRUGS WITH MULTIPLICITY OF BRAND NAMES

DEXAMETHASONE	PREDNISONE	TETRACYCLINE
Decadron	Deltra	Achromycin
Deronil	Deltasone	Panmycin
Gammacorten	Meticorten	Polycycline
		Tetracyn

PHENETHICILLIN ("SYNTHETIC" PENICILLIN)

Alpen
Darcil
Syncillin
Maxipen
Chemipen

The argument that a brand name affords assurance of quality and purity because of a responsibility imposed on the company having exclusive rights to its use is unimpressive. This responsibility should be fully assumed by the Food

and Drug Administration, which has the power of inspection and should have more means to exercise it. We do not need a complicated system of private ownership of names of drugs to protect the public. As a matter of fact, drugs presently distributed by generic names have not often been found inferior in the limited inspections the FDA has been able to make.

It is evident that a vicious circle is created by a mad scramble for a share of the market: the doctor is made to feel he needs more "education" because of the prolific outpouring of strange brands but not really new drugs, produced for profit rather than to fill an essential purpose; and then the promoter offers to rescue him from confusion by a corresponding brand of "education."

THE STYLE OF PROMOTION

Smart and sly.—The goal of promotion, even when traveling a circuitous path under the guise of "education," is to achieve uncritical acceptance of a preconceived message—to captivate the mind; stimulation of skeptical thinking could block the purpose. This is in sharp contrast to the objective of true education, which seeks to cultivate the use of the mind for independent judgments. The success of promotion does not depend on the authenticity of the message but on the skill in manipulation of belief. The psychology of persuasion has been studied more assidously and is better mastered by promoters than by professors. Not only are the rewards and competition in commerce stimulating, but the best techniques of promotion can be ascertained by the concrete measure of sales figures. The educator is hampered in evaluation of his methods because the results are deep in the mind and cannot be given specific price tags.

Preparation of promotional material is generally farmed out to specialized advertising agencies, and these have not always shown a notable sense of responsibility in their use of the mass media in matters of health. It is to be expected that an advertising agency would be more concerned about the success of a promotional campaign than its impact on medical practice. Whereas medical men of integrity may be consulted in the preparation of promotional material, it seems that they may be overruled by executives occupied with maintaining sales and profits.

Payola?—In conjunction with the actual advertising material, the pharmaceutical companies go to great extremes to sell an appealing "House Image" to the physician to soften his resistance. Lowest on the scale are overt gestures like ordinary entertainment and personal favors. One "ethical" drug company (Eli Lilly) gives medical students new diagnostic instruments each school year to foster "the close association of our two professions," with the proud boast of having enlisted "the co-operation of the dean of your college!" A particularly regrettable maneuver is the exploitation of the natural sympathy between doctors and students by hiring the needy and unsuspecting student as a detail man (Pfizer, Schering).

More subtle wooing takes the form of conspicously sponsored conferences and television clinics and give-away lavish medical magazines and newspapers sometimes made more fetching with pseudo-culture and racy human interest. Grants are made in partial support of independent research, but these usually cover only part of the cost and tend to favor utilitarian studies; and the investigator may unwittingly find his results subject to exploitation (11).

Medical organizations are given monies to support a large part of their activities, and then are in a poor position to criticize practices that infringe on the prerogatives of the medical educator and imperil the knowledge of the physician.

The question might well be raised: How does all this courting differ from payola?

Promotion is to commerce what propaganda is to politics. The physician, like the citizen, had better have a clear notion of its trustworthiness. In the application of information to the care of the ill, it is not enough for most of what is offered to be accurate; the difficulty of avoiding error is compounded when clever means of misleading the unwary are common practice. And remember, the physician is left by the present laws to look out for himself in matters of promotion to a considerable extent. New proposals are under consideration to remedy this situation.

Tricks of the trade.—Innumerable ingenious devices have been contrived to give promotional material an air of authenticity. Some of these can be mentioned to warn physicians to watch for them in "educational" material prepared by pharmaceutical concerns.

Reference is often made to unpublished data from "personal communications," "case reports in the company's files" which are collected at random, and even individual testimonials. None of these can be readily evaluated in an acceptable fashion.

Quotations lifted out of context are a favorite means of misusing sound sources, and inferior articles in the medical literature may be selected to support the claims even when superior work is available to refute them. Only one or two of an impressive list of references may have any pertinence to the claims being propounded. Certainly the copy writers cannot be counted on to evaluate the evidence critically.

There are a few privately owned magazines published in the format of medical journals that are favorite repositories for superficial studies and common sources for references in promotional material. One of these was edited and published by a drug company that then used the references in its advertisements, thus having a handy closed system of quotation.

Implied endorsement by vague allusions to use of the product by "many" physicians or hospitals is expected to be convincing, as are the results of inadequate surveys showing "9 out of 10" *answering* a mail questionnaire favored the product although it is not mentioned that only a small percentage of those questioned bothered to answer.

The appeal to the eye is seldom neglected, but the mind may not be taxed at all with useful information as to contraindications, side effects, toxicity, etc. Least of all can one hope to find any discouraging data on actual or comparative cost of "new" preparations versus established forms of a drug.

THE PHYSICIAN'S PREDICAMENT

Learning made difficult.—The body of knowledge which should be assimilated by the physician is burdensome enough without complicating his access to it. The legitimate medical journals have multiplied like insects; one must now seek his information from 5,000 journals (over 600 in the United States alone) containing about 100,000 articles a year. These publications are almost all edited and written by amateurs in the skills of communication. The usual medical journal is more a repository of data than an organ designed to interest and enlighten the reader. There are plenty of sound articles if one can find time to locate them and dig out the information. Even the review articles tend to be pedantic. The bibliographic aids such as *Index Medicus* list all articles regardless of merit and are of no help in checking on current promotion because they are months behind the journal, which in turn are months behind the claims in advertisements based on "personal communications," "exhibits," and "cases in the company's files."

Editors and publishers may seem to pursue their lonely ways without regard to duplication of effort or real concern for the practicing physician, but this is partly due to inadequate staff. Usually the editor snatches time from some primary task to turn out a journal as best he can without specially trained assistants. Quite limited resources are available to the editor for making the journal more attractive with art work and colored illustrations or more interesting through enlisting the aid of skilled writers.

Because of lavish expenditures for drug promotion, the income from advertisements is enough to make the owners of medical journals covetous of the profits. Two official journals of national societies can be cited as bracketing the field: One general journal publishes 6,000 pages of advertising a year, at $1,100 a page, or an annual income of $6,600,000; another specialty journal receives $260,000 a year from 1,300 pages at $200 a page. All the costs of producing these journals probably do not come to more than 60 per cent of the income from ads plus subscriptions, thus leaving 40 per cent for the owners. It would be hard to beat this as a profitable business, since the raw materials—the talents of the contributors—come free!

Most lamentable is the lack of concern for the authenticity of material in the advertising pages in medical journals, which almost outweigh the editorial text in bulk and influence. Few journals show signs of a determined effort to reject misleading advertisements, and in none are the standards of acceptance high enough. In this respect the owners of the journals exert a strong influence over editors, some of whom surely resent the encapsulation of the editorial text by objectionable material.

Advertisements in otherwise reputable journals are not dependable sources of education. Conflict between promotional "education" and scientific information in

the editorial text appearing in the same professional periodical is dramatically illustrated by an article and an advertisement in the same issue of the Journal of the American Medical Association (March 5, 1960).

Wilkins (19) reviewed the experience with occurrence of female pseudohermaphroditism in 36 infants born of mothers who during pregnancy had been given norethindrone (marketed as Norlutin by Parke, Davis & Company), a synthetic progesteroid compound, as treatment for habitual or threatened abortion. The natural hormone, progesterone, does not cause fetal masculinization. Norlutin and similar synthetic compounds have androgenic as well as progestational effects. The masculinizing effects of synthetic progesteroids can lead to the genitalia of female infants being mistaken for male, with dire consequences if they are reared as males and then subsequently feminize and menstruate at puberty; they may also be mistakenly assumed in the neonatal period to have congenital virilizing adrenal hyperplasia.

The same advertisement for Norlutin (Fig. 6) has continued to appear regularly in the J.A.M.A. for the ensuing 3 months since the article by Wilkins appeared in that journal; in spite of his warning: "During the past year or two, Norlutin has caused fetal masculinization with sufficient frequency to preclude its use or advertisement as a safe hormone to be taken during pregnancy." The advertisement contains no clue to this complication and no information that is "educational" or enlightening. The startled expression of the woman in this advertisement may have more significance than the artist intended!

The financial subsidy gained through advertisements is a doubtful blessing. The journals come to be regarded as profitable property and as vehicles for advertising rather than scientific periodicals. A journal with an eye toward the glitter of gold may become diverted from its proper function as an outlet of free and pointed criticism.

This lush support inflates the number of publications beyond the natural needs, and the plethora of pages encourages acceptance of inferior articles—and so the bulk with which the reader must grapple is bloated as a consequence of the very promotional material he ought to check against a discriminating literature.

Little wonder that few physicians have the stamina to struggle with the overwhelming task of keeping abreast of new developments through their own medical literature. Medical educators must be especially chargrinned to have succeeded no better in cultivating sound reading habits in students that should last through the lifetime of a busy doctor, and to have done so little to keep the medical literature serviceable and free from external influence.

Believing made easy.—The deficiencies in the medical literature and shortcomings in the education of physicians have provided the golden opportunity for the promoter. The intense discomfort the doctor feels from the frustrations of using his own literature makes him quick to turn to the appealing "educational" material of the pharmaceutical concerns.

The sellers of drugs have launched an impressive array of publications (the paramedical literature) and other devices to gain an influence over the habits and beliefs of doctors. Enviable skill and ingenuity have been devoted to production of attractive and well composed material. It cannot be denied that much of this is dignified and more useful than the journals and postgraduate programs sponsored from within the profession. The temptation to the busy physician, driven by desperation to seek short-cuts through the forbidding jungle of academic creations, is so great that in all probability the readership of the trade publications far outstrips that commanded by professional sources. Less harm would be done if the "educational" material furnished in behalf of promotion was free of bias. It is risky to depend on materials beyond the scrutiny of independent editorial staffs and of necessity dedicated to vested interests.

Tardy and taxing aids.—Valuable reports on the nature and use of drugs by authoritative bodies are regularly published, e.g., the Councils of the American Medical Association and the National Research Council. One might suppose the physican would use these to judge the accuracy of material reaching him through the channels of promotion. Reports such as these are widely scattered in medical journals or appear as separate documents not generally received by many practitioners. It would be a tremendous task for an individual to keep track of all these reports. Compilation of critical evaluations by committees takes time, and publication of their reports lags too far behind the current promotional campaigns to apply the findings when they are most urgently needed.

Even if such reports could be more timely, a busy physician does not have time or energy to check the claims in promotional material by searching out

FIGURE 6

corresponding statements from comprehensive authentic reports. It is absurd to expect the truth to prevail when it is given relatively slight circulation in a single publication or is repeated at rare intervals, while promoters have discovered that their message can be hammered home against great odds by massive relentless repetition.

Another limitation of most scholarly reports is the polite reluctance to single out specific products deserving criticism, as could be done by naming brands

or identifying fallacious presentations in promotional material by direct reproduction and quotation.

A notable effort is being made to overcome these inadequacies by an independent group of competent physicians who are circulating a Medical Letter[1] containing pointed comment on the newest products while they are still being intensively promoted.

Unfair competition.—Advertising experts maintain that their methods would not be so successful if medical educators and editors did their jobs better and physicians were so well informed that they could not be influenced by unauthentic promotional material. There is enough truth in this to make sincere professors and editors wince, but the sides in the battle to dominate the habits and beliefs of the physician are not fairly matched.

As things operate in our society, far larger resources can drift into the hands of pharmaceutical enterprises than can be raised by medical schools and professional organizations. While spending about $125,000,000 in 1959 on journal and direct-mail advertising alone, the "ethical" drug industry placated the deans and professors with donation of an unrestricted sum of approximately $243,000 as their mite to the National Fund for Medical Education (3), or about 0.12 per cent of the total budget of $200,000,000 for medical schools for that year.

To a large extent the paramedical publications thrive as parasites on the basic contributions of the profession. They may select what they wish and remold it to their purpose without the tedious task of doing the original work. The drab and prosaic legitimate journals must limp along on relatively meager resources openly raised through paid subscriptions or stoop to sharing the promoter's bounty by carrying his advertisements, which enshroud and often conflict with the editorial text. The beautiful and exciting magazines and newspapers from industry can be given away, whatever the cost, because the expense is conveniently included in the price of products the physician is led to prescribe.

Alarming trends.—Only a lapse of judgment can account for the willingness of prominent medical authorities to contribute their talents to further embellishment of the contents of the paramedical literature and other promotional schemes, as is increasingly the custom. A moment's reflection should make them realize that dominance of physicians' "education" can easily pass into the hands of those who are capturing doctors' attention with their aid and for the client's purposes. As an example, one handy little parasitic commercial magazine offers pithy extracts from the legitimate literature sandwiched between fulsome advertisements, and frequently manages to draft an illustrious panel of professors who seem content to sell rehashes of their original works to dress up the collection of abstracts gleaned from proper journals—presumably to the owner's great profit.

Prominent men seem ready to lend their names as sponsors and thus add an air of authenticity, not only to paramedical magazines, but also to subtle schemes for closed-circuit television performances and for piping information and promotion into the offices of doctors via radio and phonograph and telephone; all these devices are subject to the influence of the advertising agencies and drug companies which support them.[2]

These entanglements can become confusing and unwholesome; cooperation can unconsciously come perilously close to collaboration. The net result is to under-

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[1] Published by Drug and Therapeutic Information, Inc., 130 East 57th Street, New York 22, N.Y.

[2] Examples are:

The Advisory Committee for Grand Rounds (television), made up of distinguished names, with headquarters at the same address as the largest medical advertising agency (William Douglas McAdams), and a lay employee of that company is the Executive Director for the Committee.

Voice of Medicine, a phonograph record service, teams up Excerpta Medica Foundation with Recordo-Med, Inc.

Medical Radio System is a service of RCA–NBC for special FM radio broadcasting of medical news and promotion.

Mediphone (developed by Johnson and Lanman ad agency) will arrange for free telephone calls between physicians seeking information on any topic and drug companies which will seek the chance to provide it.

The fate of Dr. Henry Welch, who was obliged to resign as chief of the Division of Antibiotics of the Feed Administration, should be a warning to others drawn into promotional enterprises. His involvement in the schemes and dealings of two profitable trade magazine (distributed free to doctors) was brought to light in a Congressional Hearing (17).

mine the audience for the journals and postgraduate programs which were once the prerogative of the profession.

Furthermore, a mass medium is established beyond the influence of the profession which can be used to comment freely upon the affairs of doctors, while their own private and official medical publications must hesitate to examine the doings of the industry upon which they have come to depend for subsidy. When the medical audience has been more completely won over by the promotional "educational" activities, and if the pinch of a less flourishing economy should be felt, what is to prevent the subsidy to medical journals and societies from being decreased? Would enough loyalty of doctors to their own professional journals remain to make it risky for industry to force these journals to rely on their own resources?

THE POWER OF PROMOTION

At times the effectiveness of promotion may be exaggerated by the promoters. They are not so powerful as to excite fear and worship, but it would be foolish to discount the impact of their efforts. Keen businessmen do not continue to lay out huge sums without results.

The aim of the promotional campaign is to sell a particular brand of a product. Listen to the terms mentioned in discussions of treatment by students in the classroom by residents in staff conferences or whenever doctors meet, and you will note how successfully trade names have been implanted—even though the brand name may not be simpler than the generic term and it may not give any clue as to the chemical nature of the product. Also notice how quickly a new product gains favor in the best of medical circles, whether proved superior to an old product or not.

If your own observations are unconvincing, look at the following sales figures of a few "ethical" products and ask yourself if discriminating authorities could be recommending such profligate usage ot residents and practicing physicians.

Estimated total ethical drug sales at manufacturers level (1957) (8)

Antibiotics	$406,000,000
Vitamins and hemantinics	230,000,000
Adrenal hormones	88,000,000
Other hormone preparations	50,000,000
Sulfonamides	42,000,000
Biologicals	150,000,000
Tranquilizers	195,000,000

Promotion has the power to lift a product to prominence regardless of its usefulness, and though this may be a fleeting accomplishment, the "education" of physicians will be distorted and the resources available for health care will be dissipated by the hectic campaign to influence the doctor's prescription. Your attention is not being directed to a harmless "tempest in a teapot" but to a force that can twist the profession from a true course.

THE POWER OF CRITICISM

There is a remarkable dichotomy in the prevalent attitude in the medical profession toward criticism. Forthright public comment is expected from colleagues who review scientific books and articles for medical journals and during scientific meetings, but any tendency to comparably open criticism aimed at particular brands and specific abuses in promotion is frowned upon as "negative" and unsuitable for dissemination in the medical literature. Thus, a valuable exercise in the evaluation of evidence is eliminated from the continuing education of physicians from within their own ranks.

Other fields have not hesitated to employ higher criticism to foster good taste and excellence. Dramatists, authors, and artists are continuously exposed to unfettered critics who pass judgment on their creations without sparing mention of individuals and specific works. Indeed, the full benefit of higher criticism cannot be gained by vague generalizations alone.

That this procedure is equally constructive when applied to promotional material was demonstrated to the profession by the effect of a series of pointed criticisms published in a lay magazine in the past year. The *Saturday Review* (January 3, September 5, 1959) permitted their science editor to point out a few abuses in promotional material of a major ethical drug firm. Reproductions of actual advertisements for specific brands were used to illustrate the reasons for

concern. The effect was salutory. These articles were so disturbing to the profession as well as the public (and the company under fire could not deny their validity) that the Federal Trade Commission was stimulated to issue two injunctions calling for explanations from the offender. Such action had not been taken previously by the FTC in connection with the promotion of ethical drug firms, presumably because it was deemed sufficient to let the doctor look out for himself as was stipulated in the Act of 1914 (quoted in a preceding section of this essay). Far from being "negative," this was a positive service to the public and the profession.

It does not seem sensible for the profession to relegate the function of higher criticism in medical affairs to even enlightened laymen, particularly in public media. The results may not always be so fortunate for doctors, and the public may view a reluctance on the part of the profession to assume responsibility for independent criticism of any agencies affecting the public health as a form of negligence (12)—in which case the privilege may be assigned to a governmental bureau. This turn of events would seem more likely to lead directly to excessive regulation of industry and the profession than the superficial notions of "censorship" set forth by promoters to hold potential critics at bay.

Criticism from individuals submitted privately to drug houses is easily dissipated by polite evasion, but public comment cannot be dealt with so conveniently. The profession needs to bring its collective weight to bear on abuses and poor taste through pointed criticism in official journals of medical societies or by some form of public expression of pointed opinion from independent groups of physicians.

BUGABOOS

Censorship.—Whenever the suggestion is made that the consumer deserves more protection from unrestrained promotion, cries of "censorship" are heard from the captains of industry and the masters of the mass media. This word "censorship" is made more repulsive by opposing it to "freedom" and the sanctity of "self-regulation." The hackneyed trick violates sound concepts. To censor is to suppress expression of fact or opinion—and this is evil. To oppose abuses in the use of the mass media for promotion by pointed public criticism is not censorship but legitimate restraint—in the best tradition of freedom.

Censorship is abhorrent to all who aspire to freedom, but articulate criticism in the higher sense cannot be construed as unwarranted restraint or an infringement of rights. Freedom can be maintained only by providing for continuous, unhampered expression of opinion *from all parties* through equal access to the media of mass communication. There must be comparably effective presentations to the identical audience at nearly the same time; an open clash of opinion between fairly matched adversaries will finally disclose the closest approximation to the truth. This process is stifled when industry can afford to make blatant use of the mass media, while the profession remains content to express its opinion softly through outlets partially stilled by a feeling of dependency on subsidy from advertisers.

Self-regulation is a myth not likely to be realized outside Utopia. Neither citizens nor nations, professions nor trades have evolved to this day that deserve such trust, least of all when profit is at stake. It is actually presumptuous to seek exemption from that degree of regulation which safeguards the welfare of all members of society.

Socialism.—Whenever the pharmaceutical industry feels the sting of political probing, as was so apparent in the recent Congressional investigations, the most promising means of eliciting sympathy from the profession is to play on the fear of socialized medicine (5). It is argued that if private industry is subjected to further government control, medicine will soon be the next target. It cannot be denied that should the profession become too closely entangled with the drug industry, they are liable to rise and fall together in the estimation of politicians and the people.

Physicians will have to recognize the purpose of these bugaboos or they may unconsciously accept a flimsy pretext for unbridled use of the mass media and adopt an unreasonable attitude toward social advances.

THE ENTICING WEB

A look at the entire net cast out by the promoter to catch the physician's favor will reveal how easily the unwary could become entangled. The suave and mischievous methods used to entice doctors into this web are deplorable:

the whole is camouflaged as a noble plan to promote the public health and made tempting to the unsuspecting victims by the bait of "education." The grand scheme appears to be to confuse and then capture the prey.

The capacity for entangling doctors built into the network of promotion and "education" spread out by the ethical pharmaceutical industry can be readily estimated by simply listing some familiar elements in the design.

1. Entertainment and gifts (wining, dining, and floor shows, free supplies and equipment to individuals and institutions) that soften resistance to overt promotion.

2. Subsidies of medical journals through advertisements and of medical societies through direct support of activities and indirectly by commercial exhibits at meetings—that interfere with their function as outlets for objective criticism.

3. Grants for applied research and testing of products—with the risk of ensuing exploitation of favorable results.

4. Sponsorship of conferences—thus made vulnerable to infiltration by tradesmen and biased presentations.

5. Free distribution of lavish and beguiling paramedical publications, radio and television programs (exempt from independent review)—that draw the attention away from legitimate medical outlets and transfer dominance of the mass media to the promoter.

6. Attractive invitations to talented physicians to contribute to paramedical publications—that divert their talent from publications of the profession and add a veneer of authenticity to the promotional "educational" material.

7. Manufacture of a plethora of brands and preparations—that complicates the burden of keeping doctors informed without corresponding enrichment of the therapy at his disposal.

8. Clamorous competitive claims—that permeate the practice of medicine with the confusion of huckstering in the market place.

9. Loose allusions to censorship and socialism—that startle conservative freedom-loving physicians.

10. Modest unrestricted contributions to the profession's own educational enterprises (like the National Fund for Medical Education)—that may exonerate the abundant expenditures for industry-dominated "educational" programs.

The individual physician is left to escape this enticing web with too little help from his un-united, cautious, subsidized organizations, while the ethical drug companies have combined their resources in a Pharmaceutical Manufacturers Association that can effectively pursue a coherent plan and ample use of public relations to guard their interests.

THE MENACE OF ENTANGLEMENT

The prospect for free pursuit of a chosen trade or profession affecting the public health is most promising when the welfare of the people governs all actions. This means no selfish effort should be made to intrude upon the prerogatives of others or to exert undue influence through entanglement, confusion, or collaboration among the parties to whom the people have assigned separate responsibilities.

The invasion into the province of the medical educator by the drug companies must be eliminated; conscription of "education" in the service of promotion must cease. Sooner or later what may now seem like benign and noble overtures will be recognized as ominous intrusion that threaten the hard-won and reasonable boundary between the sellers and prescribers of drugs.

Neither the drug industry nor the profession would profit by mortal combat, and the public would be the victims of unseemly collusion. There is only one way to better health care for the people—cultivation of cooperation and avoidance of entanglements. If the public is the first to sense the danger, matters will pass into their hands and governmental regulation will be made the order of the day.

PROPOSALS TO LOOSEN THE PROMOTER'S SNARE

To physicians.—It would not be surprising to find that some physicians react with anger at any criticism of ethical drug companies, for surely all the bountiful gestures from industry must have forged some warm friendships. Let them hold their fire and consider!

There are ample grounds for kindly feelings between doctors and those who furnish them with invaluable remedies without the ardent wooing of promo-

tion. However, as long as the prescription remains the means to a sale, short-sighted promoters will consider it "good business" to make prescribers feel something close to kinship with the purveyors of drugs. This is a shaky foundation for true and lasting friendship. A little reflection should lead physicians to beware the eroding effects on their traditional independence and on the trust they have received from the people.

Doctors must adopt universal skepticism toward "educational" material emanating from sources outside their own publications and institutions, and even these will be suspect so long as there is any reluctance to apply critical standards in acceptance of advertisements, or to sneak out freely on other abuses, for fear of losing the subsidy of promoters. The legitimate medical literature needs overhauling, as to both source of support and techniques of communication.

In addition to looking out for himself the physician must be willing to pay his own way. He would bridle at the prospect of being considered a "sucker," or a puppet of any vested interest—a possibility he faces when he becomes beholden for entertainment or deeply entangled in the web of promotion. Never forget that the patient pays the bill.

Physicians should not discount their latent power nor hesitate to assume their full stature and call a halt to invasion of their province. Prestige is a fragile flower that demands conscientious cultivation to save it from pests and weeds blown in by the winds of promotion.

In the light of reason the bugaboos of censorship and socialism will be dispelled, and the indispensabiity of higher criticism for maintenance of excellence and good taste will be acknowledged.

Watchfulness will be required to check the increasing transfer of products from "ethical" channels into the category of "over-the-counter ethicals," a source open to patients without recourse to a doctors prescription. Casual tolerance of this trend is a form of professional suicide, which might be a boon to promoters, but not to the people, who appear only too anxious to drug themselves at the beckoning of unscrupluous hucksters.

In essence, physicians should hold themselves aloof in unhampered devotion to their calling, while exchanging a wholesome respect with others contributing to the public health but never being guilty of prescribing drugs under unconscious influence of personal favors or subtle entanglement with the affairs of drug manufacturers; nor can the profession ever shirk the task of setting its own house in order, particularly with regard to the unkempt medical literature, to inadequacies in the techniques of medical training, to easy-going ways of financing activities of medical societies, and to indulgence of wayward physicians who may be unwittingly aiding and abetting the schemes of promoters.

None of these proposals should be allowed to provoke conflict between the groups making equally vital contributions to the public health; the best interests of all parties can be fostered only by suitable cooperation, which is distinct from collaboration. Conferences between responsible representatives of medical educators and the pharmaceutical industry would be desirable, e.g., the Association of American Medical Colleges and the Pharmaceutical Manufacturers Association.

To the ethical drug firms.—The position of managers of drug companies dependent on doctors' good will to sell their products is not altogether enviable. It takes a reasonable profit to make the stockholders happy, and this must be gained in a fiercely competitive market. The manufacture of drugs is an exacting business, not only because of legal standards but because imperfections in the product can be disastrous and no excuses will satisfy the public. There are enough internal problems in such an industry, but a final obstacle must be overcome before the volume of sales will permit a profit—the man who writes the prescription must be won over to favor the product. The great body of preoccupied, conservative, and proud physicians is no slight obstruction to place in the path of any enterprise; little wonder a great blast of promotion was found necessary to move them.

Even allowing for all these difficulties, the ethical drug firms may have overshot their mark. Physicians and the public are beginning to feel they are pushed around too much. Unless the medical educator is completely overpowered, sooner or later there will be a wholesale opposition to pharmaceutical invasion of the field of medical education. To be sure, doctors and their organizations are notorious for accepting almost any offer of subsidy or entertainment, but their feeling of gratitude will not be strong enough to check their ire when they

realize their prerogative to exercise dominant influence over the habits and beliefs of physicians has been bought.

Ethical drug firms should reconsider the appropriateness of attempting to influence physicians by subtle infiltration into the educational process and through a vast meddlesome subsidization that is hard to distinguish from payola. If the pharmaceutical industry can afford to subsidize medical affairs, they should do so through larger unrestricted contributions to organizations devoted to the interests of the profession, such as the National Fund for Medical Education, rather than allowing their resources to be used as a means of undermining the control of physicians over their own affairs or as a nefarious scheme of public relations.

Matters would improve if the ethical drug industry shook off the exuberant promoters who have drawn them into the use of techniques customary in the sale of ordinary commodities but highly questionable for application to promotion of medical remedies. This industry had better take another look at that word "ethical" and make certain its meaning is applied to the manner of doing business and not just the channel of distribution of their products.

No doubt it would be impossible to curtail the plethora of brands and preparations of products in a *laissez-faire* market. This is one of the chief causes of promotional puffery and an aggravating contribution to the confusion of the doctor that makes him feel he needs more "education." The Pharmaceutical Manufacturers Association might well consider whether its members would in the long run be better off with lower sales volume and less bigness and less aggressive competition—the alternative appears to be an ever-increasing tempo of promotion until the whole business is discounted by the profession and the public. The promotional campaigns which are required to compete in a market depending on sales direct to the public are especially costly; the last barrier to this drain will be gone if the physician is removed from the path of drug promotion by loss of stature or further tendency of ethical firms to get around the doctor via the "over-the-counter ethical" line of remedies. Acquisition of proprietary subsidiaries by ethical firms and vice versa must complicate matters.

Cooperative projects.—A good step in the right direction has been the adoption of a Statement of Principles of Ethical Drug Promotion by the members of the Pharmaceutical Manufacturers Association. The next step is to abide by it faithfully. Even better would be a really *comprehensive* statement of principles prepared and adopted jointly by representatives of industry and the profession to define and govern their proper relations and separate prerogatives. This could be coupled with the establishment of a Board or Overseers made up of representatives of the public, industry, and the profession. This Board would not function as a government regulatory agency but as a private group that would be empowered to call to account either party for any infringement of the stated principles, resorting when necessary to public comment in the mass media. The freedom of each group to pursue its endeaver could be guaranteed by this continuous and equal opportunity for confrontation of opinion and exercise of influence. The people could be reassured by periodic reports from this Board of Overseers. Here again the Association of American Medical Colleges and the Pharmaceutical Manufacturers Association could cooperate in developing such a plan.

To the people.—In the final analysis, the people of a democratic society have the power to take things into their own hands. If any enterprise threatens the welfare of the public, especially in matters of health, a brisk reaction can be expected. No good will come from encouraging eager politicians to seize upon health enterprises as a ladder to power. The people should not lean too heavily on bureaucratic governmental regulation, for there is no substitute for high ideals in the development of sound practices in a free society.

Should it appear that unduly large resources have drifted into the possession of industry for the purposes of promotion, the structure of taxation may well be critically examined. It is not inconceivable that a plan could be devised that would limit the sums which can be charged to promotion in the cost of marketing drug products, thereby shrinking the size of the web the promoter could fabricate for his clients and freeing the profession from the threat of entanglement or undue influence from pharmaceutical "education."

The people do need some assurance of responsible behavior from those to whom they have assigned the rights and privileges of serving their health needs. This can only be obtained by insisting upon some arrangement for

continuous public accountability from the profession and the drug industry, such as the Board of Overseers suggested in the preceding section of these proposals.

PRESERVATION OF FREEDOM FOR ALL

Censorship is justifiably condemned in a free society, and the mass media should be open to free and equal use by all responsible persons. Restraint through higher criticism is not to be confused with censorship—on the contrary, it should be liberally applied in every field of endeavor to encourage excellence and good taste.

The mood of the times must be changed from a squeamish feeling that open criticism is "negative" to a more wholesome regard for pointed public comment and public accountability. There is no more effective way to discourage artful attempts to enlist physicians in the sale of drugs by disguising promotion as "education" and to prevent misuse of the mass media by selfish interests rather than for the welfare of everyone.

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THE MEDICAL PROFESSION AND THE DRUG INDUSTRY

(By William B. Bean, M.D.)

Dr. Bean received his B.A. and M.D. degrees from the University of Virginia. Further training in internal medicine and nutrition was received at Johns Hopkins, Harvard, and at the University of Cincinnati. He is a Diplomate of the American Boards of Internal Medicine and Nutrition. Since 1948 he has been Professor of Medicine and Head of the Department of Internal Medicine at the University of Iowa College of Medicine and Physician-in-Chief of University Hospitals. He is the former Chairman, Section of Internal Medicine, American Medical Association, and is a member of the Board of Regents, National Library of Medicine. For the past five years he has been Editor-in-Chief of the *Archives of Internal Medicine* and is presently Editor-in-Chief of *Current Medical Digest.* A prolific writer, Dr. Bean has made almost 400 contributions, including five books, to the medical literature on internal medicine, nutrition, medical philosophy, and history. His most recent book is *Rare Diseases and Lesions.* He appeared twice before the Kefauver Committee investigating the pharmaceutical industry.

Excellent herbs had our fathers of old—
Excellent herbs to ease their pain—
Alexanders and Marigold,
Eyebright, Orris and Elecampane.
Basil, Rocket, Valerian, Rue,
(Almost singing themselves they run)
Vervain, Dittany, Call-me-to-you—
Cowslip, melilot, Rose of the Sun.
Anything green that grew out of the mould.
Was an excellent herb to our fathers of old.
—*Rudyard Kipling.*

Physicians and apothecaries have had a long and turbulent history in which one sees examples of effective and friendly collaboration as well as explosively violent antagonisms with long and bitter feuds. While the problems of pharmacy and the diminishing function of the pharmacist make the skillful compounder of remedies and potions almost a thing of the past, that is another problem. Its story needs to be told elsewhere.

To some extent, the doctor-drug polarizations have shifted. We see on the one hand the academic physician trained in clinical investigation and on the other, leaders of the pharmaceutical industry who have been brought up in the free-wheeling competition of the marketplace, where policies and practices are always influenced and sometimes actually determined by the financial goals. There may be enormous profits from a new drug. Such business, furthermore, has sharp time limitations upon it since competing drugs may soon reach the market and greatly reduce the yield the price comes down. It was, I think, largely the failure of responsible physicians and members of the pharmaceutical industry to recognize these conflicts that led to the hearings on the manufacture and marketing of drugs before the Senate Subcommittee on Antitrust and Monopoly (the Kefauver Committee). Certainly these hearings were useful for catharsis and an excellent ventilation of some of the problems but did not settle or solve them all. That would be expecting too much.

The points still at issue in the controversy are vital and range over the whole spectrum of contemporary life, varying from the free enterprise system on the one hand to the frustration of a family with a desperately sick member, unable to buy necessary drugs. While to some extent the coming of Medicare has alleviated an element of the difficulty, there is still plenty of room for wisdom and statesmanlike consideration of how a cost accountant figures out the profit a company can make on a new drug, a sophisticated study of laboratory and animal reactions, the performance of a company's stock on the stock exchange, and the relationship of statistics on mortality to the wider use of certain drugs, emotionally defended by partisans on either side.

RECENT ADVANCES AND NEED FOR CHANGE

It seems evident now in the day of molecular therapeutics that we will have more tailor-made drugs, more compounds designed on the basis of expectations of performance from a sound knowledge of biophysics and biomedical reactions, and fewer compounds derived from plants. Rauwolfia was the last important new entity to come in this way. Once steroid hormones became available, newer ones and those with sometimes greatly different function, though very slightly different structure, introduced new problems. The mass production of penicillin and other antibiotics has been a marvel of industrial skill. Mass production of such things as live virus vaccines is beginning to make inroads on the biomedical equilibrium of human ecology, with all manner of implications for the future.

The application of such advances to an understanding of human physiological functions and applications of newly won knowledge to the treatment of sick people have not been a smooth and steady progression forward. In fact, I am not aware that any one has made a careful study of the very large number of therapeutic dropouts, i.e., compounds introduced with a loud noise in all the media and ballyhoo from brochure and detail man, only to vanish within a period of months or years when their lack of new virtue or better efficacy became apparent. At the very best this represents a wasteful system; at the worst it smacks of skulduggery and cant.

Conflicting interests may simply generate slightly uneasy pressure or they may result in almost explosive confrontations. In periods when the tempo of change is extremely rapid and when the stakes are high, whether it be in terms of the financial reward for an entrepreneur or the health and well-being of man and man's society, a genuine concern becomes the awesome and increasing responsibility of thoughtful members of the society because of the enormity of the stakes.

At a time when scientific advance was slow and new drugs, such as they were, were likely to be found by painstaking evaluation of herbs and their essences, the introduction of new drugs was uncommon. Therapy, not very effective, was about at a standstill. There was no incentive to go into the mass production of new compounds, for there simply were not enough new compounds. When advances began to develop explosively, the traditional function of ethical pharmaceutical houses was magnified and multiplied, and to some extent the directing forces were removed from individual or family enterprises into the large realm of big business.

At the same time, there was not at first a comparable awareness or alertness to deal with the increasingly complex problem of drug testing. In any society when problems which are new in kind, as well as new in dimension, arise its institutions are tested. Unfortunately it turns out often enough that the institutions and organizations, well geared for a slower pace and a simpler set of problems, may prove not only insufficient but dangerous. The evolution of medical practice and medical science as it relates to therapy and the employment of powerful drugs is moving fast but uncertainly. Institutions rarely have a built-in autoanalyzer, a central controlling monitor, to examine and provide a dispassionate critique of purposes, functions, and the capacity to fulfill them. This is why institutions change, or fail and are replaced.

Human nature being what it is, things may go along until some disaster appears. Some threat becomes ominously evident. Or a general quickening of the moral pulse of the community leads to an investigation or an intervention. Often a crash program of poorly thought out schemes results in passing laws to achieve ends which would be managed much better if collaborative but voluntary arrangements and agreements could be worked out by those concerned. The two parties involved here are pharmaceutical manufacturers on the one hand and the body of medical practitioners, teachers, and investigators, those who must be responsible preservers and protectors of the public, on the other.

The great majority of pharmaceutical manufacturers have a just concern for their good name and are wary lest this be sullied by entrepreneurs who have come into the field without the traditional background accumulated during the more leisurely days. They have a steady sense of responsibility and wish it to permeate the drug industry. While many of the problems which are of concern to us now have, more or less by default, gone into the hands of external agents or agencies, it is still wise for physcians and those who produce pharmaceutical agents to review jointly their common material problems.

I have commented upon the method by which the man in the street or, more generally, society protects itself in a democratic state. Such an organism has its being through dependence upon a capitalistic system in which ultimately the good of the people depends upon the knowledge, foresight, wisdom, and an effectual sense of responsibility. Of course, it is no discovery that these very virtues should be diffused widely throughout the whole of society to create and maintain stability in the various guiding forces which govern people in all walks of life. In the past, the function of the physician, various as it has been, was to a large degree to provide support and hope, to restore confidence, and to bring comfort where disease was progressing to its fatal termination. Any spectacular interference from drugs or therapeutic programs was the exception, not the commonplace. In fact, if the physician was under the governance of an erroneous set of motions, he did more harm than good; and the heroic therapy of our pioneer forefathers with their masses of calomel and huge doses of quinine, with their calamitously enervating purges and their exsanguinating program of bleeding, in many melancholy instances, were the embodiment of disaster. The few specifics were used well enough although often in heroic proportions.

In this country, pharmacy in the modern sense arose with the mass production of medicines and drugs in the Union during the Civil War. Here, for the first

time, the notion of quality control, the pharmacological necessity for pure and dependable compounds, and the slow introduction of new specifics all began. Thus out of the ancient brews of alchemy and witchcraft, the chemical and pharmaceutical industry arose, supported in part by their own research, in part by work done in university science laboratories, and in part by the increasing sophistication of clinical pharmacology and applied therapeutics.

PURITY STANDARDS, EFFICACY, AND SAFEGUARDING THE USER

One hardly needs to emphasize that before a drug is released for use through the orthodox distribution in sales channels, it must satisfy stringent requirements for purity. It must not exceed certain tolerable limits of acute toxicity and of chronic toxicity. Regulations governing the purported efficacy of drugs have always been less than satisfactory, no doubt because getting convincing evidence rather than effusive testimony has always been so difficult. Efforts to safeguard the user against the ill effects of accumulation of drugs in the body, intolerance to prolonged as compared to brief therapy for acute disorders, the risks of sensitivity reactions, and the danger of particular kinds of cell damage, particularly that of the hematopoietic system, have been much more difficult.

RESEARCH

Very conspicuous research contributions have been made in the privately owned laboratories of individual pharmaceutical concerns as well as their support of research in hospitals and medical schools. Their grants-in-aid for research may vary from completely free basic research to the applied pharmacology of specific drug testing. Within the pharmaceutical industry the freedom of the individual scientist in a laboratory varies considerably. Surely it is unrealistic to suppose that there is not some pressure to work on problems of urgent or potential interest to the parent company in the production of new or improved drugs. Investigators relieved of the responsibilities of teaching and practice may enjoy work in industry. Often financial arrangements are very attractive indeed, but just as in government laboratories, so in industry, the movements of investigators are such that they are one-way streets. They do not reproduce their own technical staff and they provide no general return to the academic arena. A burden assumed by universities and medical schools has been not just that of replacing their own corps of teachers and investigators but to supply government agencies as well as industry. This has not been a matter of much concern since we have become accustomed to it and do not worry, particularly, about those matters which have small emotional charge.

NEWS LETTER—THE INDEPENDENT CRITIC AND CRITIQUE

A very critical need of the medical profession was met rather unexpectedly, nearly ten years ago, when, in the middle of the winter of 1958–1959, the *Medical Letter* on drugs and therapeutics appeared. The first issue was dated 23 January 1959, and the long unfilled purposes of the Letter were evident at once. Its value has been demonstrated by its increasingly important function in graduate medical education and in the practice of medicine. It stands as a beacon in the sometimes bewildering crosscurrents and shoals of the conflicting and at times far from clear testimonial support particularly of new and heavily advertised drugs.

Looked at in the light of history, the *Medical Letter* assumes the function of protecting the people. The function has not always been uppermost in the minds of various organizations related to and in medicine which may speak for different fragments of medicine but have not always had equal concern for the well-being of the patient and of society. As a journal produced by a totally independent, nonprofit group, the publication is in a good position to try to provide unbiased critical evaluation of drugs. Naturally the special emphasis has been on drugs recently introduced or new variations. It has no advertising and this leaves it clear of any charges of multiple loyalties. The efforts of this journal and a few others have been conspicuous almost from the start. We have a place to which we can repair for information. Those receiving graduate training under our supervision can find new authoritative information. Fortunately, it has become increasingly important to the conscientious busy doctor. It can serve

as a court of appeal when he is bewildered by lack of information or conflicting claims.

It is not surprising that the advertising supporting some ethical drugs emphasizes what is desirable in the way of therapeutic effect and underemphasizes the side effects which may be undesirable. No one physician, in fact, no single department or laboratory, can make a satisfactory check of the accuracy of claims for all new drugs or even a few. The sad experience of the recent past and indeed medical history generally records that many more drugs are introduced than fulfill earlier expectations. In fact an enterprising and forward-looking pharmaceutical manufacturer might benefit from a comprehensive study of the discontinued drugs, the ones that never made the grade. Obviously it is greatly to everyone's advantage not to introduce drugs which do not fulfill apparent early promise or live up to expectations because of either inactivity or unwanted effects.

Medical Letter operates as a clearing house, collecting, reviewing, and evaluating, since it does not maintain its own drug-testing program. It has no equity in a compound, but in the truth. There is a real effort made to get authoritative information in a readily digestible, easily managed form as promptly as possible. To do this, a certain amount of material in *Medical Letter* has to be presented in the form of preliminary appraisals. Naturally it is impossible for the accumulation of experience gathered in periodical literature to be ready shortly after the introduction of a new drug. Alterations in positions taken in *Medical Letter*, though uncommon, have occurred. This indicates that they have no proprietary interest in pontification but try to let the facts speak for themselves.

As a teaching device for undergraduate medical student, house officer, and practicing physician, *Medical Letter* has been invaluable. Modern drug therapy with its array of powerful, helpful, and dangerous drugs is dependent upon a vigilant alerting system which will give accurate data on side effects and dangers as well as precise information on therapeutic properties. Sound practice must be based on a knowledge of the natural history of a disease, the effect of a placebo tablet or a placebo personality, the exact pharmacological effects, and the risks of minor or serious reactions. What might be well worthwhile in treating a neoplasm might be ridiculous in treating constipation or the common cold. Thus risks of serious unwanted effects may be taken in treating grave diseases but would not be permissible in minor and self-limited disorders. A drug might be used for a short period which would be unsafe for long-term use.

Medical Letter helps the physician judge the accuracy and significance of what may be reported as medical discoveries in the breathless tempo of newspaper and magazine. This may be very valuable in dealing with the insistent but perhaps confused patient who comes in with high expectations waving his clipping and calling for action. In this day of the mass media, we have not found a way to protect the average person, naïve in his knowledge of science, biology, and medicine, from the booby traps of his own ignorance.

Cost and potency of comparable or identical compounds have been brought out from time to time. The lag in getting information about newly reported toxic reactions has been reduced. Recurring audits keep the physician up to date. An evaluation of over-the-counter drug products helps evaluate preparations widely advertised in extensive campaigns and provides a check on the hard face of reality. Thus sturdily realistic and impartial appraisals of drugs are available and can be referred to as a reasonable help in making decisions.

The fact that the statements in *Medical Letter* are not signed has been distressing to some, but the nature of the publication and the fact that the statements do genuinely represent a consensus rather than an individual opinion seem to justify this. I do not believe it is because the persons concerned would be reluctant to have their names attached.

As might be expected, the pharmaceutical industry at times has been less than cordial in its reception of the *Medical Letter*. There have been a few frays here and there. But the continuing and growing demand and the immediately evident importance of the publication have justified its growing success. Its vital importance on the medical scene increases. A few efforts to tar with the brush of guilt by association or look for the devil in Sunday clothes have proved completely ineffectual. The wisest and best of the producers of therapeutic compounds recognize it as a friend which may at times act with parental sternness or even as a Dutch uncle. But every pharmaceutical manufacturer recognizes that he cannot thrive unless he knows and remembers that what is good for the patient is good for him, not the other way around.

OF DOLLARS, DEALERS, AND DEANS

No one has to be a biblical scholar to realize that it is impossible to serve two masters if their objectives are radically different and especially if their purposes are so different as to be inconsistent one with another. Other things being stable, or, as they say, equal, any doctor who happened to own a drugstore would direct his patients there to fill prescriptions rather than to a competitor. Likewise, if a physician owned stock in any pharmaceutical enterprise which was in competition with another similar organization, it would go against nature for him to promote his competitor's wares selectively against his own or even to be neutral. Thus whenever the doctor is also the apothecary, when a physician prescribes, manufactures, and sells glasses, or when we learn that an important member of a medical school's administration is promoting business for a pharmaceutical firm in which he is involved financially, we know that the profit motive will not be subservient to a calm and scholarly consideration of the scientific evaluation of drugs. When such a person actively campaigns in the promotion of certain material and exhorts his colleagues who are shareholders to try to bring in a little extra business, the public is appalled at the crass cupidity and stupidity.

In no place is a conflict of interest more flagrant and more sinister in its implications. This picture of physicians revealed to the lay public, however minuscule a fraction of all practitioners it may represent, is necessarily a shoddy and shabby one. While this might be condoned as a maneuver to promote business, those engaged in the treatment of the sick and those directing teaching in a medical school have responsibilities which outweigh their far from picayune financial interests. Theirs still is the responsibility of protecting the consumer, in this case, the patient.

ADVERTISING

One could write tomes on the bad taste as well as the extraordinary ends to which pharmaceutical concerns have gone to attract and support sales. A sad spectacle at a contemporary medical convention is the doctors' wives and friends, eyes alert with the trained skilled of the "hawk of the supermarket," making off with bundles of samples and miscellaneous gimmicks. The promotion of sales of drugs is aided and abetted by the detail man, many of whom are conscientious and reasonable. Few are steeped in the critique of scientific training. It is deplorable to have so large a proportion of physicians depend upon these men, competing as secondhand teachers, echoing the carefully prepared productions of Madison Avenue but not always separating testimony from evidence, false from true. The burden of mail that accumulates in a physician's office, including the drug samples which occasionally are tested by enterprising children, are a nuisance and may be a danger. The advertising in medical and controlled circulation journals varies from what is sensible and helpful to what is appalling and sometimes dangerous nonsense. No one of these methods is necessarily bad in and of itself. They do lend themselves readily to abuses whenever there is no internal check or external monitor to control them.

Among the unprecedented developments of modern medicine, the valuable life-sustaining and sometimes life-saving drugs made available by the pharmaceutical industry should be praised in lavish terms. This does not give a carte blanche for wasteful advertising, for foolish competition, or for license which permits the distribution of unsafe or useless compounds.

The ease with which gullible man is gulled is incentive enough for imposition, imposture, or downright fraud. Although patent medicine quackery is not a thing of the past, much larger fortunes are now being made from the legitimate sale of ethical drugs.

DRUG TESTING

In testing a new drug, there are many tasks. The investigator has to obtain true and relevant data, expunge error, correct earlier mistakes, and see that the information is widely disseminated and acted upon. Some of the rare frauds of clinical testing as well as many of the dubious tests quoted in support of the value of this or that drug do little to win confidence. The physician who is in the pay of pharmaceutical manfuacturers is in no position to keep public confidence in his objectivity. The editors and owners of medical journals which depend so heavily upon advertising are vulnerable and not only must be above taint but, like Caesar's wife, above suspicion.

THE BUSINESS ARENA

Those who have been experienced in the field of medicine for 25 years or more can remember the dreary scene where therapy was so largely expectant, so much that of providing support, reassurance, and perhaps the display of character. One is now amazed at the multiplication of specifics and the increasing power of drugs and chemicals. The industrial production of chemicals properly safeguarded so as to prevent contamination of the atmosphere, earth, air, and water, stand over against the vast and general contamination. In the manufacture of powerful pharmaceutical compounds, industrial wastes are those that result from the frenzied market competition where slight modifications in manufacture or in molecular structure may give a great though temporary advantage.

We have now an array of powerful medicines; for example, a burgeoning tribe of antibiotics, the large family of descendants of the original sulfonamide clone, scores of adrenal steroids and the related sex hormones which go to make up "the pill," as well as tranquilizers, barbiturates, and antihistamines. Each new one joins in an array which produces confusion from two sides. On the one hand, the minor molecular modifications do not often produce significant therapeutic advantages. On the other, the multiplicity of trade names for identical compounds multiplies the confusion. Metabolic antagonists, a variety of drugs used to assault the effects as well as the processes of neoplasms and the maze of psychedelic drugs, perhaps more symptomatic than causative of many of today's confusions, present us with a whole new order of problems. Of their nature, they are controversial. Perhaps, of their nature, they are insoluble just as many problems confronting us today are insoluble but more urgent problems squeeze them off to the side.

In a competitive, capitalistic society, those who gain the advantage by patenting discoveries have a clearly legitimate claim to profits. In the long run, however, when the pharmaceutical industry devotes so much of its talents to developing minor but patentable variations to deal with the competitive market rather than exploring unexplored territory, the major result is likely to be seen in conspicuous new allotments for advertising rather than a new boon for the sick man or the physician trying to take care of him.

A company with skill enough to make an original discovery in this field obviously should be rewarded for its effort. If the legal situation to ensure this award were clearer, at least some of the troubles would disappear. Even the contemplated revision of the patent laws, however, gives no clear evidence that the ends desired would be achieved. As far as trade names are concerned, if the company making the original discovery were granted the patent, only a single trade name would be needed to be used by licensee as well as discoverer. If a sufficiently different new way were discovered for making the drug, the new discoverer would market it under the generic, or nonproprietary, name, thus at once easing the job of the patient, the pharmacist, and the physician. By reducing the retailer's overhead of multiple duplicating stocks, the same drug with different names, the cost to the consumer would be reduced. The battle of generic names has gone on furiously and there seems to be very little hope that it will abate.

THE GOVERNMENT AND THE PHARMACEUTICAL INDUSTRY

At times the complexity of the problems vexes the ordinary citizen as well as the physician in trying to determine what should be the proper relationship between pharmaceutical manufacturer and the legal agents of the government which test the drug. There is the feeling of "a plague on both your houses." History gives us little cause to be encouraged that such conflicts in society can be eliminated. Social science has not yet provided any vital clues for resolving the difficulties. Thus it remains the responsibility of the physician and the scientists to study the conduct of the opposing forces and try to adjust them if society is to be healthy.

Look at it the other way around. Is it humanly possible that drug safety can be legislated any more than morality could be legislated as we found out very expensively with the Prohibition experiment?

An approach to the problem within channels already operating under present laws might be achieved if the Food and Drug Administration could become an organization with a large and wise staff of well-trained men whose professional

ability was simply paid for and whose prestige could be brought to the level of those who work in the National Institutes of Health. This idea may be Utopian but if the vast volume of tests and the increasingly cumbersome paraphernalia of approval could be speeded up without the loss of accuracy, we would all be much better off. Consider a list of facts dealing with drug testing:

1. More new drug applications are filed with the FDA each year than it can properly classify.

2. Eighty to ninety percent of all prescriptions written today in this country are for drugs not known or not available two decades ago.

3. The impetus for manufacture of new drugs comes as much or more from industrial exploration as from professional requests.

4. In testing drugs for human use, there has to be a first person and a first group if they are ever to be introduced.

5. The odds of launching a truly satisfactory drug, one with some new efficacy and minor toxic or undesired side effects, is not better than one in many, many thousands. The cost of developing new drugs with the necessarily large proportion of failures is very high.

6. Animal screening is not sufficient as a safeguard.

7. Such standards as we have, for the most part, have been established by leading, reputable pharmaceutical concerns. There is a great need for a confrontation with a meeting of minds between physicians and members of the pharmaceutical industry to settle on programs and details for clinical testing in the light of the multitude of new complexities introduced by the explosive proliferation of new, powerful, and dangerous drugs. On the average, great therapeutic power tends to be associated with more risk of undesired complications, toxicities, or idiosyncrasies.

It is impossible to examine all aspects of the question of how fair is the price of brand-named pharmaceuticals and what should be the regulation about the employment of generic names. Solution of the generic versus proprietary name is but one of a host of unsolved problems.

In a recent issue of *Medical World News* [1], the president of a large corporation, which we shall call "X," was confronted by a member of the Monopoly Subcommittee on the Senate Select Committee on Small Business. Arguments were presented in equal space. On the side of the drug industry, these points were made, each explaining expenses of production.

1. A constant search for new and better compounds is necessary and most are failures.

2. Each investigation is expensive.

3. Multiple dose forms increase the cost.

4. A new drug may require new manufacturing processes of varying complexity.

5. Pilot runs to supply adequate drugs for testing are costly.

6. Mass production introduces new problems after pilot studies.

7. The investigations must be supervised and monitored critically.

8. The design and supervision of quality control are expensive.

9. Marketing to ensure rapid distribution is expensive.

10. Clinical and scientific documentation of all aspects of a new drug must be established by the manufacturer.

11. Release must be cleared by the Food and Drug Administration.

12. A staff of detail men constitutes a large and an expensive element of the marketing organization.

13. Advertising by direct mail, journals, brochures, and exhibits is expensive.

The senator's rebuttal was as follows: Many other pharmaceutical firms which sell manufacturer "A's" products under license have comparable research going on. They license their own products to company "A." Much of the initial rsearch, for instance, on steroid hormones had been done in independent clinic, hospital, and university laboratories as well as in the National Institutes of Health. The quality control of licensed competing companies making and selling the drug under a generic name is as good as parent company "A's." In some instances, costs to pharmacists are so nearly identical, $17.88 per one hundred 5-mg. tablets from company "B" compared with $17.90 from company "A," as to imply price fixing. Company "A's" President was unable to give a breakdown of costs of research on the one hand and promotion and sales on the other. If typical of the industry as a whole, costs of promotion and advertising are 4 to 10 times the cost of research and development.

NOTE.—Numbered references at end of article.

But the real flaw in the pharmaceutical company's argument about prices is the fact that they vary all over the map, depending upon the purchaser and the country where the drug is marketed. The compound under consideration might cost the pharmacist roughly 18 cents a tablet in the United States, around 8 cents in Australia, and a little less than 5 cents in Switzerland. The disparity between bids for the huge quantities involved in government purchases and the cost to the retail pharmacist is in the order of more than 2,000 percent. To quote the article, "One is left with the inescapable conclusion, which [Company A] has done little to dispel, that the price . . . is determined primarily by nothing more than a business judgment of what the traffic can bear." The arguments solidly favored the part of the senator. The fact was obvious that the patient and the scarcely patient taxpayer foot the bill. But it is not really so simple.

FOOD AND DRUG ADMINISTRATION

Despite what at times seems to be an effort to perform the labors of Hercules, there is a creeping suspicion that the Food and Drug Administration is an anachronism, an institution which has not been able to get or keep itself prepared to deal with its responsibilities in the age of superscience and powerful drugs. One does not find on its staff, with rare exceptions, outstanding or distinguished scientists, competent to make judgment on today's drugs. They are in the leading research laboratories of medical schools and the pharmaceutical industry. The competent people attracted to FDA rarely stay, for neither salary nor prestige has kept up the incentive. Its responsibilities have long outdistanced its capacities.

What should be the relationship between government agencies which function as protectors of the people and the pharmaceutical industry? The doctor and patient seem to occupy a sometimes uneasy middle ground. The fact is that such organization and governmental institutions have not been studied scientifically. Movements to protect the consumer now have broad government support. Experience has accumulated under the aegis of the National Academy of Sciences-National Research Council and their panels which review efficacy of drugs approved before the passage of the Kefauver-Harris Act of 1962. Dr. James L. Goddard—who, to say the least, has stirred up the animals—will serve at least one more year.

The depth of the increased government interest is evident. It goes beyond the ordinary governmental and Department of Health, Education, and Welfare hierarchies, for the Congress and the President have introduced Medicare and Medicaid. This requires Health, Education, and Welfare to take a vital interest in the rulings and decisions of the Food and Drug Administration. Not only does government support under Medicare and Medicaid increase the responsibilities of Health, Education, and Welfare, but its support of medical research through the National Institutes of Health implies an interest in the development of new methods, drugs, devices, and regimens in therapy. Basically the question comes down to what good may be achieved for the consuming public. The individual patient must be the standard against which not only the organization and the staff but the practices of the Food and Drug Administration are judged.

An effort to measure the effect on public health is probably beyond the programming of any modern computer but it certainly should be thought about. We have made assumptions that a more rigid review of drug advertising, with emphasis on toxic and side effects, as well as therapeutic virtue, will be of benefit to the patient. What is the evidence that this is true? Do we know, indeed, that improving the Food and Drug Administration's staff would improve the lot of the consumer, i.e., the patient? Would the actual application of medicine to the patient, that is, the prescription practice, change substantially or be improved by requiring uniform display of generic names on all drugs? We need serious study to get valid answers to these difficult questions.

As an example of the multitudinous difficulties that the Food and Drug Administration illustrates or perhaps generates we may take Dr. Walter Modell's charges of Food and Drug Administration censorship. These arose from a statement by Mr. William Goodrich, counsel to the Food and Drug Administration, that "publishers, authors, and editors who have written, approved, and published drug dosages which deviate from those recommended by the FDA are liable for damages to the patient and to the pharmaceutical manufacturer as well" [2]. Modell's pressing of the charges hinged around the threat that

Goodrich's statement posed to medical authors, editors, and educators. He supported this by the fact that Saunders publishing company had thought it wise to remove the unbound sheets of Beeson and McDermott's revision of Cecil and Loeb's *Textbook of Medicine* to print a disclaimer. But perhaps the main focus of the charge was the FDA's alleged dereliction of duty when, in a particular case, it made an arbitrary decision to lower a dose for the purpose of reducting toxicity without any regard to the efficacy of the lower dose.

One's conclusion is inescapable that the Food and Drug Administration is overworked and understaffed; that it may have totally unrealistic demands put upon it. It is necessary for physicians, investigators, and teachers, as well as the drug producers, to attack the questions in scientifically evaluated study in order to find what is the best method of achieving reasonable legal control of drug manufacture and use, one which would protect the public and at the same time not stifle the ethical pharmaceutical industry which depends, for survival, upon a reasonable profit. In the long run, in this continuing debate, the substance of the argument on all sides hinges upon a definition of what is reasonable and then being reasonable.

REFERENCES

1. *Medical World News* 8 (Sept. 1, 1967), 56–61.
2. Modell, W. FDA Censorship. *Clin. Pharm. Therap.* 8: 359, 1967.

THE UNITED STATES PHARMACOPEIA,
Bethesda, Md., December 10, 1968.

Mr. BENJAMIN GORDON,
Staff Economist, Select Committee on Small Business,
Old Senate Office Building,
Washington, D.C.

DEAR MR. GORDON: In response to your call, I am sending my impressions of the article entitled "The Generic Inequivalence of Drugs" by Alan B. Varley, M.D. that appears in the December 2, 1968 issue of the Journal of the American Medical Association. I have noted the frequent and rather derogatory references to the United States Pharmacopeia in the text, which in departing from the usual 3rd-person style, regrettably becomes almost a personal attack on the U.S.P.

We can agree at once with Dr. Varley that the concept of "generic equivalence" is muddled, semantically and otherwise. The three proposed terms, which I believe are used in the H.E.W. Task Force Second Interim Report, should help clarify future discussion.

The data Dr. Varley presents are not at all surprising or particularly new. For years, drug firms have been making and testing experimentally drug dosage forms that have been less than fully satisfactory in comparison with other very similar products. Only comparatively recently have good methods become available that make such tests fruitful. There is very little evidence that such products get out on the market, but we can all agree that then even the risk of their doing so should be minimized.

We must take Dr. Varley at his word that both of his products A and B met the present U.S.P. specifications; certainly the 7.6 minutes disintegration time he reports for Product B is well within the 30-minute limit specified in U.S.P. XVII. It may be useful to point out, however, that the U.S.P. test was capable of discriminating between Products A and B. The one difference that was picked up in the laboratory, i.e., in dissolution time, is quite significant. The test method used is not cited, but we would assume that it cannot differ greatly from that which is being studied currently with a view to its inclusion in the U.S.P revision now in preparation for release within a year. I would expect that a dissolution time as long as 103 minutes would certainly disqualify Product B under any standard approved for U.S.P. XVIII.

We are preparing a communication to the Editor of J.A.M.A. and will send a copy to you if you wish to have it.

Sincerely yours,

LLOYD C. MILLER, Ph. D.,
Director of Revision.

[The following additional material from Dr. Lloyd C. Miller, Director, U.S.P., was received by the Subcommittee Chairman before this volume went to press.]

THE UNITED STATES PHARMACOPEIA,
Bethesda, Md., March 6, 1969.

Senator GAYLORD NELSON,
U.S. Senate,
Old Senate Office Building, Washington, D.C.

DEAR SENATOR NELSON: Enclosed is a letter to Dr. Alan B. Varley, of the medical staff of the Upjohn Company, which takes him to task for the tone of an article that appeared prominently in the November 18, 1968, issue of the Journal of the American Medical Association. Mr. Gordon and I have discussed the article and I promised to make a copy for you of any comments we might have on it.

This article reports nothing more than the successful execution of a pharmaceutical trick. For medical newsworthiness, it doesn't begin to compare with some of Houdini's exploits. Thus it seems to me that the Editor of J.A.M.A. is due criticism for assigning the lead-article position to this report and for making the very exceptional grant of 2-color treatment to the two charts. You may note the mention made of the fact that Mr. Graham of the Upjohn staff is one of the 60 members of our current Revision Committee. Mr. Graham was not aware that the article was in preparation and has been unable to obtain for our testing any of the two lots of Tolbutamide Tablets that Dr. Varley studied. In short, through accident or deliberate company policy, this attack on U.S.P. standards was planned to exploit the differences observed and to avoid making use of the most effective means of correcting them.

We have seen discussion of your bill on a federal compendium on prescription drugs S. 950. May we ask for 2 copies of it and of that portion of the Congressional Record in which your remarks concerning it appear? While we understand that the terms of S. 950 are much the same as a similar bill introduced last year, we wish to study it further.

Our renewed study will be made from the standpoint of the plan now in motion for the U.S.P. to provide information of the sort that the compendium might contain. We would like to have an opportunity to discuss this plan with you at some mutually convenient date in the near future. We would hope to have present also the chairman of our U.S.P. Board of Trustees, Paul L. McLain, M.D., who can arrange to come in from Pittsburgh if given sufficient notice to allow him to arrange for meeting any scheduled lecture commitment at the Medical School that might conflict.

I will be in touch with your office by telephone shortly in respect to the appointment.

Sincerely yours,

LLOYD C. MILLER, Ph. D.,
Director of Revision.

Enclosure.

U.S. PHARMACOPEIA, *March 4, 1969.*

ALAN B. VARLEY, M.D.,
Kalamazoo, Mich.

DEAR DR. VARLEY: Perhaps the long delay in its arrival will be the only cause for surprise in our offering comment on your article, "The Generic Inequivalence of Drugs," J. Am. Med. Assoc. 206:1745 (Nov. 18) 1968 which obviously has the object of downgrading the U.S.P. Actually, we are not sure we would be writing had you not repeatedly included the name of the Pharmacopeia in your blanket condemnation of physical-chemical specifications of drugs and drug products. However, we do see other grounds for criticism also.

Clarification of the semantically muddled concepts of "equivalence" is a laudable objective; however, we wonder if at this stage the muddling is not far beyond the corrective efforts of any single individual. The Academy of Pharmaceutical Sciences has recently issued a draft of a statement and, in our view, that distinguished body has failed utterly to improve matters. Your former colleague, Dr. John Wagner, has perhaps kept you advised on that score.

On the constructive side, we believe that it would help greatly to reserve the word "drug" for the active agent only, and to use the term "drug products" for

the drug combined with other ingredients in the form by which the drug reaches the physicians, pharmacist, nurse, and ultimately, the patient. These two terms seem to be on their way to acceptance through rather consistent use by the Pharmaceutical Manufacturers Association, the American Society of Hospital Pharmacists' computer file of drugs, by FDA staff in recent talks, and in much of the recent, pharmacy-oriented literature. I am sure that, on re-reading your article, you would find it clearer if this distinction had been made, and we will use the terms, drug and drug product, in that context in the following comments enumerated below.

1. A general condemnation of "chemical" specifications (your last sentence) for drug products is not justified, we believe—

(*a*) Pharmaceutical manufacturers generally have had excellent results in controlling batch-to-batch consistency of most of their drug products with physical and chemical tests alone:

(*b*) Such tests are usually far more sensitive in establishing differences among drug products than clinical studies of therapeutic efficacy can possibly be. For example, with physical-chemical tests we can reasonably require that Aspirin U.S.P. be 99.5% pure acetylsalicylic acid and be sure that water accounts for almost all of the remaining 0.5%; with these same tests, we might require that Aspirin Tablets U.S.P. contain 99.5 to 100.5% of the labeled amount of pure acetylsalicylic acid—but this would scarcely be reasonable, since there are more variables in the manufacture of the drug product than in making the drug. Therefore, the U.S.P. standard for Aspirin Tablets, a *chemical equivalence specification*, sets 95% and 105% of the labeled amount as the limits on the content of pure acetylsalicylic acid. This is a reasonable production standard even though it represents a degree of precision quite beyond that attainable by measurement of therapeutic response. On the basis of some personal experience with tests of analgesics and other drugs, I suggest that your "ideal criterion for establishment of therapeutic equivalence—trial of comparative efficacy in appropriately disease-afflicted patients" is wholly unrealistic for distinguishing among Aspirin Tablets or for that matter, different formulations of most other drug products. In short, at best, physicians can seldom detect drug product differences of the sort generally picked up readily by properly chosen and applied chemical and physical tests.

2. Your general condemnation of "U.S.P.-type" specifications for drug products is not justified, in our view—

(*a*) Equating "chemical" and "U.S.P.-type", as you have, betrays a glaring unfamiliarity with U.S.P. specifications. For reasons set forth above, the U.S.P. Revision Committee prefers the precision of physical-chemical tests whenever they are appropriate. However, numerous U.S.P. drug and drug product specifications are biological in nature, e.g. insulin, digitalis, tubocurarine, etc. Prior to the development of physical-chemical methods for quantifying cyanocobalamin, your "ideal criterion" was the best we could muster in standardizing Liver Extract, Liver Injection, and Crude Liver Injection on a batch-by-batch basis for nearly 15 years. The U.S.P. has a solid history of using the types of tests consistent with the expertise and scientific knowledge of the times which are best suited to the needs of the particular drug product.

(*b*) We heartily agree with the substance of your comment that "The fact remains that it *is* (italics yours) clearly possible to produce considerable differences in both availability of drug to the human patient and in eventual therapeutic usefulness by making tiny changes in the formulation which are clearly within present U.S.P. chemical equivalence standards." In short, the ingenuity of our very talented pharmaceutical chemists can be put either to good or bad use.

In the light of this, what sets U.S.P. policy in this area? Briefly stated, the pharmaceutical scientists of the U.S.P. try to set standards that will give the physicians reproducible results both between lots of a given brand and between brands of the same generic drug product.

All too often, physicians are of no help whatever in this regard. For example, there has never been an assay for Coal Tar because no one seems to know what it contains that accounts for its usefulness to dermatologists. Thus, in effect, neither the active ingredient nor its vehicle are standardized. As another example, the physicians on the U.S.P. Revision Committee have agreed that 1.1%

of hydrocortisone acetate is a desirable amount of drug to have in an ointment but decree that the choice of base should be left to the individual prescriber for the particular condition he is treating and the area of the body being treated. We might elaborate at length on the differences, but the fact is that they are numerous and substantial. We have exchanged considerable correspondence with experts in your company of this very point.

There are U.S.P. scientists and practitioners who believe that every U.S.P. drug product should have a specified formula. The very thought of such a requirement would raise hackles of foot high all through the drug industry!

3. It should be recognized that tightening of standards is rarely due to physicians' requests as a result of therapeutic failures but nearly always to efforts of pharmaceutical scientists aimed at improving the product. A case in point is the dissolution testing which you report using with Tolbutamide Tablets. Studies of dissolution rates came about as a result of attempts to improve on the disintegration properties of tablets and to correlate those properties with absorption of the drug from the drug product into the blood.

I do not wish to imply that physicians are not interested in drug standards, least of all the physicians of the U.S.P. Committee of Revision. I am merely saying that the physical-chemical methods of the pharmaceutical scientist generally lead to more sensitive and precise standards for drug products than do any measurement of therapeutic response by a physician.

The foregoing applies to "availability equivalence." The pharmaceutical scientist can set dissolution rates which help to assure batch-to-batch uniformity of the drug product. Your article reported this as the distinguishing measurable difference between the two Tolbutamide Tablets discussed. Yet absorption does not vary consistently with differences in dissolution rates. When does a dissolution rate profile, obtained with a specific instrument and procedure, reflect real differences in availability equivalence? If we can establish that for a U.S.P. drug product, it will promptly become a part of the standard even if availability equivalence is *not* an indication of *detectable* therapeutic differences!

This position evolves from the conclusion that a dissolution rate test is a reasonable addition to the physical-chemical testing armamentarium, and that some day the art of therapy using that drug product may advance to a point of greater sensitivity in detecting therapeutic differences. Conversely, if availability equivalence can indicate therapeutic differences but no dissolution rate test can be devised which consistently reflects availability from different formulations of a particular drug product, the absorption test itself can become a part of the U.S.P. standard. Then the U.S.P. Revision Committee will have to decide how the standard shall be applied; i.e., whether all formulations of that drug product should meet a specific availability standard, or whether to allow variations in the rate of availability provided the label declares the rate for each specific formulation.

4. As a physician, *you* individually have a responsibility for U.S.P. standards.

(*a*) In almost all other countries, an agency of the government sets the standards of quality for drugs and drug products. In America the professions do it (except for antibiotics and biologicals where, for one reason or another, a government agency has been given specific authority by the Congress). The United States Pharmacopeial Convention antedates both the American Medical Association and the American Pharmaceutical Association, not to mention federal food and drug legislation. The U.S.P. Convention is the only organization in this country based equally on institutions and organizations representing the scientists-educators and practitioners of medicine and pharmacy and supplemented by organizations of scientists of related skills. The members of the U.S.P. Committee of Revision, 20 physicians and 40 pharmaceutical scientists, are elected by the delegates from these organizations. Many of those elected are associated with pharmaceutical manufacturers, either at the time of their election or subsequently during their term of service. As a physician and as a researcher employed by a pharmaceutical manufacturer, you should have a special interest in ensuring that this professionally-responsible organization establishes the best standards for drug products of your manufacture. U.S.P. standards are not set by the U.S.P. staff; they are worked out through the concensus of the experts on each drug and drug product, whoever and wherever they may be.

(*b*) At present, your company is the only American manufacturer of Tolbutamide U.S.P. and Tolbutamide Tablets, U.S.P. Therefore, our U.S.P. standards largely reflect the experience and needs of your company. If there is any defi-

ciency in these standards, we would expect your firm to be the first to call them to our attention. As a matter of fact, the late Dr. Glenn Bond and Mr. C. Leroy Graham of your firm were elected to the U.S.P. Committee of Revision in 1960. In rendering service on the U.S.P. Committee, both distinguished themselves as first-rank statesmen. Mr. Graham also serves on the National Formulary Board and, furthermore, is a member of the U.S.P./N.F. Joint Panel on Physiological Availability, a panel which has been working diligently on the very object of your complaint.

The Panel was recently advised the U.S.P. and the N.F. to standardize on two dissolution test procedures from among the many which have been proposed. To build up experience and data, we welcome the receipt of samples of two formulations of any chemically equivalent drug product which have been found to provide consistent and significantly different blood levels.

Sincerely yours,

LLOYD C. MILLER, Ph. D.,
Director of Revision.

THE WM. S. MERRELL COMPANY,
April 19, 1960.

INTERDEPARTMENT MEMORANDUM

To: Dr. R. L. Stormont
From: R. H. McMaster, M.D.
Subject: Hyman Engelberg, M.D., Cedars of Lebanon Hospital, Los Angeles, California in the amount of $500.

Dr. Engelberg has made a verbal request for $500 to support his continued study of the effects of MER/29 on the lipoprotein fractions as assayed by the Codman technique using the ultracentrifuge. The results with the first two or three patients in whom this technique has been tried have been rather equivocal if not completely negative. Dr. Engelberg, however, is of the opinion that before any conclusions can be drawn, the experiment should be extended to include a larger group. He does not wish to subject these private patients to the expense of having these rather elaborate laboratory studies down and feels that The Wm. S. Merrell Company should foot at least a part of the bill. He believes that $500 will cover the costs of cholesterol determinations and the separations of the high and low density lipoprotein fractions by ultracentrifuge in another ten to twelve patients.

Although it begins to appear that any report from this study may be a negative one, we may find that we are money ahead to keep Dr. Engelberg busy at it for a while longer rather than to take a chance on his reporting negatively on so few patients. As you are aware, the Codman technique is in some disfavor and certainly has never been generally accepted as providing for a true "atherogenic index" as claimed.

My personal recommendation is that the grant-in-aid be approved only to keep Dr. Engelberg occupied for a while longer.

THE WM. S. MERRELL COMPANY,
August 19, 1969.

INTERDEPARTMENTAL MEMORANDUM

To: E. F. Van Maanen
From: Medical Research Department
Subject: M.F.R.—29—Effects on Monkey Ovaries (your memorandum of August 14 to Doctor Scanlan).

DEAR FLOR: Many thanks for the tactful way in which you defined the conditions under which the monkey ovary pictures can be used clinically. I am strongly opposed to the discussion of any finding from experimental animals until we have agreed upon our interpretation. Some potential investigators were frightened about M.E.R.—29 a year ago because of a very similar problem. In this case, I do agree that we can show the pictures to our investigators in Syracuse, but it is acknowledged that we are taking a calculated risk because of a great moral and ethical problem involved. Because of the careful selection of our investigator in Syracuse. I think that it is a reasonable risk for us to take.

R. C. POGGE, M.D.

THE WM. S. MERRELL COMPANY,
July 5, 1961.

INTERDEPARTMENT MEMORANDUM

To: Dr. H. W. Werner
From: R. H. McMaster
Subject: William Hollander, Boston, consultation fee

Hollander mentioned the matter of his consultation fee. You will recall that we have had him on a personal retainer amounting to $2,400 per year payable in 2 semi-annual installments. If we wish to maintain this relationship (which is apart from Wilkins' grant), a payment of $1,200 is now due. My own feeling is that we can't afford to chance alienation of Hollander just now (perhaps I shouldn't regard this as blackmail).

Certainly we need his help and counsel.

THE WM. S. MERRELL COMPANY,
May 20, 1959.

INTERDEPARTMENT MEMORANDUM

To: Mr. F. H. Gelman.
From: Robert H. Woodward.
Subject: MER–29 Clinical Status and Plans.

Your comments on May 11 concerning this subject were certainly appropriate and helped to focus our attention further on the job to be done.

As a matter of further information, it is our intention to closely follow the cross reference of the investigators and the problems which each investigator is assigned. It was not thought desirable to do this, however, until the investigators which we have selected have been approached and have been assigned these subjects which are best fitted into their own research knowledge and facilities. When this has been done, we certainly will then cross check the needs and determine if each has been adequately met.

The comments which you made at the end of your memo regarding the NIH and their interest in MER–29 confirm the emphasis which was placed upon this source of clinical knowledge during our planning of the entire program. In Dr. Pogge's memo to Dr. McMaster of May 15, I notice where he mentions a preliminary contact which was made by himself while in Washington on May 6. He mentions or rather suggests that no grants be made, and I think, in view of our present policy, that we should make this an emphatic point rather than a suggestion. By means of a copy of this memo I am also asking Dr. Pogge to make each of those individuals in the Medical group who may be following up this subject in Washington completely familiar with the preliminary work which he has undertaken. In fact, it appears to me that this is a special project worthy of the best effort by Dr. McMaster as a follow-up to whatever was done by Dr. Pogge. I am sure that we can get action in this area and that it will provide a case of clinical evidence which can be most useful.

The objective in contacting the armed forces was to lay the groundwork for the eventual sale of the product to the various hospitals serving each branch of the armed forces when the product is released. We were not thinking here so much of honest clinical work as we were of a pro-marketing softening prior to the introduction of the product.

[From William S. Merrill Co. Sales Talk—News, Tips, Ideas—An Answer to Medical World News, July 26, 1960]

DR. LISAN SPEAKS UP

The following letter, written to the editor of *Medical World News*, was published in the July 15 issue of that magazine:

"HYPERCHOLESTEROLEMIA

"As one of the participants in the Symposium on Hypercholesterolemic Drugs at the AMA meeting, Miami, I was quite surprised and concerned about your article 'Breakthrough on Cholesterol' (MWN, June 17) . . .

"In our experience with more than 100 carefully studied patients given MER/29 (Merrell) for periods up to two years, there has been no evidence of hepatic disease or dysfunction. Clinical side effects (nausea and skin reaction) have been almost negligible and certainly not serious.

"Dr. William Hollander, of Massachusetts Memorial Hospitals, reported at the American Therapeutic Society, June 10, that he and his associates have followed their many long-term patients with serial liver function tests. In several patients liver biopsies were obtained, and in none of these was there evidence that MER/29 altered hepatic morphology.

"The relative safety of MER/29 has been reported by others. Dr. J. Earle Estes (Mayo Clinic) has administered MER/29 in doses as high as 3 grams daily for months at a time without side or toxic effects. These studies, in addition to our studies on the safety of MER/29, were published in the May issue of *Progress in Cardiovascular Disease.*

"Your writer failed to stress that Dr. Corday's study indicated that T4F (Lilly) is not effective in euthyroid patients for lowering cholesterol. Most patients with coronary artery disease and hypercholesterolemia are euthyroid, therefore, T4F is not the 'potent answer' for cholesterol-lowering. On the other hand, MER/29 significantly lowered cholesterol in 85 percent of the patients, all of whom were euthyroid.

"PHILIP LISAN, M.D.
"Hahnemann Hospital, Philadelphia, Pa."

THE WM. S. MERRELL CO.,
June 21, 1961.

INTERDEPARTMENT MEMORANDUM

To: Dr. Bunde (3).
From: R. H. McMaster.
Subject: Trip Report, New York City, American College of Cardiology, May 16–19, 1961.

Dr. Michael Winzenried, Hamburg, Germany, Kevadon

Upset because of failure of Chemie Grünenthal to provide subsistence funds. Put him in contact with Dr. Jones.

Louis E. Schaefer, M.D., New York, N.Y., MER/29

Has followed some 25 patients very carefully. Believes that triglyceride response is favorable in hypercholesterolemic patients whose triglycerides are initially high but that a similar triglyceride response is not evident in hypercholcoterolemics with initially low triglycerides. This is not substantiated by reports we have had from other sources. It is expected that Dr. Schaefer will report his findings in the very near future. I expect to contact him on my next visit to New York City to see if he has made definite plans toward this end.

Robert A Borger, M.D. and Norman Orentreich, M.D., N.Y., MER/29 and Kevadon

These dermatologists are probably doing more research on the human hair than any other group in the nation. In addition to excellent private facilities, they are on the dermatology staff at New York University, Bellevue Medical Center and have access to patients here and from certain others of the city's chronic disease facilities. They are greatly interested in the hair effects of MER/29 and are willing to study these effects, with the hope of determining causes. Will require some financial support and have agreed to submit a protocol. Since this has not yet arrived, I shall contact them on my next visit to New York.

Dr. Orentreich has also been working with Kevadon, which he presumably obtained from sources other than Merrell. He reports that some 10 of approximately 30 cases have developed dermatologic reactions. He considers the incidence much higher than reported in the literature. Dr. Jones is now in touch with Dr. Orentreich.

Marvin C. Becker, M.D., Newark, New Jersey, MER/29

Dr. Becker's paper (prepared for the most part by us) was rejected by the American Journal of Cardiology and has now been accepted by the Journal of the Medical Society of New Jersey. We have received permission to purchase reprints.

Continues to obtain favorable results with MER/29 and may make a follow-up report for publication later if results warrant.

Arthur DeGraff, M.D., New York, N.Y., MER/29

Dr. DeGraff remains convinced that MER/29 was the responsible agent in causing the hepatomegaly and fatty metamorphosis in the patient of Dr. Mario V. Bisordi, Mount Vernon, New York. However, he was very gracious and permitted me to present our accumulation of data which certainly do not support his contention. No mention was made of an impending publication concerning this case. I was unable to contact Dr. Bisordi, who had previously promised to send us the pathologic sections and medical and pathologic report about this patient. I expect to contact him during the meeting of the A.M.A.

THE LIBRARY OF CONGRESS,
LEGISLATIVE REFERENCE SERVICE,
Washington, D.C., December 6, 1968.

To: Senate Small Business Committee (attention Mr. Gordon).
From: American Law Division.
Subject: Responsibility of director to stockholders.

This is in response to your query for a brief statement of the measure of responsibility which a corporate director owes to the corporation's stockholders.

The courts have developed standards for deciding issues relating to the performance of a director's duty to the corporation and its stockholders and these are generally applicable in state and federal courts. The basis of the duty may be expressed in Justice Cardozo's phrase, a "duty of constant and unqualified fidelity." *Globe Woolen Co.* v. *Utica Gas Co.*, 224 N.Y. 483, 489, 121 N.E. 378, 379 (1918). While directors are not strictly speaking trustees, they do occupy a fiduciary, or perhaps more accurately, a quasi-fiduciary, relation to the corporation and its stockholders. *McCandless* v. *Furlaud*, 296 U.S. 140, 156–57 (1935); *Anderson* v. *Bean*, 272 Mass. 432, 172 N.E. 647 (1930); *Markovitz* v. *Markovitz*, 336 Pa. 145, 8 A. 2d 36 (1939). Each director must exercise his unbiased judgment, influenced only considerations of what is best for the corporation. *Lattin on Corporations*, 241, 242 (1959). Many courts have spoken of the rule as being that a director owes a loyalty that is undivided and an allegiance that is influenced in action by no consideration other than the corporation's welfare. *Hazard* v. *Wright*, 201 N.Y. 399, 94 N.E. 855 (1911).

However, to note one element in the problem, courts have not prohibited a director of a corporation from entering into and engaging in a business enterprise independent from but similar to the business carried out by the corporation. Grange, Schwartz, Gray, & Woodbury, *Manual for Corporation Officers*, 756 (1967). But his participation in the other business must not injure the corporation and it appears to be the general rule that if a director's private venture comes into direct competition with the corporation he must give up one or the other. *Guth* v. *Loft, Inc.*, 25 Del. Ch. 255, 5 A. 2d 503 (1939); *Lincoln Stores* v. *Grant*, 309 Mass. 417, 34 N.E. 2d 704 (1941); *Raines* v. *Toney*, 228 Ark. 1170, 313 S.W. 2d 802 (1958).

Generally, state statutes in this area do not attempt to explicate the duty of a director but maintain the common law developed by the courts by simply requiring that directors "shall discharge the duties of their respective positions in good faith . . ." N.Y. Bus. Corp. Law. 717. See, *Kavanaugh* v. *Commonwealth Trust Co.*, 223 N.Y. 103, 119 N.E. 237 (1918).

JOHNNY H. KILLIAN,
Legislative Attorney, American Law Division.

(Whereupon at 12 noon the subcommittee recessed to reconvene at 10 a.m., Tuesday, December 17, 1968.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

TUESDAY, DECEMBER 17, 1968

U.S. SENATE,
MONOPOLY SUBCOMMITTEE OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to call, at 10:10 a.m., in room 318, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee), presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; and Elaine C. Dye, research assistant.

Senator NELSON. The Monopoly Subcommittee will open its hearings at this time.

Tomorrow, December 18, we will be hearing from Dr. Franz Ingelfinger, editor of the New England Journal of Medicine; Dr. Paul Lowinger, associate professor of psychiatry, School of Medicine, Wayne State University.

On Thursday, December 19, we will be hearing from Dr. James Faulkner, chairman, Committee on Publications of the Massachusetts Medical Society, and Dr. George Baehr, chairman, Public Health Council of the State of New York, and a professor at Mount Sinai School of Medicine, City University of New York.

Today our witness is Dr. George Nichols, Jr., clinical professor of medicine at the Harvard Medical School.

This week, the Monopoly Subcommittee of the Senate Small Business Committee continues its study into the relationships of the medical profession and the drug industry, particularly in regard to possible conflicts of interest, professional responsibility, and ethical implications.

Last Wednesday, the subcommittee heard from Dr. William Bean of the University of Iowa Medical Center—a widely known medical authority and former chairman of the section on internal medicine of the American Medical Association.

Dr. Bean asked, as far back as 1952:

> What is the most effective general teaching today at the postgraduate level? In sorrow we must admit that the artistic and artful brochures of wealthy pharmaceutical houses, sped on by a crusading band of detail men, have effectively taken over graduate teaching.

Dr. Bean went on to say:

> * * * when advertising budgets exceed the total outlay for teaching and research provided by all our medical schools, concern is justified, "for where your treasure is, there will your heart be also."

When Dr. Bean was asked how necessary and valuable it is to have the kind of full page ads that we see in medical journals and all brochures—how useful these were to the physician, he said: "I think * * * that probably a very considerable part of advertising is not primarily educational, and in many instances is not necessary at all."

Dr. Bean noted that as long ago as 1950 and again in 1959 he had called attention to the fact that "physicians and representatives of the pharmaceutical industry should work out voluntarily means of evaluating claims for drugs, evaluating therapeutic effect of drugs, and then seeing that advertising, sales, detailing, and retailing were managed according to regulations developed by joint action * * *. No formal study, joint effort, or confrontation of producer, distributor, dispenser, and user ever came about."

And so it seems that 10, even 20, years ago we were well aware of the problems involved in the relationship between the drug industry and the medical profession. In my judgment, this is a sad commentary upon the leadership of the medical profession, the pharmaceutical industry, and the Federal Government as well. Had they jointly or even severally begun to resolve these problems, it would not have taken the action of this subcommittee to bring these issues into focus.

It is my hope that these hearings will act as a forum for the clarification and future solution of the problems involved in the relationship between the drug industry and the medical profession.

We are, in these hearings, reviewing the relationship between the pharmaceutical industry and the medical profession, and the medical institutions such as schools, medical societies, their publications, and so forth.

The tie-in is obviously quite close. Is this good or bad for the industry, the profession, and the public?

As I noted, our first witness is the distinguished Dr. George Nichols, clinical professor of medicine at the Harvard Medical School, also consultant in medicine, the Boston City Hospital, and senior associate in medicine, Peter Bent Brigham, Boston, Mass.

Doctor, the committee is very pleased to have you appear today to participate in a discussion of this very important issue, and we understand what an imposition it is in terms of taking time off from your busy schedule, but we, the committee, appreciate it, and your statement will be a valuable contribution to this whole record in which we are attempting to explore objectively and in depth the relationship between the medical profession and the pharmaceutical industry.

Your statement will be printed in full in the record. You may present it in any way you desire. If you find it most useful to just proceed to read it, that is fine. Should you wish to depart and extemporize, at any time, please feel free to do so.

I take it you will have no objection if we ask questions during the course of your presentation—which I think is probably the most fruitful way to proceed.

Dr. NICHOLS. That is fine.

Senator NELSON. Thank you very much, Doctor.

STATEMENT OF DR. GEORGE NICHOLS, JR., CLINICAL PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL; CONSULTANT IN MEDICINE, BOSTON CITY HOSPITAL; AND SENIOR ASSOCIATE IN MEDICINE, PETER BENT BRIGHAM HOSPITAL, BOSTON, MASS.

Dr. NICHOLS. Senator Nelson, ladies, and gentlemen, I feel deeply honored to have been invited here to place before you my views about some of the problems which face medicine today, and I might interject that I changed the last two pages of my original statement slightly. I had to be out of town and my secretary and I didn't see quite alike on how the things should be said and she left out the piece.

I must confess that when the chairman first asked me to appear, I hesitated, for the issues at stake in these hearings involve the ethics of the profession and we all know that ethics are affairs of the heart which are far easier to feel than to put into words. However, as I considered the matter further, I realized that what was being offered was not just an opportunity to decry undesirable practices or become incensed over specific instances of malfeasance. You have already read and heard plenty about both from far greater authorities than I. Instead, it seemed to me that what was offered was an unusual opportunity to restate for the public record the principles of conduct which every medical teacher tries to inculcate into each of his students and which serve as guides for the majority of the profession in their lifework.

I would like to recall, therefore, the rights and privileges which the public affords the physician and the responsibilities which he assumes in return through his symbolic affirmation of the Hippocratic oath. It is my belief that it is only through returning to these first principles that one can look clearly at the whole matter of potential conflict of interest between the physician, the patient, and the pharmaceutical manufacturer on the one hand and examine calmly and constructively on the other the ways in which the Federal Government, through its granting and regulatory agencies, can help protect all three from unwarranted attack and exploitation by the unscrupulous.

The M.D. degree, unlike any other, gives its recipient the right to pry deeply into the most intimate, personal affairs of his fellow citizen and to make life and death decisions in his behalf. Clearly such a license can only be given to those of the highest moral character who can be trusted to carry out the solemn undertakings symbolized in the Hippocratic oath. These include four basic provisions: (1) to learn the "art" by which we mean medicine, and to teach it; (2) to place the interest of the patient first with the additional stricture, to restrain from consciously doing anything which might be deleterious to him; (3) to leave the execution of special procedures to those with special skills; and (4) to maintain inviolate any private secrets of the patient which are learned in the course of helping him to solve his problems.

These are solemn undertakings indeed which are unfortunately sometimes thought more appropriate to the hot idealism of the years of professional education than they are to the hard, cold, disillusioning

facts encountered often in professional practice. It is hard for the physician under any circumstances to live up to these high ideals; it requires constant work, constant relearning, constant sacrifice, not only of his own comfort and time, but that of his wife and family as well. In recent years, his problems have been enormously intensified by two factors: First, the geometric expansion of knowledge applicable to medicine and the huge increase in the number of new therapeutic agents of great power and specificity which has resulted from it have required that the physician virtually totally reeducate himself at shorter and shorter intervals. By this I mean that he must really completely revise his concepts of the causes of certain diseases and of the ways in which they can be handled.

Second, the public attitude toward medical care and medicine is rapidly changing. Good medicine is no longer considered a privilege but rather a basic human right—an attitude which has been greatly encouraged (and rightly so, I believe) by the Congress of the United States, through enactment of the medicare and medicaid provisions of the social security law.

Both these factors are clearly socially desirable and should be encouraged. Indeed, all would be well were it not for the fact that there are nowhere near enough physicians to meet the enormously increasing demand for medical care which the public is now making. It is small wonder, therefore, that the practicing physician, already unable to find time in the day to meet the demands of his patients, turns to the eye-catching advertising pages of his professional journals rather than to the much longer, far more complicated, even though objective, scientific articles for information about new therapeutic agents with which to minister to his patient's needs, especially if he is unaware of the existence of any simple and unbiased source of reliable information such as the Medical Letter, which has been mentioned in these hearings in the past. In view of the pressures placed upon him, it is equally understandable why the physician, in his earnest effort to help his patients, has turned so often to the ubiquitous lay drug salesman for guidance and information and to inevitably biased commercial institutions for financial support of his public meetings and so forth, moves which, on more mature and calmer reflection, he would not consider in keeping with the high principles of his calling for one instant.

These pressures do not bear on the practicing physician alone, but have extended beyond him to the very school from which he originates. Medical educators, like practicing physicians, have a strong sense of responsibility toward the care of the public, which they discharge in two ways: through research and the development of new understanding of disease and therapeutic agents, and through the selection and instruction of new recruits to join the ranks of the profession. Medical education is enormously expensive and these days rapid technological development requires constant change of curriculum content and constant retooling with extremely expensive equipment. Tuition charges could not begin to provide the necessary funds even if they could be paid in full by every candidate. Medical schools are being forced, therefore, to seek money they desperately need elsewhere. In the absence of adequate public support for teaching, it is small wonder that dona-

tions, often generous, which may have carried with them subtle pressures have had to be accepted gratefully from groups which might at some later time even insist in return that their special interests be placed ahead of those of the general public.

It is against this background of high professional principle, intense pressure from insatiable public demand, and the blandishments of seemingly easy guidance and support that the issue of conflict of interest between the physician and the pharmaceutical manufacturer must be viewed. Clearly certain practices are undesirable and should be stopped under any circumstance. For example, it is obviously not in the public's interest that the task of keeping the practicing physician abreast of new developments should fall to the necessarily biased drug salesman.

Senator NELSON. May I interrupt? Does the detail salesman have a function to play?

Dr. NICHOLS. I don't think his function should be to educate the doctor, Senator, although unfortunately it ends up all too often being his function.

Senator NELSON. You referred above to the reliance upon advertising. Supposing you didn't permit the kind of advertising that is now in the medical journals. For example, the kind that does not give information such as on chloramphenicol, the reminder ads state: "When it counts—Chloromycetin," and that is all, a full page. Do you see any value to the profession and the practicing physician in this kind of an ad?

Dr. NICHOLS. I don't; no. The problem, as I see it, is that the physician once he leaves medical school and gets off into practive becomes aware of new therapeutic developments more often through the detail men who call on him two or three times a week than he does from reading medical journals. This is a sad fact but it nevertheless is true, and some of the reasons for it are the pressures under which he is placed by the demands of his patients. So that the drug salesmen who are very carefully schooled by their companies, I am told, in what should be said, and how the mode of action and usefulness of one of their new drugs should be touted, end up by really educating those physicians who don't read too well or too often. Their education is thereby inevitably biased because one can hardly expect a drug salesman to present totally unbiased views since his job depends on his selling drugs.

Senator NELSON. What about a case of this kind? I don't know whether it is true in all hospitals, but we have found in some that there are detail men who are assigned to the hospital. It is their main function to contact the personnel in the hospital who are responsible for the purchasing of drugs. These salesmen are there daily. Assuming that those responsible for purchasing drugs in a hospital are informed, of what value are these salesmen? What is the detail man's function in this circumstance?

Dr. NICHOLS. In a good many hospitals, sir, the detail men are specifically excluded if they can be identified. This leads in some instances to a remarkable cat and mouse game. The reason that the detail men have an effect, and I am sure that the reason they are assigned very often in many hospitals, is that the hospital is a con-

venient place to find the doctor and that he can exclude detail men from his office by telling his secretary not to let him in but it is much more difficult to avoid him in a hospital corridor.

But perhaps most effective, the most effective place that the detail men work is with the younger men who are in training, the interns and residents, since they are ultimately the ones who actually write in the order book such and such a drug shall be given to so and so at such a time and in such an amount.

If the detail man is successful in persuading one of those young men to try a different drug or one that he is particularly interested in selling, then, in effect, he has made a sale. It is not a direct one but, in effect, he has still made a sale, and I am sure that this is the reason that so many of them do appear in the hospital corridors and in such large numbers, and you are quite correct, hospitals that I have worked in have had individuals assigned to them.

Senator NELSON. Even then, I suppose that if they simply persuade whoever is doing the prescribing to change from one brand of the same compound, that also is a sale.

Dr. NICHOLS. It is a sale, sure, and for that particular salesman. In point of fact I doubt that—well, I don't really know how often that would happen in a practical sense.

Mr. GORDON. We have had some testimony to the effect that in addition to getting the residents and interns to prescribe certain drugs, the companies also give gifts—through the detail men—to residents and interns. Is that your experience?

Dr. NICHOLS. You know, Mr. Gordon, if you are responsible for a service you see some things and other things are kept carefully hidden from your view even though everybody else knows all about it.

My experience as a house officer was some while ago, but I can quote from that directly. At that time detail men did appear in the hospital, and we were occasionally given gifts of drugs for trial. This still occurs. One was occasionally offered a book, and as a matter of fact, this still goes on in medical schools where drug companies frequently make available to medical students, sometimes through the dean's office, literature, some of which is worth while and some of which is clearly trash.

I have not personally had the experience of being offered anything by a drug company salesman that I can think of beyond samples of wares. On the other hand, it wouldn't surprise me unduly if such blandishments as dinners and so forth were offered on occasion.

Senator NELSON. In a paragraph on page 4 you refer to absence of adequate public support for teaching, and suggest it is small wonder that donations, often generous, which may carry with them subtle pressures, have had to be accepted gratefully from groups which might at some later time insist, in return, that their special interests be placed ahead of those of the general public.

I want to refer to a paragraph in a book by Morton Mintz entitled "By Prescription Only," and on page 69 he states:

> Most immune from criticism, for reasons that by now should be apparent, are the drug companies. In an interview in 1962 published by the Center for the Study of Democratic Institutions at Santa Barbara, Calif., Dr. Herbert Ratner of the Stritch School of Medicine of Loyola University, told what happened in the 1940s:

I showed a former dean of our medical school a talk I had prepared for a religious emphasis week at the State medical school. When he came to the lines, "Modern man ends up a vitamin-taking, antacid-consuming, barbiturate-sedated, aspirin-alleviated, benzidrene-stimulated, psychosomatically diseased, surgically despoiled animal; nature's highest product turns out to be a fatigued, peptic-ulcerated, tense, headachy, over-stimulated, neurotic, tonsilless creature," the dean said: "Gee, Herb, I wish you had not used that line. It will antagonize the drug houses, and we are trying to build up research funds."

You are aware, of course, that funds are given for research, testing, scholarships, student loans, to medical schools, and to schools of pharmacy. Would you think that this kind of a reaction by this dean would be a common one?

Dr. NICHOLS. Senator, I can't tell you how common and I don't know exactly the date of the conversation.

Senator NELSON. This was in the 1940's.

Dr. NICHOLS. It is, however, true, that in the 1940's, and particularly in the early part of the 1940's, as you know, the only funds that were available for research in any real amount were from private foundations, and through the drug houses, which were at that point beginning to really put a great deal of money into the development of new products.

So I suspect that it was probably more common in those days than it is now, but I can envision such a comment being made today, too.

Senator NELSON. You referred in your paragraph from which I quoted, to the fact that these funds are accepted and might have an influence. We have had examples of it. It may very well be, as you suggest, that it is subtle and unrecognized more often than not.

Dr. NICHOLS. Well, this was in my mind, and I think when I wrote that line, those lines, I had in mind rather particularly the notion that this was potentially possible, and to the extent that it was potentially possible it might cast doubt upon the validity of teaching or it might raise questions of conflict of interest which in their turn might cast doubt on the validity of the instruction that was being offered or the lack of bias of the information that was being used.

For example, it is obviously not in the public's interest that the task of keeping the practicing physician abreast of new developments should fall to the necessarily biased drug salesman. Similarly, a physician should never lend his name as author of any professional article of whose factual content and conceptual bias he is ignorant. By the same token, the teacher has a direct responsibility to his students and the patients whom they may treat in the future to make sure that his instruction is based on the best information available and that he does not appear by any word or act to favor any one mode of treatment over another simply because the proponents of that system or the manufacturer of that medicament has provided him with professional renown or financial support.

Other situations are more difficult to judge. Yet, if the solemn responsibilities which the profession has assumed in return for its rights and privileges are borne in mind, these questions are relatively easy to answer. Thus, while it is theoretically possible that a man might provide an objective judgment regarding the efficacy, safety, or power of a drug from whose manufacturer he was receiving ongoing financial support, it might be difficult for the public in these days of doubt and

disillusionment to believe in his objectivity with regard to that particular drug, a doubt which could not help but expand to include his professional judgment in other areas. Thus, the physician, like Caesar's wife, must be beyond suspicion if he is to hold the confidence of his patients and to whatever degree this confidence may be shaken or even potentially shaken through his association with a pharmaceutical manufacture—such association must be eschewed.

This brings us to the final and interesting question: What if anything can the Federal Government do to prevent some of the undesirable practices which have developed and which have led in turn to suspicions of conflict of interest between the physician's responsibilities to his patients and his debts to the pharmaceutical industry? In this regard, I think it is important to remember that ethical behavior has never been enforced successfully by legislation. The 18th amendment did not abolish alcoholism, the narcotics laws have not stopped our youth from smoking marihuana and the laws against prostitution and adultery, both public and religious, have certainly not put an end to extramarital sex. On the other hand, certain changes in the powers and responsibilities of some of our Federal regulatory and supportive agencies would go far toward relieving the pressure on both the pharmaceutical industry and the physician thereby, I believe, improving the situation considerably. For example, medical research in this country has become probably the finest in the world, thanks to the vision of the Congress which created the National Institutes of Health and the National Science Foundation to provide the financial support which it required. This must be continued, if the impetus already gained is to carry us forward to new and better ways of understanding and treating disease. Similar support has been proposed for medical education, but has been much slower in coming, even though the need for educated men to carry on the research has been as pressing as the need for the research itself. Unable to obtain support for educational programs directly from Federal sources, medical schools—especially private ones—all too often have had to accept funds from private enterprise such as the pharmaceutical industry for the support of critically needed programs. Many, I am sure, have been aware of the potential conflict of interest which might be considered to exist in so doing, yet have regretfully felt that the need for educational support, whether paid directly to their students or faculty, or used to provide badly needed teaching equipment outweighed such considerations. Thus, I believe that a program which provided adequate Federal support for both education and research in medical schools would go far to relieve the pressures which have led to undesirable situations.

Another area where a revision of Federal programs might well assist is in the matter of drug evaluation. The newly created Consumer Control Division under the Department of Health, Education, and Welfare—if I have the name correctly—may be a greater step in improving the system for drug evaluation that I know. Certainly the old Food and Drug Administration was often in an impossible position, lacking as it did the manpower needed to police manufacturing and packaging of drugs in truly adequate fashion. As a result, it perforce had to fall back on hopelessly complicated regulations which in more than occasional instances, I am sure, unnecessarily delayed the availability

of potent and highly useful agents. Just as, of course, they also protected the consumer on many occasions from highly undesirable agents.

Senator NELSON. What kind of instances do you refer to here—unnecessarily delayed availability of potent——

Dr. NICHOLS. Well, I have had some personal experience in that particular respect, Senator. There is a drug which I happen to use in the kinds of patients I see quite often who have bone disease which is sodium fluoride. This is a common chemical which one can buy in a laboratory supply house, but it is unpleasant to take and so it is packaged in a capsule. The way the present regulations are written, the development of a package of a sufficient size for convenience of the patient which can be marketed requires months and months and months of delay and long involved applications to the FDA in order to get clearance.

The regulations are understandable, and they can be met, but in the meanwhile I have to supply my patients directly through my authorization to use an experimental drug. Yet the drug is available in other packaged forms which don't happen to be the right size.

Senator NELSON. This is not a drug that is on the market in this package form, it is being used experimentally?

Dr. NICHOLS. It is on the market and being used experimentally in the packaged forms which I dispense but there are other forms which are available on prescription, nonexperimental, and yet it is the same drug. The way the regulations are written the two forms have to be separately cleared is the problem.

Senator NELSON. Is that an ongoing problem or does it occur just once in a while?

Dr. NICHOLS. No; it apparently occurs more—according to my friends, more—frequently than I had realized. I thought this was just an odd instance but apparently this does occur not too infrequently.

Senator NELSON. You are, then, referring to a dosage of a particular drug?

Dr. NICHOLS. Yes, correct.

Senator NELSON. And for the purpose for which you use it they require a certain specific dosage form?

Dr. NICHOLS. Well, very specifically the package size that I dispense is 50 milligrams of sodium fluoride in a capsule. The commonly available kind that is marketed by one of the well-known drug companies, I am sorry I can't remember which, contains some other stuff plus about 2 milligrams of sodium fluoride. If I am going to give my patient 50 milligrams of sodium fluoride at a dose I have got to give that poor lady 25 pills and she doesn't like that, not unexpectedly, so that what I end up doing is persuading a drug house to package an experimental form.

Senator NELSON. Is this a case where the drug has not been approved?

Dr. NICHOLS. That is right.

Senator NELSON. Is there a New Drug Application pending?

Dr. NICHOLS. Yes, this is a question of having approval, final approval, for packaging this form which is larger obviously by 25 than the one which has already been approved. In the past it was thought the dose level we were currently using was perhaps going to be ex-

cessive or at least unnecessary. Our present opinion is that this probably is the dose level we should be using.

Senator NELSON. Isn't that a kind of an unavoidable problem? In other words, isn't the FDA in a position where they are waiting for adequate demonstrated proof from clinical use by people like you and by the experiments done by the company as proof that it is a safe dosage form?

Dr. NICHOLS. Yes; I think that is quite correct, and the question really comes up how long that waiting period should be and were the arrangements such that all our experience, those who use this drug in this particular dosage form, were pooled in a convenient way and in a convenient place and made readily available to all workers then perhaps the whole time interval required to process this final approval would be considerably shorter.

Senator NELSON. Is your use of the drug also for the purpose of developing a history of experience that will be furnished to the FDA so that they——

Dr. NICHOLS. Yes; my experience will be, and is being, through the manufacturer who has the license to package it on an experimental basis, or for experimental use, I guess, is the proper term. Others are also, I am sure, trying it through him.

Senator NELSON. I am trying to clarify—what size dose is this?

Dr. NICHOLS. These are 50 milligram capsules.

Senator NELSON. The mechanics of the company putting together 50 milligram dosage in a capsule form they have solved that—that is no problem, is it?

Dr. NICHOLS. No; no problem at all.

Senator NELSON. What is the problem? When you wish to use it on each occasion you have to get approval of the FDA?

Dr. NICHOLS. No; I have to be approved as an investigator who will, who has the necessary background and experience to administer this drug and to give it clinical trial, so I signed a form which says, which testifies to the fact that, I have the following experiences in dealing with bone diseases of this type and have had some experience using the drug with someone else, and then submit this to the company and this permits me then to write a prescription for that particular experimental drug in the State of Massachusetts.

Senator NELSON. Once you have done that, where is the delay in getting the dosage?

Dr. NICHOLS. I don't have any delay in getting the drug but if any patient who doesn't happen to live in Boston but lives across the State line, say, in Connecticut, gets a prescription for it from me, she can't fill it at home. She has to get the drug from me in Boston or at least buy it in Massachusetts from a pharmacy there which has the permission to carry it, which means my hospital pharmacy is what it really boils down to.

Senator NELSON. So in developing experience with this drug you have been authorized as a physician to use it?

Dr. NICHOLS. That is right.

Senator NELSON. Then it can only be dispensed from just one place in the State of Massachusetts?

Dr. NICHOLS. It can't be dispensed for interstate sale, I believe, is the proper term. So that my patient in Connecticut must find a friend in Massachusetts to buy it for her and take it to her, or she has to call me up and my secretary buys it for her and puts it in a parcel and mails it off. This is the only way in which she can get it and this is cumbersome, and——

Senator NELSON. In doing scientific experiments of this kind prior to approval of the drug, what would you suggest could be done to improve the situation? That is the problem is it not?

Dr. NICHOLS. Yes; this is indeed the problem, and my feeling is that what is happening now is that the regulations which are complicated, and necessarily so in order to protect us, physicians and the public both, I believe that these could be made simpler if we had a more centralized system which was much less likely to be biased and in which information from many sources could be pooled conveniently.

I believe, therefore, that careful consideration should be given to overhauling the whole method for Federal control of drug manufacturing and evaluation. Perhaps a central agency for drug testing could be set up, jointly financed by the pharmaceutical industry and the Federal Government. If such an agency could be established and positions within it made sufficiently attractive to entice able scientists to join its staff, I believe the whole matter of evaluation of a new product could be speeded up immeasurably and many of the questionable practices revolving around payment to investigators for clinical trials could be eliminated to the ultimate advantage of the patient, the doctor and manufacturer alike.

Senator NELSON. If I may interrupt you, this suggestion, or something similar to it, has been discussed before the committee on other occasions, and the witnesses have commented on it and raised the same issue you have, that is, the company that, in fact, has a financial interest in putting its compound on the market is the same one that, under the present practice, is solely responsible for developing the evidence for the NDA. In other words, the same company which must prove to the FDA that the drug is safe and effective therapeutically to put on the market.

What you are suggesting is to remove the responsibility from the applicant who has an interest in the drug, as well as those who might experiment with it who are paid by the company for the experiment, and put this responsibility into a central place, where the evaluating group would have no financial interest at all in whether or not the drug got into the market, is that what you are saying?

Dr. NICHOLS. Yes; that is correct, Senator.

I must confess that when this notion was first suggested to me as a possible solution to some of the problems that we are discussing here, I felt as many of my colleagues, I am sure have, that this kind of an idea wasn't going to work and it wasn't going to work because the testing of drugs is not very exciting work, and the problem of developing such an agency, making sure that it was free of bias, making sure that the men and women who worked in it were highly skilled—because after all there is a lot at stake here—were going to be problems which were going to be much larger than the ones engendered by the present system.

Yet the more I thought about it the more it seemed to me that this was really the only solution that I could see at the moment to remove what clearly couldn't help but be an arrangement subject to bias. Whether it is biased in a given instance or not one cannot predict.

But we might say parenthetically that one of the reasons that the drug companies, I believe, end up paying clinical investigators to test their products is that the job is a dull one; it requires a lot of paperwork, and beyond a certain level of experience it is more drudgery than anything else. I think this is the reason that a good many people do end up giving or accepting financial awards for doing the work.

Senator NELSON. On the question of bias we do have some examples of cases where the company changed the investigator's results or the investigator was not allowed to express his own results. MER–29 is one of them. In a big lawsuit in Europe over Thalidomide, the charge was made that even though two witnesses had supplied information raising serious doubts about the use of this drug, their evidence was simply ignored.

Now, I would assume even if you had an independent agency of some kind who was responsible for evaluation you would still contract with medical schools and physicians who have expertise in the problem that is involved, since you would never have all those people on the staff, and you have to test drugs not only on animals but also on patients in a clinical situation.

Is there any problem that couldn't be solved as well by contracting with an independent agency rather than by a pharmaceutical house itself?

Dr. NICHOLS. Your point is well taken. I have to think about it for a second.

Senator NELSON. In other words, what I am saying is if a drug company can seek out the expertise of well-known blood dyscrasia experts, well-known doctors treating certain types of diseases in big clinics, or hospitals or medical schools, teaching hospitals—if they can find people who have the expertise, is there any reason that an independent agency couldn't do the same and thus remove any possibility of intentional bias creeping in because the company is involved? And on those rare occasions where an individual might unconsciously or consciously be biased because he is working for a company, might not that aspect be eliminated, also?

Dr. NICHOLS. I think that it would be possible for such an agency to find these people without any question at all. In fact, I believe through medical schools and medical educators it would be quite possible to find suitable testers outside of Government itself.

The thing that was running through my mind when you asked the question was how one might protect the public from the drug companies discovering that so and so had actually got the contract to test their new contract from the central agency, and so that this potentially might be another place where infiltration with conflicts of interest might occur. But I think having the intervention of a formal central agency between the two would go far to relieve the pressures that are placed upon physicians at the moment.

Senator NELSON. Thank you. Please proceed.

Dr. NICHOLS. One further and final suggestion I would like to make relates to the controversy over the use of generic versus brand names of drugs in prescription writing—a topic in which my colleague, Dr. Richard Burack, has been deeply immersed and to which I have contributed in a minor way. At issue is the right of the manufacturer to give his product any name which he wishes versus the ability of the physician to prescribe a specific chemical agent of known purity regardless of the identity of the manufacturer. Obviously, the right of the pharmaceutical manufacturer to reap the commercial benefits from his new development is a deeply rooted principle in our society. Although I might personally question whether it is truly desirable for products of such enormous importance to the public health as antibiotics, synthetic hormones, and other such potent therapeutic agents to be patented for private gain, I would be willing to accept the present system as a necessary evil, if its abolishment would truly threaten the benefits which our pharmaceutical industry brings to us all. I believe, however, that many of its detrimental aspects could be overcome by the simple expedient of requiring that any manufacturer who patents a new theropeutic agent market it under its generic name. In order to protect his interest he might even be allowed to add his firm's name to the generic one in advertising material. Such an arrangement would allow him to collect the profits of his discovery but would at the same time allow the physician to know precisely what he is prescribing and would ultimately establish the generic name as the accepted common name of the drug in question rather than the particular brand name of the company which produced it.

Senator NELSON. So long as you maintain the patent system, which I suspect we will for a long time to come, there isn't any danger in the manufacturer not reaping the benefits of his research and enterprise, is there?

Dr. NICHOLS. No; I wouldn't think so.

Senator NELSON. In other words, he has got a patent. But you are requiring that he market it from the day he goes into the marketplace and for the next 17 years under the generic name, and he is the only one who can market it for 17 years under the generic name? The purpose of the patent is performed. He makes his profit because he has no competition. He may charge what he wishes.

At the end of 17 years anybody who is qualified can manufacture and market the drug. Then, as you suggest, the doctor would be free to prescribe by the generic name. But if the doctor, for any reason, decided the drug ought to be a particular company's product—say, Merck, Pfizer, Lilly, or any other—he would write the name of the company after the generic name. I think that is a very good suggestion.

The problem we get to now is brand names. A good example of the reason the drug companies would oppose your suggestion is illustrated in the case of prednisone. I do not single out a particular company, here, because it applies to all companies. However, prednisone was marketed for many years under the trade name of Meticorten, and it still is. At least up until the time of our hearings, Meticorten dominated the marketplace at a price of $17.90 per 100 when it was available at $1.50 per 100 and even 59 cents per 100 elsewhere. But the

dominance of that name for so long a time preserved its place in the retail marketplace; however, not in the wholesale, not in the competitive marketplace where you have knowledgeable buyers like government and big hospitals. I think it is a very effective way to extend the patent monopoly.

A very fine doctor told me, after I had explained to him that the Medical Letter's evaluation of 22 drugs showed that they were all equal but that they varied in price from $17.90 for 100—wholesale—to as low as 59 cents—upon hearing this, the doctor concluded "that may be all true but I have been used to prescribing Meticorten for many, many years and I suppose I will do it for the rest of my life." That is the reason for brand name identification, and the reason we have had objection to it.

But you do believe that in terms of medical practice to use the generic name in prescribing would be valuable?

Dr. NICHOLS. I do; yes. There is no question at all about it, Senator, and the problem, as you know very well, and I am sure it has been said in this room many times before by others, is that really drugs have three names now, they have a generic name which is assigned to a great extent by the drug manufacturers. Then it has a brand name which is the way it appears over the counter for 17 years if it is patentable, and then it also has a chemical name. Well, its chemical name nobody expects anybody to remember because it is based on its structure, and it is impossibly complicated. The generic name is a shorter formulation, some of which are quite complex, but the brand name is usually a catchy title sort of affair, apt to be rather brief. Meticorten is actually a very nice example because it is a derivative of cortisone and it was named in that catchy form, I am sure, realizing that people would recognize it for being a minor chemical variation with certain specific benefits. It would have been much better if the name Meticorten had been its generic name from the start; everybody would have recognized it for what it is and prescribed it that way.

What we end up with, as you point out, is in effect a long extension of a patent which may cause the doctor often, I think completely unconsciously, to really make his patient pay a great deal more for his treatment than he needs to, and I think that is bad, bad—undesirable.

Senator NELSON. We had testimony here on thalidomide. Dr. Taussig, whom I am sure you know, testified she had been instrumental in informing the FDA of what was happening in Germany, as I recall it. She made a point—I don't have her testimony before me—but she made a point that quite some time after it was known all over the world in the medical profession that thalidomide had disastrous side effects on pregnant women, it was still being marketed under a number of different names and being used in other countries. Spain, I believe she mentioned, and South America, Brazil, it was being marketed there under brand names which the physician did not recognize as thalidomide. She testified, Mr. Gordon says, that it was being marketed under some 50 names. In any event, she made the point that she felt it would be valuable if on the prescription, itself, which the patient got, both the generic and the brand name appear—unless, of course, there was a particular reason for the doctor not wanting the patient to know what drug he was getting. It was her opinion that this would not only result in better prescribing, but in greater safety.

She mentioned that in the case of a person allergic to a particular drug, he would not be able to identify the drug without the generic name on the label—this could have dire consequences.

Is there, in your judgment, any value to requiring that a label that the patient gets contain the generic name, as well as the brand name?

Dr. NICHOLS. I think I would rather endorse such a view. As you spoke, I thought of one of my friends who recently was prescribed a drug by a physician. She accepted the prescription, looked at the name which was a brand name, didn't know much about it, filled it, took the drug and promptly developed a rash, she being allergic, as it turned out, to one of the several ingredients which was contained in this particular proprietary mixture.

Had she known what was in it she would not have taken it because she is well aware of her allergy, having had trouble before. So I believe that, yes, that it probably would be an excellent proviso that the names of drugs, and incidentally, as you well know, I think it should be reiterated most or many of the patented new medicaments are actually mixtures of well-known agents but they happen to be combined in a somewhat different way than some others, and so forth. So that many drugs that we buy under a brand name are not just one drug but four perhaps combined in a single capsule or pill. I think all the names ought to be included and I believe that it probably would protect the patient.

I happen to believe, too, that patients are kept in the dark too much by many physicians about what they are getting in terms of treatment and what their problems are. I think that, as I wrote in the foreword to Dr. Burack's book, the days when a certain amount of mumbo-jumbo was needed in order to encourage the patient and protect both him and the physician from the unvarnished truth probably are gone now.

I don't think that we need to protect ourselves in that way and I doubt that our patients are really very pleased to be kept in the dark about what their problems are really all about.

Senator NELSON. You raised a question that hadn't occurred to me before, and that is a combination drug in which you might have one, two, three, or four active ingredients. What kind of time problem does that impose upon the physician if he is going to have to identify on the label everything that is in the drug. Or might that requirement be imposed upon the pharmacist when he labels it?

Dr. NICHOLS. I think it could be done through the pharmacist, myself. The physician, however, should know, I believe, what is in the combinations. Most of the——

Senator NELSON. I was thinking of the mechanics of actually having to write out four compounds for one combination drug.

Dr. NICHOLS. I am sure that my colleagues would hate me for the rest of theirs and my lives if I imposed upon them more writing than they already have to do. So I think that in a mechanical sense it could be done by the pharmacist and, as a matter of fact, it could even consist of the pharmacist being provided by the manufacturer with stock labels with the information printed on them which he can simply glue on his dispensing vials.

Senator NELSON. Please go ahead.

Dr. NICHOLS. In closing, I would like to reiterate one thing. The practice of medicine is rooted in the solemn acceptance of high principles and heavy responsibilities by the physician. The essence of these is that he should place the interest of his patient ahead of his own and I believe that the remarkably high level of medical care which it is possible to obtain in this country provides ample evidence of the degree to which the rank and file of the profession adhere to the best of their ability to these principles. Despite this, the levels of health in this country are not as high as they should be and the physician is constantly being subjected to a barrage of new and often irrelevant information and increasing demands for care without having any time to digest the former or any way of meeting the latter save by taking shortcuts whose long-term implications he may have neither the leisure nor the vision to appreciate.

If conflict of interest arises under these circumstances, and many specific instances of it can be cited, it is understandable, even if it should be stopped. But the method of putting an end to these situations is not in specific legislation, I believe, which makes each of them a crime, but rather in findings ways to relieve some of the pressures which create them.

Ultimately, cures for most of the ills we have been talking about including the argument about generic versus brand names lies with the individual physician who has been properly provided with unbiased up-to-date information. Only he can know specifically what he has done and for what motive. Only he can know whether his acts have been consonant with, or have violated the principles which he has espoused and only he, thinking of these things in the privacy of his inner mind, can create the control for himself which will eliminate them. However, his job would be made easier and his ability to give high quality medical care immeasurably increased if (1) new drugs had only one instead of three (brand, generic, and chemical) names; (2) a simpler, quicker centralized system of new drug evaluation were devised which would provide unbiased information about new drugs; and (3) adequate support of medical education, as well as research, were provided so that schools could spend more of their time on the content of their curriculums, including the teaching of clinical pharmacology, and less at chasing the money to pay for it.

Senator NELSON. We have had testimony before the committee concerning a proposal for a compendium of drugs, a complete compendium of drugs. The FDA testified in favor of it, and the proposal was introduced in the Congress, and the President recommended it. The proposal contemplates that all drugs would be listed in this independently published compendium with a description, of course, of their indications for use and precautions and side effects. Do you believe a compendium would be valuable to the profession?

Dr. NICHOLS. I think basically; yes.

I think there are some problems with the compendium, however. One of them is the large number of drugs that everybody has to learn about. I have no idea how many different preparations of digitalis there are, for example, but there must be dozens, and ultimately each physician ends up learning about one particular type thoroughly if he is wise, and uses the others only when his particular favorite happens to be for one reason or another contraindicated.

Senator NELSON. They would, of course, list all drugs by their generic names.

Dr. NICHOLS. Oh, sure, yes; I understand that.

No; I think that the problem, Senator, is that there might be, well, to use prednisone, for example, prednisone is an excellent drug with certain very specific effects but there might be a dozen, say, of other drugs and they would all be listed as having similar kinds of effects as far as one could tell, but their relative usefulness might or might not be clear to the man who had no experience, and he might have difficulty picking out which one would really probably be the best.

Senator NELSON. How does he do it now?

Dr. NICHOLS. Well, right at the moment, he usually ends up learning about one which he uses and uses frequently. The compendium would certainly be convenient. It would certainly be a basic reference. I can conceive of it being an expensive proposition to prepare. But ultimately, if it was readily available to all physicians, I am sure that it would be a big step in the right direction. As you also know, the only thing that approaches such a compendium really at the moment is an interesting volume called the Physician's Desk Reference which is in actual fact, nothing but a reprinting of a large list of individual drug manufacturers' broadsides about their particular drugs. The information is there but the bias in the information is there, too.

Senator NELSON. The witnesses for FDA stated that a compendium should have inserts and that probably the new drug information, as it was developed, should be sent out on either a quarterly or a 6-month basis so that the physician could keep his compendium current.

Dr. NICHOLS. I just think this is one way of solving that problem. This obviously is another one of the problems that goes with such a volume.

Senator NELSON. I wish to call attention to an article by Dr. Charles May in the January 1961 issue of the Journal of Medical Education [1] in which he referred to subsidies of medical journals through advertisements and of medical societies through support of activities and indirectly by commercial exhibits at meetings that interfere with their functions as outlets for objective criticism.

We have not had the representatives of the medical journals, AMA or others, here to testify exactly as to what share of their publication, their income, and so forth, comes from pharmaceutical company advertising. We have noted comments by others that it was in the nature of 50 percent in some journals.

Do you see any problems, possible conflicts of interest, when medical societies and their publications rely heavily upon pharmaceutical manufacturers' ads—and promotion?

Dr. NICHOLS. These are hard questions because obviously, sure, there could easily be conceived of a conflict of interest arising in such situations.

I think the problem that we have to face, and I don't really know how to face it, is sort of a quantitative one. Would the journals that are supported cease to exist were the advertising entirely withdrawn? And if they should cease to exist, would that be a bad thing or a good thing? The general impression is that it would be a bad thing because

[1] See article beginning at p. 3938, supra.

scientific material of worth would no longer have a place to be published.

I suspect that probably a good many of the journals would get published anyway. Many of the ones in which I have published, even with what advertising they do carry end up having to charge the author page costs particularly in certain——

Senator NELSON. Charge what?

Dr. NICHOLS. Page costs for publication. In other words, if I write a scientific article and it exceeds x pages, say five, some journals will charge me a cost per additional printed page for production of that article.

Now these journals are not the kind that we probably really have reference to here, being more purely scientific but they do contain advertising and I think in thinking about it one should include not just the drug manufacturers and their advertising, but the hardware manufacturers, if one can use a sort of generality, who also have large ads now in the medical journals; people who make various kinds of equipment for monitoring heart action, respiratory action, and so forth in hospitals, and these—this kind of equipment is very expensive, and is widely advertised, and I am sure contributes considerably to the journal income.

Senator NELSON. Do you think that raises the same kind of question, however?

Dr. NICHOLS. So far I don't think that they have contributed in quite the same way as the pharmaceutical industry, and also the equipment which they sell is more directly a matter between the doctor and the manufacturer than it is between the doctor, the patient, and the manufacturer, because the patient doesn't buy that kind of equipment directly so that the conflict, the potential conflict, of interest is different, and less in risk, I believe. But they are there, and they are advertisers and I think they need to be thought about in the whole picture.

Senator NELSON. I don't know whether it would be possible to evaluate what happened with regard to chloramphenicol, but the testimony the committee heard, from Dr. Dameshek of Mount Sinai as well as other witnesses, was that from 90 percent to over 99 percent of the cases in which chloramphenicol was prescribed, it was prescribed for nonindicated cases. Further this testimony was unrefuted by the company—or anyone else. One doctor testified that he had never once in his practice to date seen a case of aplastic anemia caused by chloramphenicol for which the drug was administered for an indicated case.

Now I realize that these things are rather complicated. But the fact is that Chloromycetin was widely advertised in medical journals all over this country. There were people in the AMA, for example, who were aware of the vast overprescribing and misuse of this drug. Yet, the ads in JAMA continued.

As a result of our hearings, the FDA sent a "Dear Doctor" letter to every doctor in the country and to all medical journals, explaining the dangers of chloramphenicol and spelling out the extremely limited conditions for which it might be indicated. The use of the drug dropped dramatically. In the batch testing by FDA, it dropped from 23 million grams the first 6 months of 1967 to 4 million grams for the first 6 months of 1968, and in June of 1968 zero amount was batch tested.

In other words, following the subcommittee's hearings and the action of FDA, a very, very dramatic drop occurred.

Whatever the reason for this wide misuse, I think it is pretty clear that the advertising had a lot to do with it. The company was the one that promoted it through the journals, detail men, and direct advertising. And it seems to me it just indicates that there were some dramatic failures of responsibility on the part of the medical profession. The medical profession was well aware of the dangers associated with the use of chloramphenicol—and of the vast amount of overprescribing and misuse of the drug. Yet there were no blaring headlines, no emergency conferences, no attempt to alert the general public. That responsibility fell to a congressional committee, that has no expertise at all, to expose what was going on. I don't know what influence the advertising may have had, but it raises the question that here were journals accepting ads for 15 years or more while at the same time carrying articles regarding the misuse and overuse of the drug. The ads were part of the method of misleading the physician. Doesn't that raise a serious question?

Dr. NICHOLS. With all due respect to you and your committee, I agree with you I think it was most inappropriate to happen to fall to your lot to call public attention to, the attention of the medical public to, misuse of this drug by its members.

It seems reasonably clear that a lot of people have been prescribing chloramphenicol with little or any reason. The use of the drug outside of certain very specific infections is probably not needed, and in view of the risks involved, not justified.

On the other hand, there are individuals, and it is quite easy, actually quite simple to identify them by testing, who need that particular drug if their particular infection is going to be brought under control, and in these instances the drug should be used obviously because the risks of infection may be greater than the risks of the anemia.

But I think really what you are saying is something which I don't know quite how to handle at this point. It is the whole problem of the dissemination of information within the profession in a form and in a way which can be rapidly assimilated. At the moment what we are saying in effect is that much of this is being done by the detail man who goes from door to door. He is biased; he has to be, and he shouldn't be doing this. Some other mechanism needs to be found. Whether the elimination of advertising or perhaps better policing of advertising within a journal is going to really solve the basic problem I rather doubt, and I think that you share my view on that.

Senator NELSON. I doubt whether any single thing would solve the problem.

Dr. NICHOLS. Yes, I doubt that any single thing would. I think a compendium would be helpful, perhaps, in this respect. I think that more availability of, well unbiased material such as is published in the Medical Letter to more people would be valuable. One of the problems with the Medical Letter is that I know a lot of physicians don't know about it. Maybe something like the Medical Letter ought to be circulated to all physicians perhaps by some central agency. Maybe this is one of the functions that a central drug testing service should perform.

I think that the removal of the barrage of bad information is going to help but I think we have got to put in its place a barrage of good information if we are going to be really effective in terms of putting right these obviously undesirable situations.

Senator NELSON. On the advertising aspect—I don't mean to leave the impression that I think the advertising in journals was solely responsible for what happened, I am certain that it was not, but if there were better control over the advertising it would seem to me that at least, in a drug which does have dramatic side effects and very, very limited indications for use, that at the minimum, a responsible journal ought to require that every time an ad is printed, it disclose the fully approved FDA indications for use and precautions and side effects so that we don't end up with an ad that is nothing more than promotion of a name.

Here was a case where something like an estimated 3½ to 4 million people were using it and doctors testified that they didn't think more than a few thousand indicated cases occurred in the country per year. Dr. Dameshek, I believe, said that 10 percent of the cases at the most would be indicated.

In that case it certainly is a serious question whether the company was justified in advertising the drug in this fashion because there isn't that much use for the drug. In other words, the only justification was to get a vast use of the drug for nonindicated cases, otherwise you couldn't justify the advertising. So there is some breakdown someplace.

I don't know what the answer is but it raises a serious question. I don't know whether it is true of other drugs or not. We just happened upon this one, because some knowledgeable physicians told us—we wouldn't have known it otherwise.

Dr. NICHOLS. Well, I think that happens to be a good example because it has been so widely used. It is in most people so relatively benign, and yet it carries with it this sort of sword of Damocles which may destroy the patient once and for all quite unexpectedly. That is the risk, and it certainly is one that shouldn't be taken unless it is absolutely necessary. It is a small risk but it is there, it is real.

I suspect that there are other drugs that have been abused, and I find it difficult to believe that many of the drugs that I see people taking are that necessary.

Mr. GORDON. You mentioned the possibility that if you eliminated advertising some of the good journals might go out of existence.

Now, what would be wrong with having the doctors pay for their own journals; that is, raise the subscription rates to the point where they cover the costs of the journal.

As I understand it, the medical profession is the highest paid profession in the United States. I would think they would be able to afford $15, $20, or $25 a year for a fine medical journal. What do you think about that?

Dr. NICHOLS. I would—I don't have any objections at all to raising the subscription rates to the cost of publication. But I suspect that some of my colleagues might be less likely to read them because they thought the price was high.

Of course, a lot of the journals come to us sort of pari passu through membership in the medical societies, and the New England

Journal of Medicine, as you know, is a good journal and is published by the Massachusetts Medical Society and I guess tomorrow you will hear from its editor.

I think most medical journals are, subscriptionwise are, really quite modestly priced at the moment, even though the price does look sort of high because their circulation is relatively small.

The New England Journal happens to be a rather inexpensive one and a rather good one. The mass of advertising material in those journals, frankly, I don't think adds to them at all. In fact it is rather a detriment. It makes a bulky journal and it makes it more difficult to find what you are looking for. Many, as you know, confine their advertising to the beginning and end very specifically but the advertising frequently slips in betwixt and between stuff like the index and the stuff that you don't want to read.

Senator NELSON. Do you believe that many physicians would drop their subscription?

Dr. NICHOLS. I don't know. I think it is very hard to tell. I have no idea what the statistics are of physician journal buying on a national basis now, that is, journal buying outside of those that they get automatically through society membership. I think it would be an interesting number to know, because my suspicion is that it is not very large. I suspect it is quite small.

Mr. GORDON. Dr. Charles May stated in the article that the chairman previously referred to, and I quote:

> The invasion into the province of the medical educator by the drug companies must be eliminated; conscription of "education," in the service of promotion must cease. Sooner or later what may now seem like benign and noble overtures will be recognized as ominous intrusion that threaten the hard-won and reasonable boundary between the sellers and prescribers of drugs.

Is it your opinion that good medical practice requires a wall of separation between the profession and the industry? Would you comment on this subject, please?

Dr. NICHOLS. Well, Mr. Gordon, I read Dr. May's article, and reviewed it not too long ago. I suspect that there should be some kind of separation and certainly the ethics of most societies of medicine more or less stipulate that a physician, for instance, won't own a drugstore which he sends his patients to to have their prescriptions filled. The problem with medical education being supported or education coming through the drug salesman I have already commented on; I think this is an undesirable situation because of the bias that is automatically written into it.

I don't know exactly how one can erect a wall between the prescriber and the dispenser of the prescription in a legislative sense. I think that this is one of the things that the profession has to monitor for itself and keep its own skirts clean.

Mr. GORDON. Has the profession been monitoring it?

Dr. NICHOLS. I suspect it has, yes, in many instances and if there are obviously some who don't—in every profession there are individuals who will do almost anything for gain, but I think that where, in general where, this separation has been transgressed is probably more from a matter of ignorance or a matter of just not thinking of where the information that they are using is coming from, that physicians get involved in this clearly undesirable situation.

You know men get used to seeing the same detail man, for instance, many of whom are very friendly people and fine human beings, and after a while one of them gives you a drug and you try it out in one of your patients, and the patient is pleased, then you are likely to use that drug again, and you may even use that man's offering in another line or prefer it over the offering of another man who isn't as friendly or isn't as available, and so forth. So these things build up in a subtle fashion without people being really aware of what they are doing.

Yet if they stopped to think about it, they wouldn't do it that way, and this is the problem, and that is why in my statement I tried to emphasize that the pressures under which a physician finds himself in practice are really very extreme now, and it is very difficult for a man really to meet the kind of demands for personal care from his patients that he must if he is going to live with his own conscience and still keep up with some reading and occasionally see the kids, this sort of thing.

Mr. GORDON. Take a professor who teaches pharmacology and tries to teach his students how to prescribe rationally. Is there a potential conflict of interest when he receives grants from drug firms?

Dr. NICHOLS. Well, potentially yes, obviously. Whether this actually creates an undesirable situation in most instances I rather doubt, because I think most of the people that I know who teach, basically are honest men who are often aware of these pressures and do try to avoid them. Really, however, they could be accused of or suspected of a conflict of interest.

Mr. GORDON. Do the departments of anatomy or preventive medicine generally get funded by firms?

Dr. NICHOLS. That is a good question, Mr. Gordon.

I don't know the answer to it. I am not in a department of anatomy, or in one of preventive medicine. I suspect that preventive medicine may get such grants occasionally. I doubt anatomists do.

Mr. GORDON. But pharmacology does to a great extent?

Dr. NICHOLS. Pharmacology has been the place that is most obvious for the drug companies to be interested in promoting.

Senator NELSON. Doctor, I want to thank you very much for your very fruitful contribution to these hearings. Again we appreciate your coming.

We will adjourn until tomorrow morning at 10 o'clock.

(Whereupon, at 11:45 a.m., the hearing was recessed, to reconvene. Wednesday, December 18, 1968, at 10 a.m.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

WEDNESDAY, DECEMBER 18, 1968

U.S. SENATE,
MONOPOLY SUBCOMMITTEE OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to recess, at 10:10 a.m., in room 318, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; and Elaine C. Dye, research assistant.

Senator NELSON. Our first witness this morning is Dr. Paul Lowinger, associate professor of psychiatry, Wayne State University School of Medicine, and the chief of the outpatient service of the Lafayette Clinic in Detroit.

Dr. Lowinger, we appreciate very much your taking the time to come here to these hearings this morning.

You may present your statement however you wish. If you wish to read it, you may proceed, and if you wish to depart from it, to elaborate in any way, feel free to do so. I assume if we have any questions as you go along you don't object to interruption.

STATEMENT OF DR. PAUL LOWINGER, ASSOCIATE PROFESSOR, PSYCHIATRY, WAYNE STATE UNIVERSITY SCHOOL OF MEDICINE, AND CHIEF OF THE OUTPATIENT SERVICE OF THE LAFAYETTE CLINIC, DETROIT, MICH.

Dr. LOWINGER. Thank you very much, Senator. It is a pleasure to be here, and I will read my statement and make some explanatory statements as I go along and welcome any questions or interruptions.

I have been in clinical pharmacology as part of my duties in psychiatry as a teacher and a researcher over a 15-year period.

I am now at Wayne State University, department of psychiatry. Before that, I was in the Public Health Service at the Marine Hospital, New Orleans, where I began my work in clinical pharmacology. At that time, I was on the faculty of the school of medicine at Tulane University.

I have been concerned throughout this time with the development and the evaluation of new drugs in an effort to increase the effectiveness of the treatment of mental and emotional disturbances. This has been a particularly exciting 15 years because the psychopharmacologic

revolution in psychiatry has reduced the number of people in mental hospitals and made the treatment of mental illness much more effective.

However, I have been concerned throughout this time about the protection of people receiving these drugs, both during and after the research projects. I have always been told and believed that the results of my studies as they concern safety were reported to the Food and Drug Administration by the pharmaceutical companies. This belief is based on the new drug section of the pure food and drug law of 1938 which required a manufacturer to test each drug for safety and submit the data to the Government, as well as the 1962 Kefauver-Harris amendments.

With the exception of one study which we did for the Food and Drug Administration itself, the 28 studies in which I participated were all initiated by well-known, ethical pharmaceutical companies. The scientists and doctors representing these manufacturers had excellent reputations and each assured me that their research was conducted in a responsible and lawful manner.

The seeds of doubt began in 1965 when I learned that our findings on the safety of Dornwal studied in 1961 for Wallace & Tiernan had not been reported to the Food and Drug Administration. As a result of the suppression of information about Dornwal, which is a tranquilizer, a Federal district court imposed a maximum $40,000 fine on the company and placed its medical director on probation for 1 year. The reason for the Government prosecution of Wallace & Tiernan was that toxic effects of Dornwal on the blood had not been reported to the FDA. This experience led me to publish a letter in "Science" on July 8, 1966, asking how often pharmaceutical houses conducting new drug investigations failed to report the results of their studies to the Food and Drug Administration. I received no answer to this letter from my colleagues in medical science, the pharmaceutical industry, or the Government so I decided to conduct my own investigation.

The reports of 27 new drug studies made between 1954 and 1966 were reviewed and the FDA was asked in April 1966, if these reports about the safety of these drugs had ever been received from the pharmaceutical companies. Commissioner Goddard said promptly that the FDA would cooperate in this study.

I sent a copy of this rather voluminous file of my correspondence with each of these companies to the FDA and 2 years later I received a report from the Food and Drug Administration, on March 29, 1968.[1] In 1967, the FDA refused to release this information because they felt, quoting from the letter which I received from Dr. Herbert Ley: "it would be inappropriate to divulge the names of firms who have failed to submit certain clinical data." But this was overcome when I appealed to two Senators.

My full report [1] shows that the data on only nine of the 27 drug studies had been submitted to the FDA. Despite this problem of reporting on drug safety, Dr. Ley commented in his March 1968 report to me that the manufacturers were in compliance.

Senator NELSON. May I interrupt?

Dr. LOWINGER. Yes.

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[1] See pp. 4008–09, infra.

Senator NELSON. You state that the data on only nine of the 27 drug studies were sent to FDA. All 27 were studies you had worked on, is that correct?

Dr. LOWINGER. Yes. I had either been the principal investigator or a coinvestigator. The work had all been done in institutions such as the Lafayette Clinic in Detroit, the Marine Hospital in New Orleans, and the Pontiac State Hospital in Michigan, where I was either full time or affiliated.

Senator NELSON. Did the other 18 studies have information in them indicating toxicity?

Dr. LOWINGER. Yes, all the studies indicated toxicity.

Senator NELSON. Including the nine?

Dr. LOWINGER. Yes.

Senator NELSON. So these were 27 studies, on how many different drugs?

Dr. LOWINGER. There were 27 drugs studied.

Senator NELSON. Twenty-seven different compounds?

Dr. LOWINGER. Yes.

Senator NELSON. And nine of these studies on nine different drugs were submitted to the FDA?

Dr. LOWINGER. Yes; according to the report from the FDA they had in their files copies of information which I had given the pharmaceutical companies.

Senator NELSON. Did the nine studies that were submitted, indicate toxicity in each of those nine drugs?

Dr. LOWINGER. Yes, just like the ones that had not been submitted. I was able to find out from my own files what I had said years earlier.

Senator NELSON. Were there indications of toxicity on the other 19 that were not filed with the FDA?

Dr. LOWINGER. Yes; there were.

Senator NELSON. Was there any difference in the gradation or quality or seriousness of the toxicity between the nine that were filed and the 19 that were not?

Dr. LOWINGER. No; there was no essential difference in the seriousness. I was very fortunate in not finding serious toxicity in any of my studies although I studied such drugs in the course of my work as thalidomide.

Senator NELSON. Were these all different companies or were some of the 27 duplicates?

Dr. LOWINGER. The 27 drugs were sent to us by 19 companies of whom 12 did not report to the FDA while five did submit reports to the FDA. Two companies submitted a report with one drug tested but did not with another drug. So there were a total of 19 companies involved and 27 drugs.

Senator NELSON. I see. Please go ahead.

Dr. LOWINGER. Drug safety problems of some of the drugs which were unreported included the following: Dizziness, drowsiness, mood depression, anxiety, insomnia, blurred vision, loss of anal sphincter control, ringing in the ears, headaches, itching, dermatitis, weakness, fatigue, nausea, diarrhea, abdominal distress, constipation, and a possible case of hepatitis.

The 27 drugs were sent to us for research by 19 companies of whom 12 did not report to the FDA while five did submit reports to the FDA.

There were two companies which submitted a report with one drug tested but did not with another drug. We made 23 reports to companies before the Kefauver-Harris amendments in 1962. Sixteen of these were not submitted by the manufacturer to the FDA, while seven were, in fact, sent.

During and after 1962, we made four studies, two of which were not submitted to the FDA, and two of which were sent to the FDA.

Senator NELSON. Were any of these studies being made on drugs that were already in the marketplace?

Dr. LOWINGER. The drugs we tested included drugs that were already on the market. Also included were drugs that were not on the market and drugs that were in the process of being prepared for marketing. In some cases the company that asked us to test the drug was not the company that was later to put the drug on the market.

Senator NELSON. You mean it was a company that was contracting with the manufacturer to get testing done for them?

Dr. LOWINGER. My record shows, Senator, that the situation you just mentioned was true in some cases. In other cases there were companies that gave up a drug to another company although they were not originally a contracting agent.

The presence of violations of law in these situations is a matter for Government lawyers to determine. My concern is with the questions of organization, ethics and secrecy in scientific work which affects the safety of the population at large. It is quite apparent that the coordination of clinical drug evaluation is beyond the capacity of the individual investigator, the university, the Government, and the pharmaceutical industry. Avoidance of the problem, lack of determination, secrecy, and limited perspective by these institutions calls for a new public approach with enforcement provisions.

The goal to be achieved is to raise the standards of clinical pharmacology by using the most responsible investigators. These investigators require well equipped and staffed programs. They also need the right of full access to the scientific information about the products under study.

Senator NELSON. May I interrupt here?

Dr. LOWINGER. Yes; you may.

Senator NELSON. What exactly do you mean by that? Do you mean that when investigators are asked to do some testing of a drug that the companies do not furnish them all of the scientific information available about this compound?

Dr. LOWINGER. My primary concern, Senator, is the fact that oftentimes there are a number of people studying the effects of a new drug on human beings in clinical settings and they do not know who the other investigators are and, as a result of this, minor and seemingly irrelevant effects according to one investigator or perhaps an isolated serious effect are unknown to the other investigators.

If the investigators knew each other's names and could communicate that way they would be more effective and more prompt in assessing serious toxicity. In other words, if I am investigating a new drug, it is only by a chance meeting over a cocktail at a scientific meeting that I discover another doctor in Chicago or Seattle is doing the same thing and we compare notes.

It has been characteristic that I have not been given the names of other investigators, and that is true of my colleagues who have been in clinical drug investigations. That is the kind of trade secrecy which I think is unnecessary and undesirable.

Senator NELSON. Well, if it would benefit the quality of the investigations being conducted by several investigators, why isn't it simply automatic that the company would furnish the information they accumulate, and the names of the other investigators? Why wouldn't that just automatically be done if it is of scientific value?

Dr. LOWINGER. I think it should automatically be done. I can't say what the motivation is. I can only speculate about that, Senator. But I think it very desirable that this be part of our pattern of future drug investigations.

Senator NELSON. You don't see any disadvantage to it? In other words, if a contracting company has a number of medical schools and individual investigators investigating a drug, there is no disadvantage to the scientific value of the proceedings if all of them know what the others have found out?

Dr. LOWINGER. No; I can see no disadvantage to investigators being identified as doing new drug studies if they are in fact so doing. This is characteristic of the National Institutes of Health which publishes lists each year of everyone doing all kinds of studies, and everyone knows what everyone else is doing and can communicate informally, outside official Government and public channels. I think that is very desirable. I can see no disadvantage to it.

Senator NELSON. Thank you. Please go ahead.

Dr. LOWINGER. There is a need for a federally sponsored institute which will fund and supervise drug research and psychopharmacology with a special emphasis on new drug clinical investigation. Such an institution while federally controlled and funded should rely heavily on the use of outstanding scientific civilian consultants much in the fashion of the National Institutes of Health committee system. The work they approve should be conducted by universities and institutes, which conform to the highest standards of science in personnel, equipment and research design.

The pharmaceutical industry would not be relieved of its obligation to demonstrate the efficacy and safety of its products but there would be a Federal capability which would set standards and enforce them. The primary involvement of the FDA with food, cosmetics, and manufacturing indicates that this new research program should be conducted separately.

Senator NELSON. May I interrupt again?

You say the pharmaceutical industry would not be relieved of its obligation to demonstrate the efficacy and safety of the products. Are you suggesting that the company which is having its drug tested and which will be making a New Drug Application follow the same proceedings it does now in developing its NDA but in addition to that there be an independent experiment, investigation, conducted by another source?

Dr. LOWINGER. Yes; I am suggesting that.

Senator NELSON. So would you have the independent agency, whatever it may be, conduct a comprehensive investigation of the drug that

would stand on its own without any proof of efficacy and safety by the companies themselves?

Dr. LOWINGER. Well, I can see such an agency making any one of several decisions. I can see them conducting their own survey, funded, perhaps, by the pharmaceutical industry. I can see them supervising and approving research protocols for investigations by the pharmaceutical company, or some combination of these patterns. But the important thing, I think, is to have a Federal scientific capability in new drug evaluations which we simply don't have now, and in this way we can either fund these investigations out of Federal or industry funds, we can supervise them or we can conduct them as a Federal agency.

Senator NELSON. So, as I understand it, the company that desires to market the new drug will conduct its own proceedings as it does now, its own investigations, contracting with individuals and research groups and prove its own case just as it now does for NDA, and then additionally, there would be an independent agency that may set some standards or supervise whatever the private company does and which may also conduct investigations of its own. Who makes the final decision on the NDA?

Dr. LOWINGER. Well, that decision is now made by the Food and Drug Administration, is my understanding.

Senator NELSON. Yes, it is.

Would you leave it there? They would then evaluate the NDA by the company as well as the independent investigation done by this other agency and, using both of them, approve or disapprove the NDA, is that what you are suggesting?

Dr. LOWINGER. I am suggesting that the approval of new drugs be taken out of the FDA and be placed with this new institute of pharmacology leaving the FDA to its many present functions, supervising manufacturing and setting other kinds of standards.

Senator NELSON. And you are talking only about new drugs now?

Dr. LOWINGER. Yes. My own experience has been in the clinical human trial on sick or ill individuals of new drugs. I have had no direct personal experience with the many other problems the FDA supervises, food, cosmetics, manufacturing, and so on. I am commenting about clinical pharmacology which is only a part of pharmacology, not basic pharmacology, which is the animal work.

It is of importance that each investigator be required by law to send a copy of each of his reports to the appropriate Federal agency, which at the present time is the Food and Drug Administration.

Senator NELSON. You think the investigator should send a copy of his report directly to the appropriate Federal agency?

Dr. LOWINGER. Yes; I do, Senator.

Senator NELSON. The present practice is that that report, the investigational information, goes to the company?

Dr. LOWINGER. Yes; that is the present practice.

Senator NELSON. And it is their responsibility to furnish the FDA with it.

Dr. LOWINGER. Yes.

Senator NELSON. Which they sometimes in the past have not done.

Dr. LOWINGER. Yes. Such a law will close the loopholes about reporting new drug findings on safety and efficacy to the Federal

Government. This will do away with any possibility of misunderstanding, delay, and omission. The Government office which receives this data needs a staff to evaluate and communicate about these reports.

Senator NELSON. If I may interrupt again——

Dr. LOWINGER. Yes.

Senator NELSON. An investigator, I assume, may develop some rather elaborate detailed reports on an investigation which extend over a period of time, what about the simple mechanics of producing an extra copy?

Dr. LOWINGER. Actually that is not a serious problem. I was suggesting that the investigator be obliged to send perhaps a report once a year, and his final report to the appropriate Government agency, and this is, this would be a relatively small volume of information but a very important type of data. In other words, I am not suggesting the investigator be obliged to send his research design or all the paperwork he generates about the subjects in his study, but rather to report once a year and his final report, which is, generally speaking in my case, two or three typed pages.

Senator NELSON. In which you draw conclusions, from what you have found as to the effects, and side effects, is that what you are saying?

Dr. LOWINGER. Yes; that is correct.

Senator NELSON. So if there were questions of efficacy or safety which the investigator had found, that would be in the report that would go to the FDA?

Dr. LOWINGER. Yes. This would be in each of these reports since nearly all these studies are concerned with both efficacy and safety. Finally, the veil of secrecy around new drug development needs radical reappraisal in the interests of public safety.

New drug investigators need to be informed about the products that are under investigation. In this way if two scientists are working on a new drug in different parts of the country, they will know about the full effects of the studies each is conducting. The minor and seemingly irrelevant drug effects noted may be better understood by the doctors studying the same product. It has been characteristic in the past that each investigator studying a new drug did not know the others who were conducting similar investigations in other parts of the country. This led to a delay and sometimes, a loss of valuable scientific information.

A drug surveillance study by Borda in the August 26, 1968, Journal of the American Medical Association shows that 35 percent of hospital patients on a medical service have adverse drug reactions. The frequent use of potent drugs to treat disease demands better methods and more safeguards. The prevention of dangerous drug reactions begins with the evaluation of the drug. The improvement of the evaluation of the new drugs requires direct reporting by investigators to the Government, the free exchange of information among scientists and a National Institute of Pharmacology.

Senator NELSON. The National Institute of Pharmacology—is this the independent agency to which you were referring earlier in your remarks?

Dr. LOWINGER. Yes; I have simply given it this name for dramatic emphasis.

Senator NELSON. Under the present system of drug evaluation—did you conduct your investigations as part of a proceeding of the medical school itself?

Dr. LOWINGER. Yes; that is correct.

Senator NELSON. What was the arrangement? Was the arrangement to conduct the investigation between you and the company or between you and the medical school or how was that handled?

Dr. LOWINGER. Usually the initial contact was made by the company to myself or to another member of the faculty. If it was another member of the faculty or another scientist in another laboratory, the matter was referred to me, and ordinarily the arrangements were made between the institution with which I was associated and the company. I simply represented my institution in making the arrangements.

Senator NELSON. Was some kind of a contractual arrangement made?

Dr. LOWINGER. Ordinarily the kind of contract that exists in these matters is an exchange of letters in which I am asked to do something in writing and I reply that I will do so, and we set forth our agreement in that form. On occasion I was asked to fill out a Federal Government form which was also sent to the company duplicating or amplifying some of the information in the letter between myself and the company.

Senator NELSON. Is this a personal, private contract or agreement between you and the company or is it an agreement between the school, the dean of the medical school or somebody else, the institution itself and the company?

Dr. LOWINGER. It is an agreement between the Lafayette Clinic which is the department of psychiatry of Wayne State University, and the pharmaceutical company in which I act as the representative of the Lafayette Clinic. But you are quite right, it is between the medical school department in question and the company.

Senator NELSON. Are you paid a fee for your investigational work?

Dr. LOWINGER. No; I am not. The company pays for expenses over and above the ordinary cost of salaries and laboratory procedures. So they pay expenses to the department of psychiatry in the Lafayette Clinic for the work that is being done.

Senator NELSON. But you are not paid anything in addition to your salary with the clinic, is that right?

Dr. LOWINGER. No; I am not. I would regard that as an undesirable state of affairs.

Senator NELSON. In making the arrangement with the school or the clinic, do they pay the school, then, for the time that you use in doing their investigation on their product? In other words, if you spend half the time on it, that is half your salary, do they pay that or don't they?

Dr. LOWINGER. No; they don't, Senator, and I think that is one of the problems in clinical pharmacology. The things they pay are considerably below the real cost, and I think the reason is the problem you identified. In other words, they pay for laboratory work,

for secretarial time and for some time by resident physicians, but they do not pay for any proportion of my salary or for the other kinds of institutional upkeep that go into running a research program. I would hope that with the development of the new Government institute that clinical pharmacology would become better supported.

Senator NELSON. Let me see, is your university publicly supported?

Dr. LOWINGER. Yes; Wayne State University is a State university under a board of governors and money for salaries of faculty comes from the State legislature.

Senator NELSON. It comes under the university board of regents, does it?

Dr. LOWINGER. Yes, that is correct, Senator. And in order to clarify this, I am at Lafayette Clinic which is the department of psychiatry at Wayne State University, but is an institution of the State department of mental health which is likewise supported by tax money but is not directly under the board of regents of the university.

Senator NELSON. What do the firms pay for then? What are they paying for when they contract with your department?

Dr. LOWINGER. They are paying for the cost of laboratory tests.

Senator NELSON. What do you mean by laboratory tests—the materials and equipment?

Dr. LOWINGER. They are paying a proportion of the technician's time. In other words, the head of the laboratories does not have a proportion of his salary paid. They are paying for technicians' time to complete extra work in the laboratory. The workweek can be extended by the use of this extra technicians' salary money.

Senator NELSON. Who are the technicians? Are they students?

Dr. LOWINGER. No. The technicians are full-time employees.

Senator NELSON. Do they pay only for the overtime put in by the technician or do they——

Dr. LOWINGER. It is assumed that the technicians in the research and clinical laboratory of a department have a full or even above a full workload to do. If we ask the director of our laboratory to undertake a certain number of blood and urine tests in connection with a new drug investigation, he quite correctly points out to me that this is going to interfere or hold up some of the work that his laboratory is doing. So we add a proportion of money to his budget, which he may use by extending the work hours of his technicians, using overtime to complete the workload that wouldn't ordinarily get done because of this new work which has come into the schedule.

Senator NELSON. So then the objective here is simply to pay the salary cost or time cost that the technician puts in for research on the contract, is that correct?

Dr. LOWINGER. That is correct. Of course, work in a laboratory like the one I am describing goes in cycles and it may be that he doesn't need that extra time until a little later, so he has that money available to him.

Senator NELSON. That is one item of cost. Materials or whatever is another item. What other items are there? Is there an overhead cost for the use of the lab—general overhead?

Dr. LOWINGER. We have never had that in the budgets that I have

prepared or been familiar with. I think that should be in these budgets but we have never put that in.

The other items include secretarial costs, and the costs of time for work on the project by resident physicians.

Senator NELSON. What do you mean by time of resident physicians?

Dr. LOWINGER. We assume that the time spent by doctors in the training program who fill out forms and carry out more extensive studies of patients than they would ordinarily do is a legitimate budgetary charge. So that comes into making up the total costs, and also we have additional secretarial work so we introduce a secretarial charge, whatever the hourly rate is in our institution at the time the study is being done.

Senator NELSON. Why do they pay some amount for the residents' time and none for yours, as the primary researcher, the one in charge of the project?

Dr. LOWINGER. I have no good answer for that question, Senator. It simply has been the custom. This has contributed to part of the problem, which is a kind of financial anemia of this kind of research program which is inadequately funded as compared to the adequately funded research of the National Institutes of Health. They do pay full institutional costs, including the senior investigators and an overhead to the institution. I think we have fallen into the habit of using these small stipends rather than a realistic appraisal of the full costs. At least I have been guilty of this practice over the years.

Senator NELSON. Well, as I have examined some of the agreements that are made between NIH and the University of Wisconsin on any Federal contracting, of which there is a great deal, they always pay the full salaries of everyone involved. They pay it and they compute an overhead cost of the physical facilities. If 10 people use a facility and you add two from outside, then one-twelfth of the overhead costs, insofar as personnel are concerned, ought to be assigned to each of the additional people and paid for outside. Furthermore, many times they have a certain amount in addition to cover unanticipated costs.

If this is the general practice, it raises an interesting question. Why should any publicly supported institution in this country—why should the taxpayers in any State be paying the cost of investigations which are being done in behalf of a profit-oriented corporation? Why shouldn't the corporation pay all of it? I know this isn't new. I had a comment from Morton Mintz' book yesterday, I don't believe I read it into the record, in which a study was made of the fact that the companies end up using institutions, public and private, to get what amounts to subsidized research. They then turn around and put the product on the market, at a profit, and I might say, at a handsome profit, in many of the cases we looked into. I am curious to know why public institutions tolerate it. I don't know why the heads of the medical schools and presidents of the universities don't say to the drug company, "You will pay on a basis that covers the total cost and there has to be some benefit to the university or why should we let you use the facilities?"

If this practice is acceptable, I don't know why General Motors shouldn't get subsidized research at our universities, or for that matter, anybody else. It is rather a puzzle. I realize that is not a determination of yours. This is a practice which has been going on for many, many

years, but it is one that interests me and I think our committee ought to pursue it further. I don't know why the pharmaceutical industry should be paying on a less equitable basis than the Federal Government, which has lots of research done by the great private and public institutions of America.

I have had to listen to quite a bit from the drug companies about the high cost of research. I just wish I could get research done for myself on that basis if I were in private enterprise some place.

Mr. Gordon, did you have something?

Mr. GORDON. Yes.

Mr. Chairman, in the early part of Dr. Lowinger's statement he refers to Dornwal, a product of Wallace & Tiernan, and the subcommittee has documents on this particular subject in its files, including a letter to the Attorney General from the Food and Drug Administration,[1] in which the FDA asks the Justice Department to prosecute this company. Let me read a couple of paragraphs:

> The indictment charges violation of 18 USC 1000 based upon the acts of defendants in knowingly and willfully concealing material information and submitting and causing submission of false and fictitious statements, in writing and orally as to material facts, to the Department of Health, Education, and Welfare, Food and Drug Administration in a matter within the jurisdiction of the Food and Drug Administration.
>
> Between January 27, and October 11, 1961, 28 such contacts were made by the defendants in which they knowingly and wilfully concealed material facts from Food and Drug Administration, to wit, medical evidence that Dornwal was the causative agent of a severe and often fatal blood dyscrasia in man. Furthermore, subsequent to the submission of the New Drug Application for the drug Dornwal, the defendants made 10 mail submissions to the Food and Drug Administration concerning the New Drug Application in which false and fictitious statements and representations were made concerning the safety and lack of serious side effects in the use of Dornwal.

Apparently some people also died as a result of taking the drug, and I ask that the relevant material in the committee files be put into the hearing record.

Senator NELSON. That will be put in the record. I think that is one of a number of cases that does support the concept that you talked about, Dr. Lowinger, of having some independent evaluation, so that the public would be protected against cases like this which may occur from time to time.

Mr. GORDON. Mr. Chairman, there is another case which, I don't think, Dr. Lowinger referred to. Here is another letter on the drug called Flexin, which was manufactured by McNeil Laboratories, a subsidiary of Johnson & Johnson, in which the FDA asked the Attorney General to institute criminal proceedings.[1]

Senator NELSON. For the same reason?

Mr. GORDON. For the same reason. The offenses complained of were committed in 1959 and 1961, the knowing and willful concealing of material information and the submission of false and fictitious statements in writing to the Department of Health, Education, and Welfare. Apparently some people died of hepatitis which they contracted as a result of taking this drug.

I ask that the relevant material of this case also be put in the record.

[1] See pp. 4010–16, infra.

Senator NELSON. This will be done. Thank you very much, Doctor. We appreciate your very fine contribution to the hearings.

(The supplemental information submitted by Dr. Lowinger follows:)

Company	Drug	Date of report to company	FDA record of report
Armour Pharmaceutical Co	Lustica	Nov. 30, 1962	Yes.
Ayerst Laboratories	Suvren	July 16, 1957	Yes.
		Aug. 6, 1957	
Ciba Pharmaceutical Products	Serpasil	Dec. 9, 1954	No.
		Dec. 9, 1955	
Geigy Pharmaceuticals	Tofranil	Feb. 24, 1960	Yes.
		May 27, 1960	
		Nov. 7, 1960	
		Feb. 13, 1963	
		Mar. 4, 1965	
		January 1966	
Eli Lilly & Co	Compound F (or) Compound 18132 (or) Ultran.	Jan. 10, 1957	No.
Lloyd, Dabney & Westerfield	Benactzine	July 25, 1956	Yes.
National Drug Co	Contergan (or) Covatin (or) Thalidomide	Mar. 11, 1960	Yes.
	Methylnonyl dioxolane	Jan. 6, 1958	No.
Parke-Davis & Co	C1393	Aug. 26, 1960	No.
Pfizer Laboratories	Niamid	February 1960	Yes.
		May 27, 1960	
		Nov. 7, 1960	
		Feb. 18, 1963	
		Mar. 4, 1965	
		January 1966	
A. H. Robbins Co	Mephenoxalone (or) AHR233 (or) Trepidone.	Apr. 20, 1959	Partial.
		Mar. 11, 1960	
Roche Laboratories	Marplan	Feb. 19, 1960	Yes.
		May 27, 1960	
		Nov. 7, 1960	
		Feb. 13, 1963	
		Mar. 4, 1965	
		January 1966	
	Librium	July 22, 1964	No.
		Nov. 7, 1960	
		Feb. 13, 1963	
Riker Laboratories	Riker 548 (or) Trimeglamide	Nov. 17, 1958	No.
	Deaner	Jan. 6, 1958	No.
	Rauwiloid	Dec. 9, 1954	No.
		Mar. 21, 1955	
		Dec. 9, 1955	
Sandoz Pharmaceuticals	LSD25	June 9, 1964	No.
Smith, Kline & French	SKF 7003 (or) Proformiphen	Feb. 19, 1959	No.
	SKF 385 (or) Parnate	Apr. 8, 1959	Yes.
	Stelazine	Nov. 7, 1960	No.
		Feb. 13, 1963	
		July 24, 1964	
Squibb Institute for Medical Research	Raudixin	Mar. 21, 1955	
		Dec. 9, 1955	
Upjohn Co	U-12480E	December 1962	No.
Wallace & Tiernan	Dornwal	1961	No.
Wyeth Laboratories	WY 2149	Apr. 30, 1959	No.
	Equanil	Nov. 7, 1960	No.
		Oct. 8, 1962	
		Feb. 13, 1963	
		July 24, 1964	
	Sparine	October 1956	No.
Winthrop Laboratories	Win 12,267	Apr. 1, 1960	No.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
Washington, D.C., March 29, 1968.

PAUL LOWINGER, M.D.,
Department of Psychiatry, Wayne State University, School of Medicine
Detroit, Mich.

DEAR DR. LOWINGER: This acknowledges your letter of February 5, 1968.

We appreciate your kind indulgence throughout the lengthy investigation undertaken to determine whether reports you submitted to various pharmaceutical manufacturers where in turn submitted to the Food and Drug Administration in accordance with the existing legal requirements.

Our investigation has revealed close compliance with requirements in effect at the time your studies were conducted and reported to the manufacturers. The attached summary will carry a notation "Not Required" in such instances. As we

stated in our letter of December 28, 1967 there was no requirement prior to passage of the Kefauver-Harris Drug Amendments of 1962 that FDA be advised of all investigators and investigations conducted.

However, products marketed under the new drug provisions of the Act prior to 1962 are currently being evaluated by the National Academy of Sciences of the National Research Council.

Additionally, the manufacturers of prescription drugs are required to provide the medical profession with full information necessary for the safe and effective administration of the drug for the condition for which it is recommended in the labeling. Such required information includes side effects, precautions to be observed and contraindications. Such labeling information is periodically reviewed to insure compliance with the requirements of the Act.

Regulation 130.13 of the New Drug Regulations currently makes it mandatory for a firm to advise FDA of all investigators and investigations conducted. A copy of this section of the regulations is attached for your information.

We have terminated our investigation with the feeling that requirements in existence at the time were met. We believe this has been a valuable study and we wish to express our appreciation of your interest and cooperation in this matter.

Sincerely yours,

HERBERT L. LEY, JR., M.D.,
Director, Bureau of Medicine.

Firm	Product	Comments
Armour Pharmaceutical Co	Listica	Dr. Lowinger's report of Nov. 30, 1962, was included in the firm's submission.
Ayerst Laboratories	Suvren	On Sept. 23, 1957, firm submitted 2 letters and a report entitled "Final Clinical Report on Suvren." Firm also submitted the report "Outpatient Drug Therapy Evaluation Project;" also a report entitled "Explanation and Data on M Y-2241."
Ciba Pharmaceutical Corp	Serpasil	Dr. Lowinger's reports of Dec. 9, 1954, and Dec. 9, 1955, were not submitted. Not required.
Geigy Pharmaceuticals	Tofranil	Dr. Lowinger's reports were included in the NDA submission.
Eli Lilly & Co	Ultran	Dr. Lowinger's report of Jan. 10, 1957, was not submitted. Not required.
Lloyd Dabney & Westerfield	Benactyzine	A letter and 3 page report date July 26, 1956, were submitted.
National Drug Co	Contergan	The Mar. 11, 1960, report entitled "Interim Results in a Comparative Modified Double Blind Study of Tranquilizers in Psychiatric Outpatients" was submitted.
Do	Methylnonyl Dioxolane	No IND or NDA filed therefore no submission by firm of Dr. Lowinger's report of Jan. 6, 1968. Not required.
A. H. Robins Co	Mephenoxalone	Report of Apr. 20, 1959, was included in NDA for Lederle, Trepidone—Letter of June 10, 1960, authorized Robinson to Lederle's NDA for its Mephenoxalone sub.
Parke, Davis & Co	C-1393	No IND or NDA filed—Dr. Lowinger's report was submitted. Not required.
Chas. Pfizer & Co	Niamid	Reports were submitted by firm.
Roche Labs	Marplan	May 27, 1960, and Mar. 4, 1965, reports were submitted.
Do	Librium	No reference to either the capsules or reports tablets.
Riker Labs	Trimeglamide	Studies were discontinued on June 10, 1963. Dr. Lowinger's report of Nov. 17, 1958, was not submitted.
Do	Deaner	Submitted as part of annual report of Aug. 6, 1964, was bibliography section which included 3 references Dr. Lowinger. No other reports were located.
Do	Rauwiloid	No reference to Dr. Lowinger's reports of Mar. 21, 1955, or Dec. 9, 1955, were located. Not required.
Sandoz Pharmaceuticals	LSD	IND 306 listed Dr. Lowinger as an investigator. IND 302 contained references to Dr. Lowinger as follows: (a) a letter dated Apr. 20, 1966, to Mr. Craig D. Burrell of Sandoz; (b) 2 letters dated Apr. 11, 1966, and May 18, 1966, to Dr. Lowinger from the firm; (c) a statement listing the amounts of LSD-25 Psilocybin given to Dr. Lowinger. No clinical reports submitted by Dr. Lowinger located.
Smith, Kline & French	Proformiphen	No IND or NDA filed-no reference to Dr. Lowinger reports of Feb. 19 or Feb. 23, 1959, was located. Not required.
Do	Parnate	Report of Apr. 8, 1959, was submitted.
Do	Stelazine	Report of July 24, 1964, was submitted.
Squibb	Raudixin	Reports of Mar. 21 and Dec. 9, 1955, were not located. Not required.
Upjohn Co	U-12480 E	Studies were discontinued on Mar. 1, 1963. Report of December 1962 or January 1963 were not submitted. Not required.
Wallace & Tiernan	Dornwal	The 1961 report was not located. Not required.
Wyeth Labs	Equanil	Report of July 24, 1964, was submitted. Other report (Nov. 7, 1960, Oct. 8, 1962, and Feb. 13, 1963) were not located. Not required.
Do	Sparine	The October 1956 report was not located in the NDA files.
Winthrop Labs	Win 12-267	No IND or NDA filed. No reference to Apr. 1, 1960, located. Not required.

(The supplemental information submitted by Mr. Gordon follows:)

DEPARTMENT OF HEALTH, EDUCATION AND WELFARE,
Washington, D.C., June 5, 1961.

The HONORABLE ATTORNEY GENERAL,
Department of Justice,
Washington, D.C.

DEAR MR. ATTORNEY GENERAL: We request the institution of criminal proceedings under Title 18, United States Code, Section 1001, against Wallace & Tiernan, Inc., 25 Main Street, Belleville, New Jersey (a Delaware Corporation) and the following individuals, all employees of Wallace & Tiernan, Inc. at the time of the alleged offense:

Charles E. Hough, M.D., Medical Director, Maltbie Laboratories Division, Wallace & Tiernan, Inc.

Robert T. Conner, Ph. D., Successively Director of Research and Development for Maltbie Laboratories Division and Strasenburgh Laboratories Division, Wallace & Tiernan, Inc.

John F. Reinhard, Ph. D., Successively Director of Pharmacology Laboratories for Maltbie Laboratories Division and Strasenburgh Laboratories Division, Wallace & Tiernan, Inc.

Harold O. Thomas, Sales Manager, Maltbie Laboratories Division, Wallace & Tiernan, Inc., Now with Strasenburgh Laboratories Division in a sales capacity.

Henry C. Marks, Staff Director of Research, Wallace & Tiernan, Inc.

Harold W. Crogan, Vice President, Wallace & Tiernan, Inc., Manager of Maltbie Laboratories Division.

Robert T. Browning, Executive Vice President, Wallace & Tiernan, Inc. (now President).

Robert J. Strasenburgh II, President, Strasenburgh Laboratories Division, Wallace & Tiernan, Inc., Vice President, Wallace & Tiernan, Inc.

The offense complained of was committed between January 27, 1961, and October 18, 1961, and it involves the knowing and willful causing of material facts to be concealed and false and fictitious statements and representations to be made in a matter within the jurisdiction of the Food and Drug Administration.

NATURE OF VIOLATION ALLEGED

The indictment charges violation of 18 U.S.C. 1001 based upon the acts of the defendants in knowingly and willfully concealing material information, and submitting and causing the submission of false and fictitious statements. In writing and orally as to material facts, to the Department of Health, Education and Welfare, Food and Drug Administration in a matter within the jurisdiction of the Food and Drug Administration. On May 13, 1959, Wallace & Tiernan, Inc. submitted to the Food and Drug Administration, pursuant to section 505 of the Federal Food, Drug and Cosmetic Act [21 U.S.C. 355], a New Drug Application for a drug known as "Dornwal". This application was made conditionally effective on April 16, 1959. In the letter to Wallace & Tiernon, Inc. which made the application conditionally effective, the firm was notified that a label statement limiting the duration of treatment by this drug to three months would have to be maintained until the safety for prolonged use had been established. In the same letter the firm was notified that if further experience with the drug showed it to be unsafe for use, the effectiveness of the New Drug Application No. 11-973 could be suspended.

Subsequently, the firm made mail, telephone and personal contact with the Food and Drug Administration concerning the New Drug Application for "Dornwal". Between January 27, 1961 and October 11, 1961, 28 such contacts were made by the defendants in which they knowingly and willfully concealed material facts from the Food and Drug Administration, to wit, medical evidence that "Dornwal" was the causative agent of a severe and often fatal blood dyscrasia (disorder) in man. Furthermore, subsequent to the submission of the New Drug Application for the drug "Dornwal", the defendants made 10 mail submissions to the Food and Drug Administration concerning the New Drug Application in which false and fictitious statements and representations were made concerning the safety and lack of serious side effects in the use of "Dornwal".

A discussion of the count and the evidence already acquired in regard to the count is contained in the two loose-leaf notebooks transmitted with this letter. Further material has been collected and we will gladly furnish it if you so desire.

BACKGROUND

The defendant corporation has for several years been a manufacturer of pharmaceuticals. The acts alleged took place shortly after acquisition of another corporation, Maltbie Laboratories. The acquired corporation had developed a New Drug, subsequently referred to as "Dornwal". Dr. Crane was the medical director for Wallace & Tiernan, Inc. during the period of final development of the drug. He felt the drug was therapeutically ineffective and this resulted in disagreements with the management which led to his severance from the firm. Dr. John Vincent Scudi, under whose direction research and development of "Dornwal" was carried out, stated that he warned the management, and many of the individual defendants, that "Dornwal" was a compound which could cause agranulocytosis, a form of blood dyscrasia.

After laboratory and clinical trials, a New Drug Application No. 11-973 was submitted and made conditionally effective. The firm then marketed the product throughout the country. The "Dornwal" labeling approved by the Food and Drug Administration limited the use of the product to 3 months. In order to remove this sales inhibiting restriction, the company proceeded to supply the Food and Drug Administration with further clinical, pharmacological, and toxicological evidence of safety. The firm submitted supplements to the New Drug Application between October, 1959 and October, 1960. In a transmittal for one such supplement dated October 31, 1960, the firm reported that a patient to whom "Dornwal" had been administered had developed a blood dyscrasia. However, the company noted that the patient had been taking many other drugs and that it was highly unlikely that "Dornwal" had been the cause of the blood dyscrasia. In a reply letter dated December 29, 1960, the Food and Drug Administration notified the firm that the Supplemental Application of October 31, 1961 would be considered incomplete until all available details of this case of blood dyscrasia were obtained and presented to the Food and Drug Administration. In a communication of late January of 1961 to the Food and Drug Administration, concerning the case, great emphasis was placed by the defendants upon the use of other drugs in order to convince the Food and Drug Administration that "Dornwal" could not have been the causative agent. However, prior to this January, 1961 letter the firm had been notified of an additional case of blood dyscrasia in which "Dornwal" was strongly implicated as the causative agent.

It will be clearly demonstrated that Dr. Hough and the other individual defendants had full knowledge of this later case when providing evidence to convince the Food and Drug Administration that the previous case of blood dyscrasia was not caused by "Dornwal." In the process of concealing and making false statements and representations, the defendants concealed from the Food and Drug Administration, and from the medical profession, significant information which created a threat to the public health. Before this concealment was finally discovered by the Food and Drug Administration, 11 cases of blood dyscrasia attributable to "Dornwal" had occurred. When it became clear that some of the physicians, whose patients had developed blood dyscrasia, upon the use of "Dornwal," were planning to publish the reports of their adverse experience, Dr. Hough recommended that the Food and Drug Administration be notified at once. However, even then the Food and Drug Administration was not so notified. In October of 1961, while attending a medical conference, Dr. Frances O. Kelsey, then a medical officer of the Food and Drug Administration, came across information of a case of blood dyscrasia caused by the use of "Dornwal". When contacted in regard to this case, the defendants admitted they knew of five other such cases. Subsequently, the defendants were requested to submit full information on all cases of blood dyscrasia of which they had knowledge. A total of eleven cases were reported to the Administration. The New Drug Application for "Dornwal" was suspended on January 19, 1962, by order of Commissioner Larrick of the Food and Drug Administration.

VENUE

In view of the provisions of 21 U.S.C. 355, for the filing of New Drug Applications with the Secretary of Health, Education, and Welfare, in the District of Columbia, the venue in regard to a violation of 18 U.S.C. 1001, in the case of a New Drug Application, the concealment of material facts and causing false and fictitious statements to be made in a report to an agency of the United States Government, must be placed in the District of Columbia, the District in which the office of the Secretary is located.

WITNESSES

The principal witnesses will be former employees of the defendant corporation who will testify to the knowledge of the corporation and the individual defendants of the danger involved in the drug "Dornwal" and of the adverse reactions. It may also be desirable, on trial, to have the testimony of some of the physicians who submitted reports of adverse side effects to the defendants. There will also be considerable documentary evidence in the form of letters, memoranda, data sheets, and monthly reports which will show the fact that all the individual defendants had knowledge of the adverse reaction produced by "Dornwal" at the times that they communicated with the Food and Drug Administration, and concealed this knowledge from the Food and Drug Administration and made false and fictitious statements to the Food and Drug Administration as to the safety and absence of adverse side effects in the drug "Dornwal".

RESPONSIBILITY OF THE DEFENDANTS

The defendant company and individual defendants willfully concealed material facts and made false and fictitious statements and representations to the Food and Drug Administration. The defendants knew of cases of blood dyscrasia resulting from the use of "Dornwall". They concealed reports of cases of blood dyscrasia with knowledge of the importance of this information and the fact that the Food and Drug Administration should be informed of it. In the many communications with the Food and Drug Administration, for which the individual defendants and the corporation are responsible, there were false and fictitious statements as to the safety of "Dornwal" and the complete absence of serious side effects. The individuals, as the responsible officers of the corporation, are responsible for the occurrence of the acts.

It is requested that if the Indictment is changed, the United States Attorney furnish us with a copy thereof. Also, that we be kept informed of the progress of the case and other cases that may arise from it, and their dispositions. Upon request, we shall be glad to furnish any such further assistance as may be possible. The services of those who have conducted the investigation and counsel who assisted are available at your request.

Sincerely yours,

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

By direction enclosures [omitted].

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
Washington, D.C., April 20, 1964.

The Honorable ATTORNEY GENERAL,
Department of Justice,
Washington, D.C.

DEAR MR. ATTORNEY GENERAL: We request the institution of criminal proceedings under Title 18, United States Code, Section 1001, against the McNeil Laboratories, Inc., Fort Washington, Pennsylvania, and the following individuals, employees of the McNeil Laboratories at the time of the alleged offenses:

Robert L. McNeil, Jr., Chairman of the Board, McNeil Laboratories, Inc.
James Shaffer, M.D., Director, Division of Clinical Investigation, McNeil Laboratories, Inc.

and any others who may have shared responsibility for the alleged offenses.

The offenses complained of were committed between 1959 and 1961 and involve the knowing and willful concealing of material information, and the submission, and causing of the submission of false and fictitious statements in writing to the Department of Health, Education, and Welfare, Food and Drug Administration in a matter within the jurisdiction of the Food and Drug Administration.

There is transmitted herewith a suggested form of criminal indictment enclosed in two looseleaf notebooks which also contain a selection from the evidence developed by the Administration.

NATURE OF VIOLATION ALLEGED

The indictment consists of 8 counts. Four of the counts charge violation of 18 U.S.C. 1001 involving the drug Flexin. These are based upon the acts of defendants

in knowingly and willfully causing the submission of: a supplemental New Drug Application on September 28, 1959 [Count I]; a New Drug Application on January 6, 1960 [Count II]; a document in connection with a New Drug Application on March 21, 1960 [Count III]; and a letter in connection with a New Drug Application on April 17, 1961 [Count IV], which submissions contained statements and representations which were false, fictitious and fraudulent, or which concealed material facts, concerning the safety and lack of side effects of the drug, Flexin, when used by man. Counts I and IV are concerned with the drug marketed under the name Flexin, and Counts II and III involve Tablets Triurate, a drug consisting primarily of Flexin.

Counts V through VIII also charge violations of 18 U.S.C. 1001 and involve the drug Paraflex [Count VI] and two paraflex-containing products: Parafon [Counts VII and VIII] and Parafon with Codeine [Count V]. The company is charged with knowingly and willfully causing the submission of: A New Drug Application for Parafon with Codeine on May 18, 1959 [Count V]; a Supplemental New Drug Application for Paraflex on June 10, 1960 [Count VI]; a Supplemental New Drug Application for Parafon on June 10, 1960 [Count VII]; and an additional Supplemental New Drug Application for Parafon on February 8, 1961 [Count VIII]. Each of the submissions contained false and fraudulent statements as to the lack of side effects in man associated with use of the drug involved.

BACKGROUND

The defendant, McNeil Laboratories, Inc., for a number of years has engaged in the research, development, manufacture, and distribution of drugs in this country. It is a Pennsylvania corporation. On January 1, 1957, the company became a wholly owned subsidiary of Johnson and Johnson, Inc., but has retained its separate identity. Some of the drugs are New Drugs [drugs defined under the Federal Food, Drug, and Cosmetic Act as not generally recognized by experts to be safe and effective for use under the conditions recommended in the labeling. At the time of these alleged violations, effectiveness was not a part of the definition]. A New Drug may not be legally marketed in this country without a New Drug Application having been approved by the Food and Drug Administration. Any application or supplemental New Drug Application [proposed changes by the holder of an effective New Drug Application] must include, among other things, full reports of investigations which have been made to show whether or not such drug is safe for its intended use.

Pursuant to these requirements, McNeil Laboratories, Inc., on November 14, 1955, submitted to the Food and Drug Administration a New Drug Application for Flexin. Data in the application included clinical and pharmacological studies. The application was made conditionally effective on January 13, 1956. On December 2, 1955, however, a physician had notified the firm that one of his test patients using Flexin had developed hepatitis and died. On January 5, 1956 a pathologist who reviewed sections of the liver from the deceased patient had informed the company that death of the patient may have been due to the drug therapy. The Food and Drug Administration was not informed. Between April 1956 and July 1956, the company received reports of 5 additional cases of Flexin-related hepatitis, and in four of these cases the reporting physician ascribed the damage directly to the drug. During this period, and until August 1956, the brochure in use for Flexin bore the following statements "Flexin has produced no irreversible toxic reactions when administered to patients daily for periods of 6 months" and that "Anemia, leukopenia, agranulocytosis, jaundice or kidney damage has not been reported in any patient receiving Flexin."

In August, the phrase "jaundice or kidney damage" was removed from the labeling. There was no other change. Between August 1956 and October 13, 1958, McNeil Laboratories, Inc., received reports of 26 cases of liver damage in Flexin patients, including 7 deaths. During this time, McNeil Laboratories made several submissions of information relating to the New Drug Application for Flexin. No reports of liver damage were made to the Administration. The company took very little action to investigate the liver damage cases reported to it.

Count I is concerned with the submission by the company of a supplemental New Drug Application filed pursuant to the provisions of 21 U.S.C. 355 on September 29, 1959. False statements contained in that submission are set out in detail in the looseleaf notebooks accompanying this letter. Among other false statements are statements that a lower number of Flexin-associated hepatitis cases had been reported to the firm than was actually the case, false statements concerning a lack of causal relationship between the drug and hepatitis, and exaggerated reports of

the extent of the investigation made by the company into the hepatitis cases reported to it. In addition, no report was made concerning the deaths of patients.

On January 6, 1960 the company filed a New Drug Application for the New Drug known as Tablets Triurate. One of the major components of that drug is Flexin. The false and fraudulent statements and representations as well as concealed material facts concerning the safety and lack of serious side effects involved in the use of Flexin form the basis of Count II. These statements involve the liver damage associated with use of Flexin.

The company, on March 21, 1960, as a part of the New Drug Application originally filed on January 6, submitted samples of proposed labeling. In a paragraph entitled "Side Effects" the only reference to hepatitis and its connection with the administration of the drug Flexin is a statement that in isolated instances hypersensitivity reactions thought to be due to Flexin have been reported such as transient reversible renal irritation or hepatitis. The firm had been informed of 50 cases of Flexin-related liver damage including 11 deaths. This is the basis for Count III. On April 17, 1961 the firm submitted a request for a change in the New Drug Application relating to the packaging of Flexin. No reference was made to the association between the use of Flexin and liver damage. By this time, the company had learned of at least 57 cases of Flexin-related hepatitis including 15 deaths. This is Count IV.

On July 13, 1961, officials of the company contacted the Food and Drug Administration and related that the firm had received a considerable number of reports of Flexin-related hepatitis, and they believed that the labeling should carry a stronger warning about these possible reactions. After an exchange of correspondence between the Food and Drug Administration and McNeil Laboratories, during which the firm sought to devise some way to label the drug to keep it on the market, the Food and Drug Administration determined that the risks involved in the use of Flexin outweighed any therapeutic value contributed by its use. Therefore, on October 13, 1961 the New Drug Application for Flexin, and all amendments and supplements, were formally suspended by order of the Commissioner of Food and Drugs.

Paraflex, a chemical analogue with similar properties to Flexin, was developed about the same time as Flexin. A New Drug Application was filed on November 1, 1957 for this product, and two New Drug Applications for drugs containing Paraflex were filed on May 23, 1958. One application concerned Parafon, a mixture of Paraflex and Tylenol and the other concerned a product called Tablets Paraflex-Tylenol-Prednisolone which contained the drugs as named. All were made effective. Between June 28, 1958 and July 15, 1959, McNeil Laboratories had been informed of three cases of hepatitis which occurred during Paraflex therapy.

Count V is concerned with the submission by McNeil Laboratories of a New Drug Application for Parafon with Codeine on May 18, 1959. An accompanying draft of the physicians index card for the product stated "Paraflex . . . has not caused serious toxic reactions or undesirable effects on . . . liver . . .". Two cases of Paraflex-associated hepatitis had by this time been reported to the firm. On June 10, 1960, the company submitted a Supplemental New Drug Application concerning the basic product Paraflex. An accompanying proposed brochure stated "Paraflex has produced no serious toxic reactions . . . Daily administration for as long as one year had produced no evidence of damage to the liver . . .". This is Count VI. Count VII involves the submission of a Supplemental New Drug Application for Parafon on June 10, 1960 which contained wording in its brochure identical to the above. Count VIII is involved with similar false statements made in a subsequent New Drug Application for Parafon submitted on February 8, 1961. In addition, the false statements made in each of Counts VI through VIII, were repeated by the company in forwarded specimens of final printed labeling submitted to the Food and Drug Administration at a later time.

In response to a letter mailed to McNeil Laboratories by the Administration on August 23, 1961 which had requested reports of hepatitis associated with Flexin or of any chemically and pharmacologically related chlorzoxazone, the company admitted that they had received 3 reports of Paraflex-related hepatitis.

RESPONSIBILITY OF THE DEFENDANTS

The defendant company and individuals not only furnished false information in their submissions but also concealed information directly relating to the safety of Flexin and Paraflex when used by man. Safety, of course, is the prime con-

sideration in evaluating New Drug Applications. Each of the submissions by the company to the Food and Drug Administration involved in Counts I through VIII were signed by Robert L. McNeil, Jr., Chairman of the Board of McNeil Laboratories. All of the reports concerning liver damage which were received by the company from the various doctors were routed directly to Dr. James Shaffer and Dr. Shaffer signed all correspondence emanating from the firm to the doctors concerning these complaints. The falsification of the documents was so wide spread that one can only conclude that there was a deliberate attempt on the part of the company and the individual defendants to deceive the Food and Drug Administration as to the safety of Flexin and Paraflex.

VENUE

In view of the provisions of 21 U.S.C. 355 for the filing of New Drug Applications with the Secretary of Health, Education, and Welfare in the District of Columbia, the venue in regard to a violation of 18 U.S.C. 1001 must be placed in the District of Columbia.

WITNESSES

The principal witnesses in the case will be officials from the New Drug Division of the Food and Drug Administration who received and reviewed the New Drug Application and Supplements in regard to the drugs and who, upon request, were sent copies of the letters written to the company from physicians reporting liver damage and replies sent to those physicians by the firm. Evidence will also be obtained by means of subpoenas duces tecum to be issued to McNeil Laboratories and its parent company, Johnson and Johnson, Inc. A suggested form for such a subpoena is included in the looseleaf notebooks enclosed with this letter.

STATUS OF THE DRUGS INVOLVED

Flexin was removed from the market on October 13, 1961. This was accomplished by a suspension order signed by the Commissioner of Food and Drugs. No New Drug Application is currently pending for Flexin or Flexion-containing products. Paraflex is still subject to an approved New Drug Application, but the company is required to include in the labeling the number of cases in which these drugs were suspected as being the cause of liver damage.

It is requested that if the Indictment is changed, the United States Attorney furnish us a copy thereof. Also, that we be kept informed of the progress of the case and any other cases that may arise from it and their dispositions. Upon request, we shall be glad to furnish any such further assistance as may be possible. The services of those who have conducted the investigation and of counsel who assisted is available at your request if you feel it may be of any possible assistance to you.

Very truly yours,

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

Enclosures [omitted].

U.S. DEPARTMENT OF JUSTICE,
Washington, D.C., September 28, 1964.

Re Proposed prosecution against McNeil Laboratories, Inc., et al., under Title 18 U.S.C. 1001

Mr. WILLIAM W. GOODRICH,
Assistant General Counsel, Department of Health, Education, and Welfare, Washington, D.C.

DEAR MR. GOODRICH: This is in reply to your letter of April 20, 1964, to the Attorney General, concerning the possible violation of Title 18, United States Code, Section 1001, by McNeil Laboratories, Inc., Robert L. McNeil, Jr., and James Shaffer, M.D., in connection with the submission of New Drug Applications for compounds containing the drugs known as Flexin and Paraflex.

As you are no doubt aware, any criminal action which may have arisen by virtue of falsehoods or omissions in the New Drug Application submitted prior to April 20, 1959 were already barred by the statute of limitations at the time of your referral. After a careful review of all the evidentiary material petaining to

this matter we have concluded that criminal proceedings are not justified as to later submissions. One of the principal factors in our determination is the fact that from time to time the Supplemental Application with reference to Flexin and Flexin containing compounds contained language which progressively gave greater recognition to the possibility that Flexin might cause jaundice. This recognition was highlighted in the September 29, 1959 Application which revealed that in 32 instances Flexin patients had suffered hepatitis. The literature reported disclosed that on some occasions the disease had been fatal.

Since the Applications, do therefore, disclose on their face the possibility that Flexin might cause jaundice, we are of the view that criminal action is not warranted, especially since the Food and Drug Administration medical officers approved the Applications, including that of September 29, 1959 without further inquiry concerning the hepatitis cases.

Prosecution is therefore declined.

Sincerely,

HERBERT J. MILLER, Jr.,
Assistant Attorney General, Criminal Division.
By HAROLD P. SHAPIRO,
Chief, Administrative Regulations Section.

RESEARCH AND DEVELOPMENT DIVISION,
SMITH KLINE & FRENCH LABORATORIES,
Philadelphia, Pa., February 20, 1969.

Hon. GAYLORD A. NELSON,
Chairman, Senate Subcommittee on Monopoly, Select Committee on Small Business, Washington, D.C.

DEAR SENATOR NELSON: A misleading and possibly injurious reference to Smith Kline & French Laboratories appears in the testimony presented to your Monopoly Subcommittee on December 18, 1968, by Dr. Paul Lowinger, Associate Professor of Psychiatry, School of Medicine, Wayne State University.

Dr. Lowinger testified that, for the eriod 1954 through 1966, some 19 drug companies, including Smith Kline & French, had passed along to the Food and Drug Administration reports on only 9 of the 27 "new drug studies" he transmitted to them. Whether intended or not, the implication in Dr. Lowinger's testimony is that the alleged failure of the drug houses to turn his reports over to the Food and Drug Administration was violative of the federal drug law and contrary to the best interests of the American public.

This implication is regrettable. Our handling at Smith Kline & French of the five reports relating to three different drugs received from Dr. Lowinger for the period in question complied in every detail with applicable federal drug regulations. Moreover, our conduct in these matters conformed to the highest ethical and scientific standards and we acted in a fully responsible fashion.

Let me place the matter of Dr. Lowinger's reports to Smith Kline & French and all relevant facts in proper perspective for the benefit of your Monopoly Subcommittee and those who are following its drug hearings:

1. Dr. Lowinger advised the Monopoly Subcommittee of a report on SK&F 7003 (proformiphen) which he said was sent to our company on February 19, 1959, but was not then passed on to the Food and Drug Administration.

In this report, Dr. Lowinger described the result of a clinical investigation with this compound in out-patients with symptoms of depression and anxiety. Among the ten patients described in the report, three reported side effects of tinnitus, feeling of unreality, dizziness, and rash. Prior to the Drug Amendments of 1962, there was no requirement to submit information on investigational drugs to the FDA outside of the NDA procedure. The information on this compound was not submitted to the FDA because in March 1959 Smith Kline & French management decided to discontinue the clinical investigation of SK&F 7003 and no NDA was ever filed.

2. Dr. Lowinger also told the Subcommittee of three reports he sent us regarding a "double blind study" he made of a number of tranquilizers, including our 'Stelazine'. Other drugs in Dr. Lowinger's study were Librium, Equanil, Marplan, Tofranil, Niamid, and a placebo.

Interim progress reports on the "double blind study" were sent to Smith Kline & French by Dr. Lowinger on November 7, 1960, and again on February 13, 1963.

These reports did not contain any information on new or serious side effects and, thus, were not sent on to the FDA. Such routine reports were not required for 'Stelazine' until October 29, 1963, when the FDA approved a supplement to the new drug application for 'Stelazine'.

On July 24, 1964, Dr. Lowinger sent Smith Kline & French a final report on his "double blind study" and, again, there was no reference to any new or serious side effects. Our records show that this final report was included in our annual report for 'Stelazine' submitted to the FDA on September 24, 1964.

3. Dr. Lowinger's final mention of Smith Kline & French was in connection with his report on 'Parnate', dated April 8, 1959, a report which he noted was sent on to the FDA by our company and this is correct.

This Lowinger report was submitted to the FDA as a component of our company's new drug application for 'Parnate', dated March 2, 1960. Receipt of the 'Parnate' including the Lowinger report, was promptly acknowledged by the FDA.

I respectfully request that this letter be made a part of the public record on your Subcommittee's hearing held December 18, 1968.

Sincerely yours,

MAURICE R. NANCE, M.D.,
Medical Director.

Senator NELSON. Our next witness is Dr. Franz J. Ingelfinger, editor of The New England Journal of Medicine; also clinical professor of medicine at Boston University School of Medicine.

The committee appreciates your taking time to come here today. Everyone in the medical profession has a high regard for the very famous magazine of which you are the editor. I find it approvingly referred to by physicians from all over the United States who have testified from time to time before this committee.

Doctor, your full statement, including your biographical summary, will be printed in the record.[1] You may proceed however you desire. If you want to depart from the text, to elaborate on any particular aspect, feel free to do so.

I realize that to reduce everything to writing takes a great deal of time. You may want to comment somewhat more broadly on some aspects of your written testimony.

I assume you have no objection if we interrupt with a question from time to time?

STATEMENT OF DR. FRANZ J. INGELFINGER, EDITOR, THE NEW ENGLAND JOURNAL OF MEDICINE, BOSTON, MASS.

Dr. INGELFINGER. Thank you very much, Senator Nelson, for asking me to come here, and I hope we proceed as you proceeded with Dr. Lowinger, and I will be perfectly ready to answer questions if I can.

Possibly I should amplify a few things. My main reason for being here, the reason you invited me, I presume, is because I am the editor of The New England Journal of Medicine. This journal, of which I have the latest copy with me, fortunately is respected not only by the medical profession, but also by the lay press. The lay press—I hope this continues—practically never mentions it without the adjective "prestigious," and this is not due to me, because the credit belong to my predecessor, Dr. Joseph Garland. I have been editor of the journal for a year and a half. He had previously been editor for 20 years.

The journal, I think, is a good example of some of the problems that one faces with respect to news about drugs and drug advertising.

[1] See p. 4037, infra.

It is highly respected. It also has, I believe, the second largest circulation of the regular, not the controlled circulation journals, but the regular subscription medical journals in the world, the Journal of the American Medical Association being No. 1.

Senator NELSON. What is the circulation of the New England Journal?

Dr. INGELFINGER. It is currently 110,000.

Senator NELSON. And how much of that is domestic circulation within the continental United States?

Dr. INGELFINGER. Practically 90 percent of it.

Senator NELSON. Ninety.

Dr. INGELFINGER. Close to 100,000, somewhat short of 100,000.

Senator NELSON. Out of the total of——

Dr. INGELFINGER. Out of 110,000, approximately 90 percent is domestic.

One other thing of, I think, importance, at least to us, is that we have a very high subscription list among medical students and interns and residents, that is house officers, people who might be lumped together as trainees in medicine. About 35,000 of our subscribers are in this category, roughly a third.

We are, we believe, the largest—have the largest circulation in terms of voluntary subscriptions.

The New England Journal of Medicine is owned by the Massachusetts Medical Society, so the only captive audience we have, so to speak, are the members of the Massachusetts Medical Society, some 8,000 in number.

So our voluntary subscription of about 100,000, I think, is about the highest there is of that type.

Well, I am saying this not to boost the Journal so much as to indicate that even a journal with such favorable and fortunate position has problems that I will discuss later.

Second, as I have indicated in my statement, previous to becoming editor of this journal, my work was chiefly in academic medicine, in the subspecialty of gastroenterology, diseases of the intestines, esophagus, liver, pancreas, and gall bladder.

I have had extensive experience in this, and have conducted a long-term research and training program.

As part of this, and also this may come up later when we discuss some other problems related to NIH-like institutions—I have served for more than 12 years on various NIH advisory bodies, including 4 years on the Advisory Council of the National Institute of Arthritis and Metabolic Diseases.

Earlier in my career, when I was doing less administrative and editing work, I carried out drug studies, support for which came from drug companies, which you may want to question me about more later.

Now, I have tried to answer chiefly two of the questions or two major questions in the letter that you sent, Senator, relating to some of the problems of drugs, of pharmaceutical firms, and the influence they have on the education of physicians and on physicians' use of drugs in treating patients.

One of the questions deals with the payment by firms to investigators to evaluate drugs, and also payment to academic institutions for general support.

The other deals with the problems of the Journal.

Would you prefer I start with the Journal, because that may be slightly different from Dr. Lowinger's testimony, or should I go right ahead?

Senator NELSON. Any way you desire. It is all right to follow just the way you have it here.

Dr. INGELFINGER. All right.

Well, the first item relates to the acceptance by physicians of funds paid by drug companies for the evaluation of their products or for other purposes, such as fellowships, salaries, general research support.

It is my impression that the objectivity of such studies and the freedom from undue influence related to the source of support depends a great deal on the circumstances under which this testing is carried out.

Currently, at least, the testing is often carried out, not invariably, often carried out, (*a*) in a medical school setting, and this means that administrative officials rather than the investigator will handle the financial arrangements; that is, with no direct payment to the investigator, and (*b*) which, I think is also important, others besides a solitary investigator, that is, technicians, referred to by Dr. Lowinger, graduate students, other physicians, house officers, will participate in the test procedures.

These young people are some of the most severe critics in the world, and their involvement in this type of work makes in very difficult, I think, to fudge the results. So I think the study of this type is safeguarded, in that there is participation by a number of people who have no financial interest in the nature of the results.

Senator NELSON. Let me ask this: I do not know what percentage of investigatory drug testing is done under this precise circumstance; that is, where it is in a medical school setting, and so forth. We have not had any testimony from the companies on that. However, it does appear that some percentage of the testing is done by contracts with individual physicians who may or may not be involved in a teaching hospital and who are paid a fee for the testing they do.

As I say, we have not taken testimony to find out just how widespread this practice is. We do have, however, specific examples of drug testing and there have been questions as to the validity of the results obtained.

What is your view of that kind of an investigation, an individual contract for a fee, not under the supervision of an institution of any kind?

Dr. INGELFINGER. I come to that on the next page, Senator. May I continue because it gives sort of a little more background?

Senator NELSON. Yes, of course.

Dr. INGELFINGER. Another reason why testing, particularly in academic settings and under certain conditions, is not too much of a concern to me is that the testing is carried out during the preliminary stages of the development of a drug.

For example, my laboratory used to screen agents for their ability to affect gastric acid secretion or to decrease the motor function, the contractions of the gut. On other times we were asked to determine whether or not certain drugs were well absorbed if injected into the upper part of the intestine, into the stomach or lower down, in an

effort to determine where the absorptive functions might be most effective and applicable.

Now, testing of this type means that measurements are taken with various types of equipment. We can record contractions, we can measure chemical levels in the blood and, therefore, again this type of testing, I think, is more difficult to distort by bias unless one is purposely unscrupulous.

The objective data so obtained cannot easily be distorted, as I say, by personal bias.

Furthermore, this is an important point and possibly I am prejudiced, but under such circumstances an investigator who misleads a financial sponsor is not doing that sponsor any favor. Drug companies, I have found, are not anxious to spend money on developing an inferior product, and for their own protection tend to seek a valid appraisal.

For example, if I were testing a drug on its intestinal contraction-inhibiting effect, and it turned out to be no more effective or even less effective in our screening type of tests than atropine, a standard well-established drug known for many, many years, then I felt that the manufacturer or the man developing this drug would benefit by my telling him so, so I was under no pressure to tell him good news. I thought I was doing him a favor by telling him bad news.

So far I have been talking about measurements and of specific biological activities, that is contractions, chemical measurements, things that you can record on a device, done in a university setting. Clinical testing of a product, the type of testing that Dr. Lowinger carried out, that is, where you give a drug to a patient and determine whether or not it is helping him or harming him or doing nothing, I think, is extremely difficult under any conditions; and my belief is it is the most difficult type of investigation that can be done.

The criteria available for measuring a drug effect are often extremely vague and highly subjective. There is no yardstick, for example, whether an abdominal pain is better or worse. The desires of both patient and investigator may color the interpretation. Hence, studies of this type must be carried out under optimum conditions—and here I am coming to answer your question, Senator—optimum conditions mean investigators who are equipped by training and facilities to carry out such testing, and who use a protocol incorporating procedures that characterize a well-controlled study.

If these conditions are observed, I doubt that the results are likely to be influenced in any way by subtle economic pressures.

However, if a study is carried out by an individual without such facilities, without a protocol which is generally accepted as being satisfactory, and under direct payment of that individual evaluating that study, possibly in a solo private office setting where the facilities are not available, I would disapprove of such studies.

Senator, may I ask you a question—a question for my information as to how to proceed. I do not want to repeat what you have been told many times at these hearings, but have you been told about some of the difficulties clinical testing, what a terribly tough job it is?

Senator NELSON. We have heard such testimony. However, we would be pleased to have for the record anything you wish to present on this subject.

Dr. INGELFINGER. Let us assume that we are studying whether a certain agent, let us say X, helps a certain condition—and once in a while there is a dramatic new agent, such as penicillin or oral diabetic agents where the results are obviously clearly beneficial.

But in the case of the vast majority of agents, the difference between drug A, B, C, and X may be not great, it may be an improvement in one fashion or another. The first condition that has to be set up is a controlled situation. The investigator has to choose two groups of patients or subjects. Group A gets the drug and group B does not.

Under the usually practiced procedure it is a double blind study in the sense that neither the investigator nor the patient knows whether he is receiving a tablet with the active agent or with a so-called placebo, that is, just a dummy tablet that looks identical. This is a standard type controlled condition.

It is not easy to achieve without an adequate study population, several groups of large enough size. You cannot do this with three or four people. You need enough to make the observations statistically valid, unless the drug happens to be a most unusually effective one.

Then the investigator runs into the problem of ethics, medical ethics, quite apart from drug advertising. He may be challenged for (*a*) giving a new agent to the study group or (*b*) he may be criticized, as some have been, in the past when this sort of study was carried out with penicillin early in the study of that agent—he may be criticized for not giving the active agent to the control group who, in retrospect, should have had it.

Do you understand what I mean?

Senator NELSON. Yes.

Dr. INGELFINGER. Then the investigator has to establish yardsticks of improvement and, finally, he has to show that improvement is greater with drug X than the control, and sometimes the control is not a dummy placebo but may be a competitive agent or one that has already been used for the same purpose.

So the differences between the substances tested may be even closer, and the investigator has to show that the side effects are the same or less than with the competitive agent or with the dummy.

I would not have talked about this until I heard Dr. Lowinger mention, among the side effects he described, headache, lassitude, and constipation. I wish I could remember the exact figures—I cannot—but the New England Journal of Medicine recently published an account of a study in which the investigators merely went around and inquired as to the appearance of such common complaints in normal subjects who had not taken any drugs within 3 days.

Well, in about 20 percent of the people, as I recall the figure, maybe a little bit more, those symptoms will start spontaneously for no apparent reason.[1]

Therefore, to prove that a drug is causing side effects of this general type, you have to have higher frequency of such side effects in the drug group than you do in the control group.

Conversely, placebos often are credited, that is a dummy preparation, with making about a third of the people feel better or think they feel better.

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[1] Dr. Ingelfinger subsequently submitted the following: "The exact figure is 81 percent. (New Eng. J. Med., vol. 279, p. 678, 1968.)"

So I thought it is important to point out—and I did not want to belabor the question if you had heard it many times—that you are dealing, Senator, with clinical investigations which are extremely tough.

It is much easier to study a bunch of mice and give them a drug and then measure whether their blood level, hemoglobin, the redness of their blood, is more or less. I could do this tomorrow with no trouble at all. I would shy away from a big clinical study because it is so difficult.

Mr. GORDON. Dr. Ingelfinger, you referred to studies that you have conducted in which you have tested one drug against another drug, a competitive product.

Did you find in your experience that pharmaceutical houses would finance the type of study in which their product would be tested against another product?

Dr. INGELFINGER. Oh, yes.

Mr. GORDON. Do you have any specific examples?

Dr. INGELFINGER. Well, many times we studied so-called antispasmodics, drugs which inhibit the contractions of the intestines. It is a field I got into fairly early. We inserted balloons at the end of long tubes in people's intestines and measured the squeeze on the balloons on a recording drum. That equipment which we used early in the 1940's gradually became more sophisticated, but that is more or less the essence of it; and we almost invariably compared the agent under study to atropine, which I mentioned a while ago. It did not seem worthwhile for any company to develop an agent which was not at least as effective as atropine.

Now, if a drug company could make an agent as effective as atropine, but has less side effects, relative to the specific beneficial effect desired, then, of course, they would be justified in developing it.

Mr. GORDON. Do you know if comparative studies, such as we are talking about, are carried out in antibiotics as well as in other categories of drugs?

Dr. INGELFINGER. Again it is somewhat harder to measure. One can measure certain blood levels with antibiotics, and certainly compare that, and I believe that has been done.

The comparative clinical efficacy of giving somebody with active pneumonia one agent versus another in a controlled study is very difficult.

On the other hand, one may compare a study done in New York with agent A with a study done subsequently with agent B, but there the problem is that the patient and the locale are not the same, although they both got the same ingredients.

Mr. GORDON. Do you have any knowledge as to the amount of testing done in medical schools under situations such as you have described as compared with testing done by individuals who get direct payments? I looked through the New Drug Application for indomethacin at the Food and Drug Administration, and most of this testing seemed to have been done by individual physicians.

Dr. INGELFINGER. I do not know the answer to that. I have no idea. It would be nice to know, but possibly one suggestion that I should like to make is that this be an avenue of exploration in terms of trying to obtain more valid judgments. I am not trying to say that all universities are honest or that they are so much better than an individual.

I am just saying that safeguards are provided when a group of people with less personal involvement than that of a solitary investigator are at work, and the general attitude of clinical investigation which obtains in these institutions, is much more likely to yield a valid evaluation. It is not going to be perfect.

Mr. GORDON. What do you think of testing done by private firms for the drug industry? I have in mind, for example, the Cass Associates in Massachusetts.

Dr. INGELFINGER. Well, you are picking on one in which I think, that there is some specific evidence that their reports were not reliable. On the whole, I would not recommend this type of testing but again I would have to be a little bit informed as to the nature of the firm and who was running it and what their qualifications were. I do not think I can make a categorical statement.

Senator NELSON. We will take a 5-minute recess to let the reporter rest his fingers.

(Short recess.)

Senator NELSON. You may proceed, Doctor. I do not know exactly where we left off.

Dr. INGELFINGER. On page—I interpolated quite a bit of extraneous discussion on clinical testing, but I am going back to page 3, the next to the last paragraph.

Senator NELSON. Right.

Mr. GORDON. There is just one more question I want to ask you. As I told you before, I have looked through the New Drug Application for indomethacin which numbers, I think, well over 65 volumes, and I noticed that most of the reports were from individual investigators. Many of them merely have cards on which the investigator checks off certain things.

Would you comment on that type of clinical investigation?

Dr. INGELFINGER. I have seen the same in the past, not recently because I have not been doing that type of work, but certainly previously.

I do not think this is appropriate. It is too hard for the individual to make these judgments. The reason I talked so much about the difficulty that clinical investigation encounters, was to indicate that under even optimum conditions, with some of the best facilities available it is difficult.

How much more difficult it would be if I—and I am not trying to attack the competence of the individual physician, I am just talking in terms of his general medical ability. I am saying if I, as gastroenterologist, tried to evaluate a certain antacid, along with a busy practice taking care of my patients, I do not see how I could get a meaningful result.

Senator NELSON. As I understand it from what you said, I believe on the first page, the ideal circumstance for testing is in the institutional, the medical school or teaching hospital. Is that what you are saying?

Dr. INGELFINGER. Yes. I mean where there exist facilities in terms of training, that is, intellectual facilities, and educational of the investigators, as well as whatever equipment is needed.

Most of these drugs we are talking about, most of the drugs reported in the task force report are drugs given for chronic conditions that

fluctuate; spontaneous changes in the illness make it very hard to know whether one's treatment has really helped or not, and this is why these carefully controlled studies are so necessary.

Senator NELSON Please go ahead, Doctor.

Dr. INGELFINGER. One suggestion that has been made to prevent undue influence of sponsor on investigator is the establishment of a central independent agency that would act as a clearinghouse in arranging for the testing of drugs.

Under such an arrangement, drug testing for its clinical efficacy would be, in a sense, triple blind in that the investigator and the agent's maker would also be unaware of each other's identity.

Such a central agency might be established under the jurisdiction of a committee in which pharmaceutical firms, Government and the American Medical Association would have adequate and satisfactory representation.

I am here talking about sort of a variant of what Dr. Lowinger discussed, I believe it should be sort of a tri- or multi-partisan type of structure rather than something analogous to one of our National Institutes of Health studying categorical types of illnesss.

And the reason I do this is because I believe findings have to be accepted, and they have to be accepted by the medical profession. The medical profession and the Government have their problems of understanding each other, and it seems to me the way one can overcome some of this unfortunate distrust is to have—if there is to be such an agency that will supervise drug testing—all the people concerned represented, including the pharmaceutical manufacturers because, after all, they are making the drugs. It is an industry which, in our free enterprise system, we depend on.

If we had such an agency or institute however, the increased objectivity and the trustworthiness of drug testing procedures so attained, would have to be balanced against the added expense and delays entailed if such a scheme were implemented.

Furthemore, I am not sure that total blindness could be achieved. Why not? Well, the investigator certainly is going to know something, he is going to know what conditions he is going to use his drug on. He is going to be given the chemical formula, he is going to be given background information on animal studies.

If Dr. Lowinger's proposal is implemented, and I certainly agree that exchange of information with other investigators be required, it seems to me the man who is experienced in a given field is pretty well alert as to who is making certain kinds of agents, and he knows what drug companies have reported preliminary studies in various pharmacological journals. Hence, I am not sure that a completely blind approach would be easily achieved in the sense that the investigator and drug firms would be completely unaware as to who is testing what.

Senator NELSON. But it would be true, would it not, that if the group to which the investigator were responsible was an independent group and not a company that had a financial interest, the possibility of bias or of being unintentionally influenced is removed? Is it not?

Dr. INGELFINGER. Well, it could be partly removed, but possibly I am a little more cynical about it. Suppose that company came up to my professor, dean, or chief of medicine and said, "Would you

like another fellow in that department? We will be glad to contribute $10,000 a year for its support."

In other words, there are other ways of getting around if you are determined to get around it.

Senator NELSON. But all I am getting at is that it reduces it.

Dr. INGELFINGER. It reduces it, yes.

Senator NELSON. As to the delay factor, why is there necessarily any delay if you followed something like the procedures suggested by Dr. Lowinger in which the company proceeded with its own method of producing its new drug application, but you also had a group, such as you suggest, that was independent of it that contracted arrangements with medical schools for some independent testing along with it. Why would they necessarily take any longer that way than they do the present way?

Dr. INGELFINGER. I am not sure that it would necessarily, but I suspect it might in terms of the arrangements that are necessary.

If it is a plum, so to speak, if the study is of a financial magnitude and particularly also of intellectual content so that a number of investigators were interested, then somebody has to make a decision. A study section might consider contract applications and award priorities as at the National Institutes of Health.

Conversely, if it is a rather dull study, why then you have to go out and scout around to find someone, and in this connection again, I think it is very difficult to get good people to do this kind of study.

I have already indicated how difficult, how hard clinical drug studies are to do mechanically. But beyond that is the motivation, and again, I would much rather carry on an investigation designed to find out what causes a peptic ulcer than testing some new antacid which is terribly dull intellectually. It is not stimulating, it is not motivating.

Occasionally a drug may produce an unusually dramatic effect, and the investigator can feel that he has achieved some status by studying this drug. But most drug studies are pretty humdrum affairs, and I do not think it would be easy to get many people for this.

Therefore, it seems to me it would be more direct if drug firms tried to make their own arrangements with universities, to have drugs studied rather than having an intermediate agency, which in its arrangements with investigators would unavoidably introduce delays.

I also mention at the end of the next paragraph perhaps some honor system, such as the NIH has established with various medical schools, could be initiated, with the individual universities assuming responsibility for the trustworthiness of drug studies carried out by their staffs. This is an amplification of what I mentioned before.

The question of fellowships, salaries, and general research support may be similarly answered.

If funds made available by the pharmaceutical industry for such purposes are paid to educational or other nonprofit institutions, a hospital, say, through regular administrative channels, there is little chance that the donation will distort the scientific efforts of any laboratory or individual.

Even if a dean received a huge sum of money from a certain drug firm to build a new building, for example, he would not be well advised to tell one of his professors that he must find in favor of that firm's products.

On the other hand, and this goes back just to complete the same statement I made before extemporaneously, I would tend to disapprove of direct payment to individual physicians who might be tempted to evaluate a drug in spite of the limited investigational facilities that usually characterize the sole and private practice.

I have a paragraph here on retainer or consultation fees paid to professors by the drug industry.

This, I am sure, is a difficult question because in this situation certainly it would be a private transaction with payment to the consultant.

I try to point out, however, that the problem is the same one faced by NIH in choosing its advisory boards. Although an expert might himself be a grantee of the Institutes, he must also at times be an adviser to the same Institutes, unless these Institutes would deprive themselves of his exceptional and, perhaps, unique knowledge.

Similarly, in matters pertaining to the pharmaceutical industry, I do not see how this industry can be prevented from seeking the best advice it can obtain. The same men will be sought by the Government as advisers, and it is likely they will occupy major academic positions, and the only safeguard I can propose is that all consultants and advisers who are paid for their services by drug firms on any sort of basis be publicly identified as employees of such firms.

This more or less completes what I have to say about drug testing, Senator, unless you wish to ask me some questions about it.

The next section deals with the journal.

Senator NELSON. Please go ahead.

Dr. INGELFINGER. And is related to the dependence of medical publications on the income derived from drug advertising.

Now, a year's subscription to this journal, the New England Journal of Medicine, costs $10. For students, interns, or residents, a third of our subscribers, the price is only $5.

Now, the actual cost of publishing and mailing a year's subscription, including advertising, is close to $30.

What makes up the difference so that we can survive economically? Advertising, and three-fourths of this is pharmaceutical advertising. On the way down I counted the pages of advertising in this recent issue, that of December 12. We have 52 pages of advertising, and it just turned out that 13½ were nonpharmaceutical, so three-quarters of the advertising in this issue was pharmaceutical.

Mr. GORDON. How many pages of text do you have?

Dr. INGELFINGER. Usually we run about 60.

Mr. GORDON. And you say 53——

Dr. INGELFINGER. I have not counted this particular one, but it will be pretty close.

Mr. GORDON. Sixty text, and how many of advertising?

Dr. INGELFINGER. This particular one is 52.

Mr. GORDON. Fifty-two pages of advertising?

Dr. INGELFINGER. Dr. Garland and I, too, although I have had less of a probelm this way because we are not besieged by advertisers the way we used to be, had the policy that during a year he would never publish more advertising pages than text pages. So the average ratio per year would never be more than 50–50. It might be per issue, you understand, but another issue would balance it.

Currently our average is running about 60 text versus 50 pages advertising. Sometimes the advertising has been as low as in the thirties, occasionally up in the seventies, but our average is 50.

Mr. GORDON. Why do you have a 50–50 sort of understanding?

Dr. INGELFINGER. I suppose a line has to be drawn somewhere. This was a decision Dr. Garland made that he did not want his journal, when you pick it up, to be a great big fat thing, in which one has to search in the middle for a few pages of text, and I think he decided this might be an appropriate balance, and as one that we have kept up, although there really has been no problem about it recently.

Senator NELSON. What does a page of advertising cost in the journal?

Dr. INGELFINGER. I cannot tell you that, I am sorry. I can provide you with that information. It depends a great deal on how often it is—whether it is run 52 times a year or just a one-shot affair.

Senator NELSON. If you could provide us with that we would welcome it.

Dr. INGELFINGER. I can give you that, and I can tell you also what our total advertising revenue for the year is, but I will have to send you a schedule.[1]

Senator NELSON. Thank you.

Dr. INGELFINGER. One other thing we maintain that some other journals do too, and some do not, namely, we still keep advertising and text pages quite separate. You will not find an advertising page in the text as you go through it. Others, of course, have them interdigitated. Advertisers would like it, but Dr. Garland kept the text separate and I have not made a change. Again you may ask why? I suppose it is a feeling of trying to keep some sort of balance.

Senator NELSON. Yes.

Dr. INGELFINGER. Because so much of our economic support depends on advertising, the potential exists that (1) in our efforts to please a big advertiser we will accept and print advertising that contains misleading information and, (2) allow our editorial judgment to be warped when we evaluate acceptability of a manuscript for publication.

A number of safeguards against such threats can be erected by the respectable medical journal. It can and does create its own advertising committee or some comparable group to evaluate both the product and the copy, that is, what the advertisement claims for the agent.

Such a committee, however, functions better in theory than in practice. Most journals cannot command the expertise necessary to cover the broad range of pharmacology.

As a result, a committee tends to operate unevenly with harshness toward some and leniency toward other products, harshness being evident in the field of the committee members' competence, and leniency in the areas about which they know little.

The advertising committee of the New England Journal of Medicine, for example, has benefited from having experts in infectious disease among its members for a number of years. For this reason, antibiotic advertisements have, by and large, been very carefully scrutinized.

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[1] Dr. Ingelfinger subsequently submitted the following: "Total advertising revenue for 1967—$2,109,684.25; 1966—$2,055,673.74." See also schedule beginning at p. 4043, infra.

On one occasion indeed, the sharp-eyed committee found that an FDA approved package insert quoted in an advertisement was not up to date in that it identified lymphogranuloma and trachoma as virus diseases; I have submitted this in appendix I.[1] Toward gastrointestinal advertising, on the other hand, the committee has been rather permissive.

But even if there were no variable of competence, evaluation of the propriety of an advertisement is like trying to draw a fine line in loose and dry sand, and I am going into this whole problem of committee evaluation of advertising because it is such an important thing.

If we could really have a very effective, dependable censorship, and never have a questionable advertisement and never a misleading one, never one of questionable taste, then I think some of the questions you and others have about advertising in journals would not be so serious. But I am trying to indicate why efforts in this direction are difficult in spite of conscientious efforts.

Even if there were no variable of competence, evaluation is difficult. As examples, and I want to show you some of the fine borderline cases that have been faced by the committee, and I am dealing with antibiotics because in this area the committee has been particularly tough. A copy of an ad claimed that a penicillin-type agent had "unsurpassed bactericidal activity." The committee objected because they knew that it was just like many other penicillins. But literally, even if the agent was no better than 20 other penicillins, the advertisement was correct. I mean it could not be challenged for falsehood as long as it was equal, even if it was equal to many others.

Another ad for a penicillin derivative occasioned unfavorable comment by the committee because of the claim "no risk of tooth staining."

Now, the committee pointed out that this statement, though true, was superfluous and misleading, for penicillin-like agents as a class do not stain teeth. This was a penicillin agent, so this statement they said was superfluous. It was put in, I suppose, because other types of antibiotics may stain teeth, but the committee objected because this agent was obviously penicillin. So the statement in itself is perfectly valid but was thought to be misleading in its implications.

Sometimes the advertising committee objects to advertisements on other grounds, and recently a submitted copy contained the following lines, and this is similar to ones Mr. Gordon has shown me—nothing really wrong in terms of the scientific claim, but a questionable type of wording:

> When bacteria proved wilder than children and cause a complicated upper respiratory infection, you can choose no better antibiotic than X.
>
> Wild children are healthy children—and antibiotic X helps brings about cures that are prompt and uneventful.

We felt this copy was undignified and meaningless and, hence, unsuitable for the journal.

In another instance, and this is possibly one of the most extreme cases of how one can get tangled up, a firm appropriately advertised an agent as a prophylactic for a common illness, that is, to be used to prevent the illness. This ad was eventually accepted, but acceptance was delayed for some time because the advertising committee feared

[1] See pp. 4042–43, infra.

that physicians, in spite of the legitimate claim of the advertisement, would use the agent not only to prevent the illness but also to treat it once it had started, which would be a definite misuse.

In spite of the efforts, ability, and high standards of our advertising committee the New England Journal publishes material which pharmaceutical houses subsequently under FDA pressure have to withdraw. I have indicated how carefully they go over some ads to pick on wording which may be questionable, and yet we have published ads which contained false information, particularly as seen in retrospect.

A number of years ago, I am sorry to say, we accepted and published advertising material extolling the now notorious agent MER–29. I can only conclude that advertising committees are unevenly effective, but the reasons are operational, not moral.

What actually happens in the journal as a result of some of these advertising committee activities, and what are our policies? Because of the recommendations made by the advertising committee and, at times for other reasons, the journal rejected 14 new product advertisements during the 2 years 1967–68. During the same time we accepted 54 advertisements for new products.

During one volume of the journal, that is during the first 6 months of 1968, we published 26 text items, and by that I mean articles, letters, editorials, dealing specifically with drug actions favorable and unfavorable. Six of these were major articles dealing with the untoward effect of drugs.

If someone sends us a letter that is critical of a drug or a drug advertisement, we do not hesitate to publish this provided its point appears valid and informative. Appendix II presents such a letter. It happens to question an advertisement which appeared 22 times in the journal, in other words, a fairly big advertisement. This same advertisement was featured in other medical publications. We have not hesitated to publish letters from such critics of medicine as Mr. Morton Mintz.

On the other hand, this is not a one-way street. The journal believes that all sides should be heard. Hence, we also published a reply from the drug manufacturer to the letter which criticized the advertisement. This reply is shown in appendix III.

In a forthcoming issue of the journal there is another letter from another firm objecting to a statement made in one of our regular articles. However, and I want to emphasize this as much as I can, neither during my relatively brief tenure as editor or during the 20 years' tenure of my distinguished predecessor, Dr. Joseph Garland has, to the best of my knowledge, any material either been suppressed or printed in an effort to please the advertiser. I cannot speak with firsthand knowledge concerning other medical publications, but I believe that other respectable and standard medical journals observe the same policy.

In essence, what it comes down to, we have published ads, and we are still publishing them, that can be criticized. Some possibly contain or probably contain misleading information, but our errors, our difficulties, are that we have not got the expertise and screening procedures to detect this.

We do not know, for example, in the case of MER–29 when this was accepted, which was before my time, but I doubt if there was any

discussion about it. The toxic effects of the drug were not known to the committee, and they were misled as much as anybody else.

Now, it has been suggested that the journal accept no drug advertising whatsoever. This suggestion is based on the assumption that our readers are indifferent to pharmaceutical advertising—an unwarranted assumption in my opinion.

This is a very difficult question, Senator. But I ask myself: suppose our advertisements were impeccable, that they promoted a drug with the claims were circumspect, and they could not be criticized for bad taste or for false indications, would we thereby provide our reader with valuable information as to what is available? In the absence of a drug compendium that is all-inclusive and all-informative, I feel that some of our readers look at our advertisements for information to see what is on the market and where they can get it. But I am really not sure how much they really depend on it, and if we stopped all advertising, I am not sure how many of our readers would complain. I would suspect some, but I have no idea of the percentage.

I believe the students, the house officers, would not object, for they use agents that the hospital has available. But I would guess that some 20,000 or 30,000 of our subscribers look at the ads for informational purposes.

Furthermore, if pharamceutical advertising were omitted our subscription price would be raised to at least $25.

Why not, it may be asked, shouldn't this be done, since physicians are well-to-do, and even residents these days make a living wage? Bargains, however, are also sought by the well to do. Hence, I suspect that an increase in our subscription price to $25 would reduce the number of our subscribers in a rather drastic way. Since our principal reason for existence is education, we would, indeed, have created a paradox—this is the important point, I think—if in a backward leaning effort to avoid misleading advertising we decreased the number exposed to whatever information and education we may bring them.

We are currently planning to provide our readers with an abstract service; at the beginning of each of our articles we have a short summary. These now appear in the regular soft pages of our journal, but we hope to print them in addition on little perforated cards, on card stock with little perforations, so the reader can tear out abstracts and file them.

We estimate from preliminary surveys that some 30,000 of our readers we have heard would make use of this particular device.

Senator NELSON. What kind of information will be on that?

Dr. INGELFINGER. A summary of the article. Each article is preceded by what we call an abstract, a summary, stating in as concise way as possible what it is about and what was found.

Many students and doctors like to keep such abstracts as a quick reference. They can file it under index terms which the National Library of Medicine provides. So it is a nice retrieval system for an individual, and it also helps quickly to decide whether you want to go back and read this article in more detail. It is a retrieval system.

To publish and mail such abstracts would cost us $100,000. The only way we can do it is if some firm is willing to put some ad on the front and the back of a booklet containing these abstracts which we are thinking of mailing out once every month.

You see, here is the dilemma. Should we provide this service and, at the same time, send out advertising which might be criticized? Or should we not do it at all? Do we give up educational efforts to avail whatever stigma drug advertising produces?

These considerations lead me to the following conclusions:

(1) Economic pressures dictate that we continue to carry advertisements, including advertisements of drugs.

(2) An individual journal cannot adequately evaluate the propriety and accuracy of such advertising. Through ignorance and error, but not because of venality, misleading advertisements will at times be included; and at other times, basically proper advertisements will be excluded.

(3) It is not realistic to expect business enterprises that are actively competing in a capitalistic society to impose upon themselves the tradition and ethics of a profession.

(4) Legislative control of improper information or advertising is extremely difficult, particularly when fine semantic problems or questionable implications are at issue. I have tried to give some examples of those.

(5) The proper use of drugs in the final analysis rests with the physician, and it is the physician who must be amply provided with broad and inclusive information, with all sides represented, so that he may have the opportunity of making a sound judgment. He must be even more aware than he is that drug advertisements, or the statements of detail men, like many other advocating the virtues of a product in the best terms possible. Rather than attempting to restrain this publicity of the advertiser, a more persuasive case can be made, I believe, for increasing publicity to the consumer. The danger of smoking has been emphasized for some time, but it is only recently, with increasing publicity—not increasing knowledge but with increasing publicity—that the number of new smokers seems to be increasing less rapidly than previously. Through proper publicity, with cons as well as pros emphasized, the physician will be in a better position to decide whether or not a drug is worthy of being advertised.

How can this be done? Basically, I would favor a compendium listing, describing and evaluating all drugs that a patient may purchase. Eventually, this might be a two volume affair devoted to prescription and nonprescription drugs respectively It is most important, however, that such a compendium be issued under the auspices of a united, multipartisan authority that is satisfactory to the major parties concerned. Perhaps the new AMA publication will satisfy the need; I do not know enough about it to discuss it. If it does not satisfy the need, I believe a compendium should be issued under the joint sponsorship of the AMA, the Pharmaceutical Manufacturers Association, the FDA, and the American Pharmaceutical Association, possibly represented in a ratio of 2:1:1:1, that is, with the AMA with major representation. Such a joint sponsorship is essential if the compendium is to be an acceptable, and I emphasize acceptability, authority to all users.

Other devices also deserve consideration. Medical journals that accept drug advertising such as ours might index the agents advocated with a bibliography of appropriate references to the established and recognized medical literature. If no such references, that is acceptable

references, could be provided because of limited or questionable documentation, the absence of a citation should alert the physician that the agent in question is of uncertain effectiveness or safety.

Mr. GORDON. These devices that you are mentioning actually are designed to try to counter or undo any possible damage from advertising; isn't that correct?

Dr. INGELFINGER. This is to give both sides. Perhaps an arrangement could be made with the Medical Letter to reprint evaluations that appear in its publication. A number of such schemes could be tried with a two-fold objective: on one hand, they would not infringe on the right of a company to advertise and praise its products, but on the other, they would present the physician with all available information and opinions so that he could be misled only if his reading of a given journal were decidely one-sided.

After all, this is what we do in the journal anyhow. Somebody publishes an article which says this disease is caused by such and such an agent. Well, pretty soon somebody publishes an article which says, no, it does not, he is wrong. Then a discussion develops. I do not see why a journal could not also attempt to present all sides with respect to drug use, but it would have to make a conscious, not only conscientious but conscious, effort to increase the evaluation of drugs that are mentioned, whether in advertising or in regular text.

The crucial question, of course, is whether an individual practicing physician has the time and the ability to make the necessary judgments, especially since I have indicated that journals cannot screen advertising properly, even with committees. I believe the answer is "yes", because an individual physician presumably uses only a limited number of drugs to which he adds, once in a while, a new product. Before he does so, it should be his responsibility to check on all the information he can, that provided in a compendium, that to be found in the pages of his medical journals, and that provided by any consultant whose advice he seeks. The American Medical Association, I hope, would be willing to emphasize this responsibility of the physician and, indeed, has done so at times.

If the physician's management of patients is to be relatively free—this is what he wants, to be relatively free—from outside interference—and I believe it should be relatively free—this freedom can only be sustained by the physician's determination to keep himself well informed.

Actually, I wrote this before I read the task force report, and I was interested to find the task force report also ends up with the point that the person who is really responsible, one who has to make the ultimate decision, is the physician, and that it is his continuing education which will support his judgment as to whether or not to use a given drug.

The task force may be a little more pessimistic than I am that this education can be achieved, but to me it is the main area deserving of emphasis in trying to encourage a proper use of drugs. This, I believe, is more practical and ultimately more effective than imposing restrictive legislation on advertising or exactly on what the doctor can or cannot do.

This more or less concludes, sir, my rather long discourse on drug advertising in medical journals. The rest is just rather brief statements

dealing with other questions which are of relatively minor importance in terms of the discussion.

Senator NELSON. The committee has been interested in the question of the promotional practices involved in advertising in medical journals, which is the only place that they advertise, that is, medical publications of some kind, and direct mailing and the promotion of drugs through detail men.

Part of this still puzzles me. You state, as you go along here, that there should be competing sources of information to the physician and that perhaps the drug companies should be permitted to advertise as they see fit so long as it meets some kind of a standard.

In the face of all this, nevertheless, there is the lack of response on the part of the medical profession. Look at the situation of chloramphenicol. The point is that some $700 million a year is spent in advertising and promotion by the industry. As in the case of chloramphenicol, it obviously is very effective.

Here is a specific case of a drug widely promoted in medical journals and by direct advertising, too, the consequence of which was that the medical profession in this country was prescribing the drug for nonindicated cases on a massive basis. In fact, here is a case where it was perfectly clear to the medical profession, including the AMA which understood the drug, that indications for the use of the drug were very, very limited. In fact, the six witnesses who testified before this committee, I think it was six, including Dr. Dameshek of Mount Sinai, and a number of others—these eminent medical authorities all testified that in their judgment 90 to 99 percent of the people who were administered this drug were receiving it for nonindicated cases.

One of the witnesses testified that he had never yet, in his practice, seen a patient suffering from aplastic anemia who had received the drug chloramphenicol for an indicated case. It was being prescribed for sore throats, acne, tooth infections, head colds, and the like. The most conservative estimate was, I think Dr. Dameshek's, who stated that, in his judgment, only 10 percent of the patients who received this drug received it for indicated cases.

One of the witnesses thought there could not be more than 10,000 cases a year for which the drug would be indicated in this country.

Dr. Goddard felt the same. But 3½ to 4 million people a year were receiving the drug. The drug was widely advertised in medical journals. I did not look at any——

Dr. INGELFINGER. I am sure we had it.

Senator NELSON. I looked at a number in the Journal of the AMA, very clever promotional ads, "When it counts use Chloromycetin." A full page, that many words or about that many.

The consequence was that one way or another the medical profession was convinced that they should use the drug for nonindicated cases. Our files are full of letters, tragic letters, from parents whose children received it, who had sore throats. As Dr. Dameshek said, most of these patients, the patients who received it for nonindicated cases, would have gotten well if they had taken nothing at all.

This went on a long, long time. The medical profession did nothing about it. At the same time many of these journals were carrying the ads on chloramphenicol, they printed articles warning of the danger

of the drug and its extremely limited indications. One article by Dr. Dameshek—was it the New England Journal which carried that?

Dr. INGELFINGER. It was the New England Journal.

Senator NELSON. Yet, at the same time, the ads continued to be carried.

We conducted hearings, and Dr. Goddard said, "I am at my wit's end as to how to stop the medical profession from misprescribing this drug."

I would have thought the medical profession somewhere, some place would have felt a sense of responsibility. They might have called a national conference of leaders, headlined stories in all medical journals, told the doctors they were killing people by improperly using this drug.

But it did not happen. So it came to the committee's attention—a committee of Congress with no expertise in this field at all—and we conducted hearings. As a result of our hearings, Dr. Goddard's testimony, and the FDA's "Dear Doctor" letter sent to all 200,000 doctors and to all medical journals, front page stories appeared across the country, solely as a consequence of these hearings, the certification of the drug dropped from 23 million grams in the first 6 months of 1967, to 4 million grams in 1968, and down to zero in June of 1968.

Now, here is an example, it seems to me, where the argument about balance in informing doctors just collapses. Here is a case where a company successfully and widely promoted a drug. Where ads were accepted by medical journals even though every consultant they had who knew anything about the use of chloramphenicol would have told them it is a strange thing that a company should be spending lots of money to advertise a drug which has such extremely limited use and further that if the drug were used only for the purposes for which it was indicated, it would not come anywhere near repaying the cost of the ads.

So in my judgment it raises very serious ethical questions as to the whole business of advertising, promotion, and acceptance of ads. The ads are still running and, in fact, one of the officers of the company stated—I do not have his exact quote—that once all the fuss and feathers were over—those are not his words—he assumed the use of the drug would rise again.

Well now, I think it is a sad commentary on the medical profession as a whole, with everyone having some responsibility for what happened, but it seems to me, if a company came with a chloramphenicol ad, it ought to be told "You run the whole package insert in your ad or we won't take it because the history is that you have misled the profession."

What is your comment on that whole picture?

Dr. INGELFINGER. Well, Senator, I cannot defend the whole story that developed on chloramphenicol, and I am sure most physicians and all of those responsible, editors and people connected with journals and the like, feel very badly about the fact that on occasions the agent was so indiscriminately overused.

But is not the problem now—you and your group having demonstrated this—what can be done to prevent it in the future, and this is really what I have been trying to come to grips with a little bit.

I do not think, just to take the easiest thing first, that merely for the New England Journal of Medicine to stop taking advertising would do anything since there are thousands of others——

Senator NELSON. I have not suggested that.

Dr. INGELFINGER. No, I mean it has been suggested—I know you did not, but I mean that for one, two, or five journals not to accept pharmaceutical advertising would accomplish nothing. In fact, you would lose something, thereby.

Second, I doubt that overuse of a drug is entirely attributable to advertising. People who have testified here before your committee probably have indicated that other agents have also been overused. I am sure penicillins have been greatly overused—many articles in medical journals have said so. But, fortunately, except for patients who have been sensitive to the agent, serious side effects have been few. I am not sure it is all due to the advertising, for when physicians are called to see an acutely ill patient, their tendency is to use something that is fairly powerful. If they fail to treat a patient with an antibiotic sensitive infection, they are severely criticized. Even the patient is often interested in getting that powerful new drug he has been reading about in his papers and magazines. I am sure patients have demanded penicillin on many an occasion.

So here is this physician—he is under pressure to use a new agent and an effective agent. He has not had the time possibly, or the facilities to determine why the patient is having a fever. He is not sure of the indication. This is continuing dilemma for the physician, and when faced with the alternative of over- or under-treating, he will usually avoid undertreatment.

Third, I do not know enough about business or law to indicate what the Government can do to keep people from advertising, but I do not see how the Government can tell an industry, "You cannot advertise."

You can apply certain rules to advertising, but I am not sure, Senator, that insistence on including in the advertisement the package insert, or a long list of counterindications is worthwhile. Indeed, I think it is self-defeating. Few read this. One of the main things we are taught as editors is the importance of brevity and succinctness. Here we have in this advertisement in our December 12, 1968, issue, four pages about an antibiotic. The first three pages present dramatic pictures, and here on the fourth page, complying with the rules, is the package insert. Who is going to read all of this? One out of 100 at the most. I think it is useless.

This is why I think it is a mistake for the Government to say that in advertising you have to list all the toxic effects, or, for that matter, to make many detailed rules. More practical ways have to be found.

Now, I agree that medical journals, including the New England Journal of Medicine, and all medical educators were delinquent in not emphasizing more the dangers of chloramphenicol. The fact that it caused aplastic anemia was recognized early when the drug was tried, there was no question about it, and in medical school these dangers were taught.

However, apparently it was not emphasized enough in general, and this is why I am making the suggestion that besides any rules that are made, beside any compendium which necessarily would have to be printed in small print, journals have to accept the responsibility, or possibly be forced to accept the responsibility, of publicizing the dangers as well as the advantages of certain drugs not emphasizing the

dangers out-of-proportion, but giving a fair evaluation of the pros and the cons.

Suppose the New England Journal or the Annals of Internal Medicine had come out early during this story of chloramphenicol that you have recited and had kept emphasizing its dangers and its restricted indications, I am not sure whether it would have prevented anything or not, but at least these journals would have discharged their responsibility.

My guess is if there was enough publicity which had been given to some of these dangers, along with indicating conditions in which the drug was valuable, then possibly so many people would not have suffered from the untoward consequences.

So I am really agreeing with you, Senator Nelson. If we medical journals instituted a procedure whereby any actively advertised agent that we carry would be accompanied by evaluations other than those provided by the drug companies—evaluations from the Medical Letter or from other objective reports, for example—then I think the doctor would be exposed to the whole picture. And this is what counts, for he is the one who prescribes the drug. Is not this a possible approach?

Senator NELSON. I do not know what the answer is. I would wonder whether any method would be successful against $710 million worth of advertising and promotion.

The ads are clever, they are eye-catching, as I suggested earlier. The fact is, at least so far as chloramphenicol is concerned, the whole country would be better off if they had never run a single ad. If the only thing told about chloramphenicol was in medical publications stating that in certain extremely limited conditions—rickettsial diseases, and so forth, where the patient was seriously ill and no other antibiotic was effective, this would be the only type case in which the drug is indicated.

After all, if there are only 10,000, 20,000 people a year for whom it is indicated, we probably would have been a whole lot better off if there had never been an ad on it in this country.

It raises the whole question of what is the effect, purpose, and value of advertising. In fact, I notice you mentioned this earlier yourself. Dr. Frederick Wolff, director of research, Washington Hospital Center and professor of medicine at George Washington University School of Medicine, stated before our subcommittee that the advertising promotion of drugs has had a great impact on prescribing habits of doctors, no less than advertising has had on the buying habits of the average American housewife.

Dr. Wolff also estimated that out of every $10 spent on drugs about $6 are spent unnecessarily, and that advertising and promotion of drugs are to a great extent responsible for the situation.

Dr. INGELFINGER. Senator, that is it. I am not an economist nor am I an expert in what is possible by legal means, but also it is not economically and legislatively possible and justified to just prohibit advertising by pharmaceutical firms which it seems to me is rather inconceivable in view of all the advertising that goes on about all sorts of things.

The only answer to prevent what you have just said, meaning what you have just recounted about chloramphenicol, is counter publicity, and if the medical profession is so unresponsive that they will not

listen to it, then I think it is a terrible indictment of the medical profession. I hope the profession is better than that, and I think it is better than that.

Senator NELSON. I do not know what the answer is either.

Dr. INGELFINGER. Well, I am sure our common aim is to prevent misuse of drugs?

Senator NELSON. Yes; just as I said, it raises a question of whether there is, in fact, any way that counterinformation, so to speak, can successfully compete——

Dr. INGELFINGER. May I say one more thing?

Senator NELSON. Yes, sir.

Dr. INGELFINGER. You have achieved much through the medium of counterinformation.

Senator NELSON. Yes. This happened to be a very dramatic case. We got involved in it accidentally. It would not have occurred at this time if it had not been for this congressional committee. But it has been going on since 1953. In other words, the problem has existed for many, many years with everybody wringing his hands but no one concerned enough to do something about it. When it came to the committee's attention and we decided to look into it, the consequences were quite dramatic.

But I do not think you can count on that kind of a circumstance to be a balance wheel to the improper promotion of drugs. That is what bothers me.

Dr. INGELFINGER. Yes; I think this is more potent publicity than one can develop in the pages of a medical journal.

Senator NELSON. Well, that is the question we are exploring. I do not have the answers to it. Perhaps we will find some.

It seems to me it will not be resolved until the medical profession itself becomes involved it. And that is as it should be. I only regret the profession did not see fit to take the initiative in the beginning. Had it done so, this subcommittee would not be holding these hearings today.

We appreciate your coming here today and we thank you for your very thoughtful contribution to our hearings. We want to thank both of you for contributing so much of your time to these hearings.

Dr. INGELFINGER. Thank you for letting us speak.

Senator NELSON. Thank you.

We will adjourn until tomorrow at 10 o'clock.

(The complete prepared statement and supplemental information submitted by Dr. Ingelfinger follows:)

STATEMENT OF DR. FRANZ J. INGELFINGER, EDITOR, THE NEW ENGLAND JOURNAL OF MEDICINE

My name is Franz J. Ingelfinger, and I am Editor of *The New England Journal of Medicine*, a position I have held for one and a half years. I am also Clinical Professor of Medicine at Boston University School of Medicine. Prior to July 1, 1967 I was Professor of Medicine at that institution for a period of ten years. My sub-specialty interest is gastroenterology, a field in which I have taken care of patients, taught, edited, carried out clinical research, and conducted a productive post-graduate training program. I am also a past president of the American Gastroenterological Association. In the 27 years during which I was engaged in gastroenterological investigation, I carried out numerous drug studies for at least one half dozen pharmaceutical firms, the funds received for such studies being used to support the unit of which I was in charge.

Of the various areas of possible conflict of interest cited in Senator Nelson's letter of November 22, 1968, may I submit comments on the following:

1. Acceptance by physicians of funds paid by drug companies for the evaluation of their products, or for other purposes such as fellowships, salaries, or general research support

Physicians may test drugs with support from pharmaceutical firms under various circumstances, and the nature of these circumstances will to a large extent determine the objectivity and the integrity of the work. Under many circumstances, the likelihood that the source of the support will influence the result is negligible for the following reasons:

A. The testing is often carried out in a medical school setting. This means (a) that administrative officials, rather than the investigator, will handle the financial arrangements (i.e., there is no "direct" payment to the investigator); and (b) that others besides a solitary investigator (i.e. post-graduate students, other physicians, laboratory workers) will participate in the test procedures. Thus the study is safeguarded in that there is participation by a number of people who have no financial interest in the nature of the results.

B. The testing is often carried out during the preliminary stages of the development of a drug. For example, my laboratory used to screen agents for their ability to affect gastric acid secretion or to decrease intestinal contractions. On other occasions, we measured the absorption of certain drug formulations in different parts of the intact human intestine. In all these instances, effects could be measured by means of mechanical recording devices or by chemical determinations. The objective data so obtained cannot be easily distorted by personal bias. Furthermore, under such circumstances, the investigator who misleads a financial sponsor is not doing that sponsor any favor. Drug companies are not anxious to spend money on developing an inferior product, and for their own protection tend to seek a valid appraisal.

Clinical testing of a product ready for marketing or already marketed is, however, extremely difficult under any conditions. The criteria available for measuring a drug effect are often extremely vague and highly subjective. There is no precise yardstick, for example, to determine whether or not pain is worse. Furthermore, the desires of both patient and investigator may color the interpretation. Hence studies of this type must be carried out under optimum conditions by investigators who are equipped by training and facilities to carry out such testing, and who use a protocol incorporating procedures that characterize a well-controlled study. If these conditions are observed, I doubt that the results are likely to be influenced in any way by subtle economic pressures.

One suggestion that has been made to prevent undue influence of sponsor on investigator is the establishment of a central independent agency that would act as a clearing-house in arranging for the testing of drugs. Under such an arrangement drug testing for its clinical efficacy would be, in a sense, "triple blind" in that the investigator and the agent's maker would be unaware of each other's identity.

Such a central agency might be established under the jurisdiction of a committee in which pharmaceutical firms, government and the AMA would have adequate and satisfactory representation. However, the increased objectivity and trustworthiness of drug testing procedures so attained would have to be balanced against the added expense and delays entailed if such a scheme were implemented. Furthermore, I am not sure that total "blindness" could be achieved. Although this is a pure "armchair" opinion, I doubt that such a clearing-house is worth the effort, provided that the conditions under which clinical tests are carried out are reasonably well standardized along the lines indicated in the proceeding paragraphs.

In this connection, I sould like to recommend that any specifications that the government establishes for the control of clinical testing be not too detailed and rigorous. Observation of certain broad principles should be required, but if the regulations are too elaborate and rigid, the very investigators whom one would like to see at work at the task would shy away. Perhaps some honor system such as the NIH has established with various medical school could be initiated, with the individual universities assuming responsibility for the trustworthiness of the drug studies carried out by their staffs.

The question of *fellowships, salaries, and general research support may be similarly answered.* If funds made available by the pharmaceutical industry for such purposes are paid to educational or other non-profit institutions through regular administrative channels, there is little chance that the donation will distort the scientific efforts of any laboratory of indivisual. Even if a dean receives a huge sum of money from a certain drug firm, he would not be well advised to tell any of its professors that they must find in favor of that firm's

products. On the other hand, I would tend to disapprove of direct payment to individual physicians who might be tempted to evaluate a drug in spite of the limited investigational facilities that usually characterize the solo private practice.

2. Retainer or consultation fees paid to professors by the drug industry

In this case, direct payments to individuals by drug firms does constitute a theoretical conflict of interest. The problem, however, is the same one faced by the NIH in choosing its advisory bodies. Although an expert might himself be a grantee of the Institutes, he must also at times be an advisor to the same Institutes, unless they would deprive themselves of his exceptional and perhaps unique knowledge. Similarly, in matters pertaining to the pharmaceutical industry, I don't see how this industry can be prevented from seeking the best advice it can obtain. These same men will be sought by government as advisors and it is likely that they will also occupy major academic positions. The only safeguard I can propose is that all consultants and advisors who are paid for their services to drug firms be publicly identified as employees of such firms.

3. Dependence of medical publications on income derived from drug advertising

A year's subscription to *New England Journal of Medicine* now costs $10.00. For students, interns, or residents—i.e., a medical trainee—the price is only $5.00. The actual cost of publishing and mailing a year's subscription is close to $30.00. What makes up the difference so that we can survive economically? Advertising, and three-fourths of this is pharmaceutical advertising. The potential therefore exists that in our efforts to please a big advertiser we will (1) accept and print advertisements that contain misleading information and (2) allow our editorial judgment to be warped, when we evaluate the acceptability of a manuscript for publication.

A number of safeguards against such threats can be erected by the respectable medical journal. It can and does create its own advertising committee to evaluate both the product and the "copy"—i.e., what the advertisement claims for the agent. Such a committee, however, functions better in theory than in practice. Most journals cannot command the expertise necessary to cover the broad range of pharmacology. As a result, a committee tends to operate unevenly, with harshness toward some and leniency toward other products, harshness being evident in the field of the committee member's competence, and leniency in the areas about which they know little. The advertising committee of *The New England Journal of Medicine*, for example, has benefitted from having experts in infectious disease among its members. For this reason, antibiotics have been most carefully scrutinized. On one occasion, indeed, the sharp-eyed committee found that an FDA approved package insert, quoted in an advertisement, was not up-to-date in that it identified lymphogranuloma venereum and trachoma as virus disease (see appendix I). Toward gastrointestinal drugs, on the other hand, the committee has been rather permissive.

Even if there were no variable of competence, evaluation of the propriety of an advertisement is like trying to draw a fine line in loose and dry sand. Recently, for example, our committee rejected an advertisement because the copy claimed that the penicillin-type agent had "unsurpassed bactericidal activity". The committee objected because they said, "the agent is like other penicillins". Literally then there is nothing wrong with the word "unsurpassed", provided that the agent is as good as other penicillins, even if there are dozens of others.

Another advertisement for a penicillin derivative occasioned unfavorable comment by the committee because of the claim "no risk of tooth staining". The committee pointed out that this statement, though true, was superfluous and misleading, for penicillin-like agents as a class do not stain teeth. Again the statement in itself is perfectly valid, but its implication is misleadng?

Sometimes the advertising committee objects to advertisements on other grounds. Recently a submitted copy contained the following lines:

"When bacteria proved wilder than children and cause a complicated upper respiratory infection, you can choose no better antibiotic than X."

"Wild children are healthy children—and antibiotic X helps bring about cures that are prompt and uneventful."

This copy was regarded as both undignified and meaningless-and hence unsuitable for the *Journal*. In another instance, a firm appropriately advertised an agent as a prophylactic for a common illness. Eventually we accepted this advertisement, but acceptance was delayed for some time because the advertising committee feared that physicians, in spite of the legimate claim in the

advertisement, would use the agent not only to prevent the illness but also to treat it once it had started.

In spite of the efforts, ability and high standards of our advertising committee, the *New England Journal* publishes material which pharmaceutical houses subsequently, under FDA pressure, have to withdraw. A number of years ago, I am sorry to say, we accepted and published advertising material extolling the now notorious agent MER 29. I can only conclude that advertising committees are unevenly effective, but the reasons are operational, not moral.

Because of the recommendations made by the advertising committee, and at times for other reasons, the *Journal* rejected 14 new product drug advertisements during the 2 years 1967–1968. During the same time 54 advertisements of this type were accepted. During one volume of the *Journal*, that is, during the first six months of 1968, the *Journal* published 26 text items dealing specifically with drug actions, favorable and unfavorable. Six of these were major articles dealing with the untoward effect of drugs. If someone sends us a letter that is critical of a drug, or a drug advertisement, we do not hesitate to publish this provided its point appears valid and informative. Appendix II presents such a letter. It happens to question an advertisement which appeared 22 times in the *Journal*; it also was featured in other medical publications. We have not hesitated to publish letters from such critics of medicine as Mr. Morton Mintz.

On the other hand, this is not a one-way street. The *Journal* believes that all sides should be heard. Hence we also published a reply from the drug manufacturer to the letter which criticized the advertisement (appendix III). In a forthcoming issue of the *Journal* we are printing a letter from another firm objecting to a statement made in one of our regular articles. Neither during my relative brief tenure as editor, nor during the twenty years' tenure of my distinguished predecessor, Dr. Joseph Garland, has, to the best of my knowledge, any material either been suppressed or printed in an effort to please the advertiser. I cannot speak with firsthand knowledge concerning other medical publications, but I believe that other respectable and standard medical journals observe the same policy.

It has been suggested that the *Journal* accept no drug advertising whatsoever. This suggestion is based on the assumption that our readers are indifferent to pharmaceutical advertising, an unwarranted assumption in my opinion. In addition, if pharmaceutical advertising were omitted, our subscription price would be raised to at least $25.00. Why not, it may be asked, since physicians are well-to-do, and even residents these days make living wages.

These considerations lead me to the following conclusions:

(1) Economic pressures dictate that we continue to carry advertisements, including advertisements of drugs.

(2) An individual journal cannot adequately evaluate the propriety and accuracy of such advertising. Through ignorance and error, but not because of venality, misleading advertisements will at times be included; and at other times, basically proper advertisements will be excluded.

(3) It is not realistic to expect business enterprises that are actively competing in a capitalistic society to impose upon themselves the tradition and ethics of a profession.

(4) Legislative control of improper information or advertising is extremely difficult, particularly when fine semantic problems or questionable implications are at issue.

(5) The proper use of drugs in the final analysis rests with the physician, and it is the physician who must be amply provided with broad and inclusive information, with all sides represented, so that he may have the opportunity of making a sound judgment. He must be even more aware than he is that drug advertisements, or the statements of detail men, like any other advertisement, represent the prejudiced statements of an interested party advocating the virtues of a product in the best terms possible. Rather than attempting to restrain this publicity of the advertiser, a more persuasive case can be made, I believe, for increasing he publicity of the consumer. The danger of smoking has been emphasized for some time, but it is only recently, with increasing publicity, not increasing knowledge, that the number of new smokers seems to be increasing less rapidly than previously. Through proper publicity, with cons as well as pros emphasized, the physician will be in a better position to decide whether or not a drug is honestly advertised.

How can this be done? Basically, I would favor a compendium listing, describing and evaluating all drugs that a patient may purchase. Eventually, this might be a two volume affair devoted to prescription ad non-prescription drugs

respectively. It is most important, however, that such a compendium be issued under the auspices of a united, multi-partisan authority that is satisfactory to the major parties concerned. Perhaps the new AMA publication will satisfy the need; I do not know enough about it to discuss it. If it does not satisfy the need, I believe a compendium should be issued under the joint sponsorship of the AMA, the Pharmaceutical Manufacturers Association, the FDA, and the American Pharmaceutical Association, possibly represented in a ratio of 2:1:1:1. Such a joint sponsorship is essential if the compendium is to be an acceptable authority for all users.

Other devices also deserve consideration. Perhaps medical journals that accept drug advertising should index the agents advocated with a bibliography of appropriate references to the established and recognized medical literature. If no such references could be provided because of limited or questionable documentation, the absence of a citation should alert the physician that the agent in question is of uncertain effectiveness or safety. Perhaps arrangements could be made with *Medical Letter* to reprint the evaluations that appear in this publication. A number of such schemes could be tried with a two-fold objective: one one hand, they would not infringe on the right of a company to advertise and praise its products, but on the other, they would present the physician with *all* available information and opinions so that he could be "*misled*" only if his reading of a given journal were decidedly one-sided.

The crucial question, of course, is whether an individual practicing physician has the time and the ability to make the necessary judgments, especially since I have indicated that journals cannot screen advertising properly, even with committees. I believe the answer is "yes," because an individual physician presumably uses only a limited number of drugs to which he adds, once in a while, a new product. Before he does so, it should be his responsibility to check on all the information he can, that provided in a compendium, that to be found in the pages of his medical journals, and that provided by any consultant whose advice he seeks. The American Medical Association, I hope, would be willing to emphasize this responsibility of the physician. If his management of patients is to be relatively free from outside interference—and I believe it should be relatively free—this freedom can only be sustained by the physician's determination to keep himself well informed.

May I submit brief comments concerning some of the other questions put by Senator Nelson:

4. If doctors lend their names for articles and letters written by members of the pharmaceutical industry, and these letters represent the opinions and statements of such members and not of the doctors, I would term the practice fraudulent.

5. Except if large holdings are involved, presumably an infrequent situation, I doubt that ownership of stock in a drug company will influence either the man carrying out an evaluation of a drug or the man prescribing it for patients. If physicians hold stock in chemical or pharmaceutical firms, they often have multiple holdings. Furthermore, a vast proportion of physicians probably have invested in mutual funds.

6. Physicians obviously should not prescribe merely on the say-so of a detail man. As I have suggested above, the pressures by a detail man can be better resisted if measures are taken to provide physicians with better information and if their responsibility in choosing drugs is vigorously publicized.

7. The problem of "so-called independent giveaway sheets" would be taken care of if all medical publications were required to provide full information—for example, compendium, *Medical Letter*, or other evaluations as well as advertisements.

May I conclude with a philosophic comment. Critics as well as admirers of medicine have recognized that doctors are placed in a position that requires unique trustworthiness. The relation of physician and patient is such that an unscrupulous doctor can exploit a patient's illness unmercifully; the same unscrupulous physician will exploit other opportunities such as drug testing. To restrain such practices by legal means is extremely difficult. Fortunately, the overwhelming majority of physicians are not unscruplous. They do not order unnecessary treatments or report dishonesty on the action of drugs merely for economic gain. Some may sneer at the physician's claims of adherence to ethical standards, but the care of the patient by the physician, as we know it now, could not survive without a large measure of trustworthiness.

If I am correct in this assessment, and I believe most of our population would subscribe to it to a greater or lesser degree, then the more effective approach to a

correct use of drugs by physicians is through education rather than through legislation. The average physician is not out to do the patient in, and if he has an unconscious basis this is best controlled by providing him with the information that he needs to make the best choice of which he is capable. His patients will not benefit from a series of hard and fast rules, a set of do's and don'ts with respect to a multitude of drugs. They will benefit if he is provided with the necessary information, and, even more important, with the motivation to keep his education up to date.

APPENDIX I

BRIEF SUMMARY FOR ERYTHROCIN, ERYTHROMYCIN, ABBOTT

INDICATIONS

For all infections susceptible to erythromycin; primarily, gram-positive cocci—staphylococci (most strains), pneumococci and streptococci (including enterococci). Also active against other pathogens, such as *Corynebacterium, Hemophilus, Clostridium, Nesseria, Treponema pallidum,* the agents causing trachoma and lymphogranuloma, *venereum* and *Mycoplasma pneumoniae* (Eaton agent). When practical the susceptibility of the pathogenic organism should be established. Therapeutic levels should be maintained for 10 days in the treatment of streptococcal infections to prevent rheumatic fever and glomerulonephritis. In localized infections, antibiotic therapy does not obviate the need for local measures or surgery whenever these are indicated.

CONTRAINDICATION

Known hypersensitivity to erythromycin.

PRECAUTIONS, SIDE EFFECTS

Side effects are infrequent. Occasionally mild abdominal discomfort, nausea or vomiting may occur; generally controlled by reduction of dosage. Mild allergic reactions (such as uticaria and other skin rashes) may occur. Serious allergic reactions have been extremely infrequent; if encountered, appropriate countermeasures (e.g. epinphrine, steroids, etc.) should be administered and the drug withdrawn. Overgrowth of nonsusceptible organisms is rare. If this should occur, withdraw drug and institute appropriate treatment.

APPENDIX II

[From the New England Journal of Medicine, vol. 277, No. 20, p. 1099]
(Correspondence)

ADVERTISEMENTS OF ANTIBIOTICS

To the Editor:

In a recent series of full-page color advertisements, carried in many journals, sections of fresh tissue obtained from animals given large intramuscular injections of lincomycin are shown as producing a small, but clear, zone of inhibition on plates seeded with various bacteria. The statement "for antibiotic tissue penetration" is juxtaposed. These advertisements stimulated us to conduct a simple, short-term experiment that can be performed by medical students interested in antimicrobial chemotherapy.

We wondered whether other antibiotics might also be shown to "penetrate tissues" by this method and whether it would be important to consider variables such as dose, time of sacrifice, species, test organism and route of administration. We wish to report the first experiment.

A series of mice were given 1 mg of penicilin G, tetracycline, erythomycin or lincomycin intraperitoneally and sacrificed at intervals. The organs were rinsed of blood, sliced and applied to a plate seeded with a staphylococcus sensitive to all these drugs. The plates were examined after twenty-four hours' incubation at 37° C for zones of inhibition about the pieces of skin, muscle, liver, heart and bone. Large zones were noted with all the drugs except lincomycin, which, as in the advertisements, showed only a small, clear area about the tissue. Thus, we have preliminary evidence that other antibiotics do "penetrate tissue" under the conditions of this experiment.

The student who conducted this study is now a somewhat more sophisticated

reader of advertisements. He cannot be satisfied with his own experiment, because many more questions can be raised. He will have to consider whether the drugs penetrate into areas of abscess formation and, of course, examine some of the variables noted above. In addition, the significance of zones about tissues will have to be critically compared with ability of the drugs to cure experimentally infected animals and eventually man.

We hope that others may benefit from the message of this simple exercise.

CALVIN M. KUNIN, M.D.,
RICHARD HUNTER,
University of Virginia School of Medicine.

CHARLOTTESVILLE, VIRGINIA.

APPENDIX III

[From the New England Journal of Medicine, vol. 278, No. 20, p. 1125]
(Correspondence)

ADVERTISEMENTS OF ANTIBIOTICS

To the Editor:

Recently in this journal (*New England Journal of Medicine* 277:1099, 1967), Kunin and Hunter commented on "Advertisements of Antibiotics." Lincomycin was the subject of the particular advertisement that was discussed, and the presentation involved "sections of fresh tissues obtained from animals given large intramuscular injections of lincomycin * * *." The statement "for antibiotic tissue penetration" was juxtaposed.

The fact of lincomycin tissue penetration was demonstrated by the inhibition of microbial growth in the vicinity of the tissue sections. Only the fact of penetration was shown—without attempt to quantitate the amount of the antibiotic in the tissue section or to make comparison with the tissue penetrating qualities of other antibiotics. We have made such quantitative comparisons, however, of the bone-penetrating characteristics of erythromycin, tetracyline and lincomycin (*Antimicrobial Agents and Chemotherapy*—1965, pp. 201–205), and as Kunin and Hunter suggest, these antibiotics and lincomycin do penetrate this tissue to the extents reported. The fact of erythromycin and tetracycline penetration of tissue is demonstrated well in the long record of clinical effectiveness of these antibiotics. Lacking such a long clinical experience, a graphic representation of lincomycin's tissue penetration has been made in the cited advertisement.

Even only moderately sophisticated readers of antibiotic inhibition data and photographs of zones of inhibition of microbial growth will recognize that the area of inhibition is dependent on diffusion characteristics of the antibiotic molecule, agar concentration of the medium, temperature of incubation, sensitivity of test organisms and so forth.

If more experiments are to be done as Kunin and Hunter indicate and quantitation is desired, these important variables are also recommended for consideration: route of administration (intraperitoneal, as in Kunin and Hunter, or intramuscular, as in the subject advertisement); and dose (approximately 50 mg per kilogram as in Kunin and Hunter or 25 mg per kilogram as in the subject advertisement).

JOSEPH E. GRADY, Ph. D.,
KURT F. STERN, M.S.
Department of Microbiology, Upjohn Company.

KALAMAZOO, MICH.

Page One

AUGUST 1968

Eastern Representative:
A. DOUGLASS BREWER
1160 Third Ave.
New York City
Tel. 212-249-9330

Western Representative:
JOHN H. HARLING
104 S. Michigan Ave.
Suite 314
Chicago, Illinois 60603

NEW ENGLAND JOURNAL OF MEDICINE
Publisher: THE NEW ENGLAND JOURNAL OF MEDICINE
10 Shattuck St.
Boston, Mass. 02115
Tel. 617-734-9800

GENERAL INFORMATION

1. **ISSUANCE:**
   - *a. Frequency:* Weekly
   - *b. Issue date:* Thursday
   - *c. Mailing date, mail class, mailing cover:* Monday, second class mailing, wrapper

2. **ESTABLISHED:** January, 1812

3. **ORGANIZATION AFFILIATION:** Massachusetts Medical Society

4. **SUBSCRIPTION DATA:**
   - *a. Subscription Rates:* $10.00 per year, postage paid, for the United States (residents, interns and medical students, $5.00 per year). Long-term rates: 2 years $18.00, 3 years $25.00. All foreign rates, United States funds: Canada, $11.00 per year; other foreign, $12.50 per year. Long-term rates: Canada, 2 years $20.00, 3 years $28.00; other foreign, 2 years $23.00, 3 years $32.50.
   - *b. Annual Percentage of Subscription Renewals:* 80%
   - *c. Number of Issues Sent after Subscription Expiration:* 4-6

5. **SPECIAL ISSUES:** None

6. **EDITORIAL:**
   - *a. Editorial Content:* Original manuscripts, no abstracts
   - *b. Special Editorial Features:* Case Records of Massachusetts General Hospital; Seminars in Medicine, Beth Israel Hospital, Boston; Physiology for Physicians.

7.) **REQUIREMENTS FOR ACCEPTANCE OF NEW PROFESSIONAL PRODUCTS FOR ADVERTISING:**
8.) **REQUIREMENTS FOR AD CLEARANCE:** Copy for advertisements is accepted by the Advertising Committee of the *Journal* on the basis of the apparent quality and usefulness of the product and the manner of its presentation. Proprietary names of pharmaceutical products must be accompanied by the chemical, or generic or official names, and the quantity of all active substances must and the recommended dose should be stated. Copy should be factual, conservative and in good taste. Documentation for new products should be sent to the Advertising Manager. Allow two weeks for clearance.

9. **ADVERTISING ACCEPTANCE OF NONPROFESSIONAL PRODUCTS OR SERVICES:** Copy should be submitted to Advertising Manager.

10. **POLICY ON PLACEMENT OF ADVERTISING:** Full pages only, front form when possible; full and fractional pages rear form.

11. **ADVERTISER'S INDEX:** If space permits.

12. **EDITORIAL-ADVERTISING RATIO** (latest six-month average): 50% Advertising, 50% Editorial

13. **SERVICE TO ADVERTISERS:**
   - *a. Availability of Mailing List:* Information on request.
   - *b. Availability of Editorial Reprints:* Advertiser must get author's permission; publisher prefers to supply reprints; Advertising Manager should be contacted regarding reprints; quantity of reprints is limited.

14. **STAFF:**

Editor: Dr. Franz J. Ingelfinger, 10 Shattuck St., Boston, Mass. 02115, 734-9800, Area Code 617
Advertising Manager: Milton C. Paige, Jr., 10 Shattuck St., Boston, Mass. 02115, 734-9800, Area Code 617

CIRCULATION

15. CIRCULATION

Jan.-June 1967		*Jan.-June 1968*	
Paid	99,596	Paid	107,912
Comp.	370	Comp.	320

16. GUARANTEED CIRCULATION: 100,000

17. CIRCULATION VERIFICATION: Post Office Receipts

18. RATES PER THOUSAND (Based on latest six-month average circulation):
   a. Full page, black-and-white, one-time: $8.33
   b. Full page, black-and-white, based on number of issues per year: $6.94

19. COVERAGE AND MARKET:
   a. Coverage: Journal circulates nationally and internationally.
   b. Market Served: Physicians in all specialties and general practice subscribe to the *Journal* independently in addition to the 8,300 members of the Massachusetts Medical Society. Also subscribing are approximately 13,000 medical students who receive the *Journal* at the special rate of $5.00. The *Journal* is in its one hundred and fifty-seventh year of publication, and is the oldest medical journal in the world today.
   c. Breakdown of Circulation by Classification of Reader: See "Classification Chart."

20. TERRITORIAL DISTRIBUTION: June 27, 1968

New England States	
Connecticut	2,053
Maine	403
Massachusetts	10,809
New Hampshire	446
Rhode Island	493
Vermont	400
	14,604
Middle Atlantic States	
New Jersey	2,947
New York	13,181
Pennsylvania	5,738
	21,866
South Atlantic States	
Delaware	159
Florida	2,138
Georgia	1,386
Maryland	3,389
North Carolina	1,636
South Carolina	495
Virginia	2,083
Washington, D.C.	1,220
West Virginia	525
	13,031
East North Central States	
Illinois	4,537
Indiana	1,121
Michigan	3,321
Ohio	3,950
Wisconsin	1,544
	14,473
East South Central States	
Alabama	767
Kentucky	937
Mississippi	372
Tennessee	1,248
	3,324
West North Central States	
Iowa	680
Kansas	729
Minnesota	1,777
Missouri	2,177
Nebraska	546
North Dakota	151
South Dakota	143
	6,203
West South Central States	
Arkansas	386
Louisiana	861
Oklahoma	652
Texas	3,368
	5,267
Mountain States	
Arizona	520
Colorado	1,075
Idaho	146
Montana	166
Nevada	105
New Mexico	382
Utah	373
Wyoming	64
	2,831
Pacific States	
California	9,794
Oregon	931
Washington	1,355
Alaska	91
Hawaii	253
	12,424
U.S. Territories	2,057
Canada	5,724
Foreign	8,348
	16,129
Grand Total	110,152

RATES

21. **ISSUANCE:**
    a. Frequency: Weekly
    b. Issue date: Thursday
    c. Mailing date, mail class, mailing cover: Monday, second class mailing, wrapper

22. **CLOSING DATE FOR SPACE:**
    a. Reservations: } 17 days prior date of issue; copy and set-up, 23 days prior.
    b. Cancellations: }

23. **AGENCY COMMISSION:** 15%

24. **CASH DISCOUNT:** 2% fifteen days

25. **RATES:** Effective Jan. 1, 1966

	1	*6*	*13*	*26*	*52*	*78*	*104*	*130*	*156*
One page (per insertion)	$900	$860	$825	$790	$750	$725	$701	$688	$666
Half page (per insertion)	475	460	440	420	400				
Quarter page (per insertion)	250	240	230	220	210				
Eighth page (per insertion)	150	141	133	126	120				

26. **EARNED RATES:** Rates are based on total amount of space used within a 12-month period. Minimum rate on unit size will apply when several sizes are used. (For example, if 6 half pages and 6 full pages are used the 13-time half page and 6-time full page rates will apply.)

27. **COLOR:**
    a. Standard color rate (2nd color): $200
    b. List of standard colors; availability of color charts: 4A colors
    c. Matched color rate: $225
    d. Color rate for spreads: $400 standard — $450 matched
    e. 3-color rates: $400 standard — $450 matched
    f. 4-color rates: $750 (Four color process)
    g. Commission data: Color charges are commissionable

28. **BLEED:**
    a. Black-and-white bleed:
    b. Black-and-white plus color bleed:
    c. Color bleed:
    d. Gutter bleed:
    e. Spread bleed:
    f. Oversize plates (non-bleed): 7″ x 10″ — No charge
    g. 4-color bleed — No charge
    h. Commission data: Bleed charges are commissionable.
    } Bleed charge is 10% of black and white space rate regardless of type of bleed.

29. **INSERTS:**
    a. 2-page inserts: 3 times page rate
    b. 4-page inserts: 6 times page rate
    c. Larger units, gate folds, tip-ins, die-cuts: } Since special handling charges are charged at cost by the job for unusual
    d. Special handling charges, etc.: } inserts, samples are necessary to determine charges.

30. **COVER AND PREFERRED POSITION RATES:**
    a. 2nd cover: 33⅓%
    b. 3rd cover: 33⅓%
    c. 4th cover: 100%
    d. Other preferred positions: Facing first text page, 50%; facing last text page, 33⅓%; page III, 33⅓%.

31. **SPECIAL POSITIONING:**
    Consecutive right-hand pages: 10% of space charge, additional.
    Consecutive pages beginning with right-hand page: 10% of space charge on 1st right-hand page, additional.

32. **MISCELLANEOUS:** All advertising copy is subject to approval of the Advertising Committee of this journal. The acceptance of an advertising space contract therefore does not make the publisher liable to publish the copy submitted. Right of the publisher to omit advertising for delinquent payment of space charges is conceded. The publisher guarantees to maintain the schedule of rates appearing above to all advertisers without discrimination.

MECHANICAL REQUIREMENTS

33. PLATE SIZES:

Full page	7 x 9 in.	(42 picas x 55 picas)	**Quarter page**	3¼ x 4½ in.	(20 picas x 27 picas)
Half page	7 x 4½ in.	(42 picas x 27 picas)	**Eighth page**	3¼ x 2 in.	(20 picas x 12½ picas)
	3¼ x 9 in.	(20 picas x 55 picas)			

7" x 10" plates will be accepted at no extra charge

34. BLEED SIZES:

a. Plate sizes:
Full page: 8⅛" x 11¼"
Fractional units: 8⅛" x 5⅜" or 4⅛" x 11¼"
Gutter bleed: 8⅛" x 11¼"
b. Trim size of publication: 8" x 11"

35. INSERT REQUIREMENTS: Multiple page inserts are to be furnished folded.

a. Sizes:
2-page inserts: 8¼" x 11⅜"
4-page inserts: 8¼" x 11⅜" folded
6-page inserts: Do not accept inserts larger than 4 pages.
b. Trimming:
Head, foot and side margins: margin for live matter: Head ¼", Foot ⅛", Side ⅛", Margin ½". All inserts (tipped or gathered) always jog to the head.
c. Stock weights acceptable: Not to exceed 100 lb. coated offset.
d. Quantity: Information on request.
e. Closing date for inserts: 16 days prior date of issue.
f. Packing and labeling of inserts for shipping: Packed one up, folded if 4 pages, flat if 2 pages on skids with runners at least 8" high and 26" apart. There must be a skid top on the load and waterproof wrapping with steel strapping both ways. The labels must show quantity and issue date insert is scheduled to run.
g. Shipping address for inserts: NEW ENGLAND JOURNAL OF MEDICINE, c/o POOLE PRINTING CO., 1909 North Magnolia Avenue, Chicago, Illinois 60614.

36. PAPER STOCK:

a. Inside pages: 55 lb. machine coated
b. Covers: 80 " " "
c. 4-color process: 55 " " "

37. TYPE OF BINDING: Saddle

38. HALFTONE SCREEN:

a. Covers: } 120 preferred, 133 acceptable
b. Inside: }
c. 4-color screen: This should be decided by engraver, depending on type of ad and color contrast desired.

39. REPRODUCTION REQUIREMENTS:

Electros — blocked; original zinc or copper plates, resist removed — will use; plastic plates and mats — will not use. Four-color process ads will be produced 4 colors wet in the following color rotation: yellow, red, blue, black. Progressive proofs should be proofed wet in the same rotation on S. D. Warren's Webcote, 55# basis on comparable paper. Inks: 4A standard inks. The publisher, to be responsible for quality, must receive progressive proofs pulled as described above. *(For additional detailed information see our booklet on acceptable materials for reproduction.)*

40. CLOSING DATES — MECHANICAL:

a. Complete plates:
Black-and-white:
2-color:
4-color:
Covers:
} 17 days prior date of issue
b. Publication set copy — with proofs, without proofs: With proofs — 23 days prior date of issue; without proofs — 17 days prior date of issue.
c. Patches: }
d. Inserts: } 16 days prior date of issue

41. DISPOSITION OF PLATES: Plates not called for within one year will be destroyed without notification.

42. ADDRESSES:

a. For contracts:
b. For insertion orders and other instructions, publication set copy: } 10 Shattuck St., Boston, Mass. 02115
c. For complete plates and patch electros: NEW ENGLAND JOURNAL OF MEDICINE, c/o POOLE PRINTING CO., 85 W. Harrison St., Chicago, Ill. 60605.
d. For inserts: NEW ENGLAND JOURNAL OF MEDICINE, c/o POOLE PRINTING CO., 1909 N. Magnolia, Chicago, Ill. 60614.

Prepared in accordance with recommendation of the Media Committee, The Pharmaceutical Advertising Club, Inc.

(Whereupon, at 12:40 p.m., the committee adjourned to reconvene tomorrow, Thursday, December 19, 1968, at 10 a.m.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

THURSDAY, DECEMBER 19, 1968

U.S. SENATE,
MONOPOLY SUBCOMMITTEE OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to recess, at 10:10 a.m., in room 318, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; and Elaine C. Dye, research assistant.

Senator NELSON. The hearings of the Monopoly Subcommittee will open.

We have two very distinguished physicians here this morning, Dr. George Baehr and Dr. James Faulkner.

Before we commence, I would like to say that we know that we have, in addition to these two distinguished physicians, a distinguished visitor in the audience today, Dr. Frances Kelsey of the Food and Drug Administration. The American public will be forever grateful to her for her untiring efforts and devotion to duty which prevented a thalidomide disaster from occurring in this country.

Dr. Kelsey, despite great pressure from the drug firm, Richardson-Merrell, refused to approve the drug because she was not satisfied with the research work submitted in the New Drug Application. It is heartening to know we have such public servants like Dr. Kelsey, who are dedicated to protecting the public.

We are pleased to have you here as a visitor this morning, Dr. Kelsey.

Our first witness is Dr. Faulkner, of Boston. Dr. Faulkner has a long and distinguished record as a practicing physician and as a professor.

Doctor, your full statement, including your biographical summary, will be printed in the record. You may proceed however you desire. If you think it is more economical to read your prepared text, you may proceed that way, and if at any time you wish to elaborate on anything that you have reduced to writing, please feel free to do so.

I trust that if some questions occur to us, you won't mind being interrupted.

The committee is very appreciative of your appearing today to make your contribution to these rather extensive hearings which we have been conducting for nearly 2 years now. We have had the privilege of having a number of distinguished members of the medical profession testify before the committee, and we certainly welcome your testimony this morning.

Go ahead, Doctor.

81-280—69—pt. 10——10

STATEMENT OF DR. JAMES M. FAULKNER, CHAIRMAN, COMMITTEE ON PUBLICATIONS, MASSACHUSETTS MEDICAL SOCIETY, BOSTON, MASS.

Dr. FAULKNER. Thank you, Senator Nelson.

With your permission, I will read my biography and then proceed with my statement.

Senator NELSON. Fine.

Dr. FAULKNER. I want to make it clear that I am speaking here completely as an individual, not representing any particular institution or organization.

Mr. Chairman, my name is James Faulkner, from Boston, I am a retired physician and medical educator. I graduated from Harvard Medical School in 1924, was intern in medicine at the Massachusetts General Hospital and assistant resident in medicine at the Rockefeller Institute and the Johns Hopkins Hospital. Up to World War II I was in private practice in internal medicine and cardiology, and did part-time clinical research and teaching for Harvard. I served in the Medical Corps of the USNR for 4 years and was discharged as a captain. After the war I went to Tufts Medical School as professor and chairman of the department of medicine. From 1947 to 1955 I was dean of Boston University School of Medicine. From 1955 to 1960 I was medical director of Massachusetts Institute of Technology. I was a member of the Council on Medical Education of the AMA from 1949 to 1960, of the National Board of Medical Examiners from 1956 to 1968, of the National Fund for Medical Education since 1959 and president from 1964 to 1966. I was a member of the board of overseers of Harvard College from 1958 to 1964. I have contributed about 80 articles to the medical literature. Since 1960 I have been chairman of the committee on publications of the Massachusetts Medical Society which is responsible for the publication of the New England Journal of Medicine.

In November, Dr. Philip R. Lee, Assistant Secretary for Health and Scientific Affairs of the Department of Health, Education, and Welfare sent a letter to physicians throughout the country calling their attention to the Second Interim Report of the Secretary's Task Force on Prescription Drugs and inviting their comments on it. In his letter, Dr. Lee called particular attention to certain recommendations of the task force, namely: that Federal support be given to improving the teaching of clinical pharmacology or drug therapy at both the undergraduate and postgraduate level; that a journal of prescribing completely independent of the drug industry for support be established to provide practicing physicians with "objective evaluations of new drugs and reevaluation of old ones;" and, finally, that the Department of HEW be authorized to distribute to all physicians without charge a regularly updated compendium of all prescription drugs including an indication of relative costs.

With these recommendations I heartily agree.

Senator NELSON. May I interrupt a moment, Doctor?

Dr. FAULKNER. Yes, sir.

Senator NELSON. Dr. Lee recommended Federal support for the teaching of clinical pharmacology—is this because it is necessary if the

subject matter is to be adequately taught in the medical schools? I don't know the present status of the teaching of pharmacology in the medical schools and whether or not it is sufficiently emphasized. I know that you and/or Dr. Baehr——

Dr. FAULKNER. I am going to develop that a little further on. Clinical pharmacology, or therapeutics, as a discipline used to be taught in the medical schools, usually by part-time practitioners of medicine. Of course most of the faculty were part time 20 years ago, but there were members of the faculty who took a special interest in medical therapeutics as opposed to basic pharmacology, physiological action of drugs.

As the full-time system took over, more and more of the positions in the medical school, the basic pharmacologists more or less preempted the field, and the part-time teachers of clinical medicine became fewer and fewer. So that the emphasis became much more on physiological aspects of pharmacology, basic pharmacology, and less emphasis on bedside therapy, ambulatory therapy, as well and the actual practical application of the use of drugs. This, I think, has become somewhat neglected in recent years.

Senator NELSON. Isn't that because those who decide policy for medical education in the school haven't considered it of preeminent importance? Or is it because they don't have sufficient money? What would Federal aid accomplish? If they don't teach it now as one of the fundamental subjects, what would cause them to teach it if there were some Federal assistance to do so?

Dr. FAULKNER. In recent years Federal aid has been very largely for research and not for instruction, and this has increased the interest in basic aspects of pharmacology and research in that field, without concomitant improvement in the actual practical application of the use of drugs.

The physician who is going to follow me, Dr. Baehr, is a magnificent example of the physician in practice who has been particularly interested in the actual application of the use of drugs, but he is becoming a very rare type on the faculties of our medical schools.

Senator NELSON. Is it becoming generaly recognized in the medical profession that the teaching of clinical pharmacology has been neglected?

Dr. FAULKNER. I can't say that it is recognized very generally as yet. The medical schools are in the midst of tremendous changes in curriculum now, and what will issue from it within the next few years is very difficult to say, but I don't think this has been recognized generally.

Senator NELSON. I believe that it was the Task Force's position that it hadn't been given adequate emphasis. That is why Dr. Lee and the Task Force recommended it, and I assume why you endorsed the recommendation. Is it your feeling that if there were some Federal assistance for the teaching aspects, as contrasted with research, that in fact the medical schools would more quickly, more rapidly begin to teach clinical pharmacology?

Dr. FAULKNER. I would hope that would be the case. I wouldn't be able to say.

Senator NELSON. Is it that the profession, or those who manage the curricula, just don't think it is that important? Is that the problem?

Dr. FAULKNER. I think it could be much more effectively done if the teaching were concentrated at the postgraduate level. There, I think, is no question but what it would be accepted, and you would find graduate physicians who would be impressed with the actual problems that they were up against in practice, and it would be much easier to develop this kind of teaching which must be constantly changing with new discoveries so that in every year there would be fresh subjects to teach, it would be more effectively taught at that level than at the undergraduate level.

Senator NELSON. When you say postgraduate, are you referring to the practicing physician or to the intern?

Dr. FAULKNER. I am—well, both, but particularly the practicing physician. It must be taught at both levels.

Senator NELSON. And you would expect that if such a course were available that practicing physicians would or could take the time to take courses in clinical pharmacology?

Dr. FAULKNER. Yes, I think they could be made attractive enough so that they would be interested. I think practicing physicians, when they are given the opportunity of choosing what they want to hear at county medical society meetings and that sort of thing are very apt to choose what is the latest treatment for this or that and are particularly interested in therapy.

Senator NELSON. But if you were talking about the suggestion of Dr. Lee that support be given to improving the teaching of clinical pharmacology, that would mean more than occasional lectures, would it not? Are you talking about a course at a teaching hospital or medical school?

Dr. FAULKNER. Yes. I would strengthen the teaching of clinical pharmacology, not necessarily by formal courses, as encouraging people skilled in clinical pharmacology to participate in the clinical teaching in the hospital, in the ward rounds and in the seminars that are constantly going on in the teaching hospitals.

Senator NELSON. Then you endorse the recommendation of the Task Force that a journal of prescribing, completely independent of the drug industry for support, be established to provide practicing physicians with objective evaluations of new drugs and reevaluations of old ones?

I assume you are referring to what might be called a compendium of all the drugs. Is that what you are referring to?

Dr. FAULKNER. Well, I think the compendium would be something different. It might be something that is issued annually to bring it up to date. But the journal would contain articles of current interest of new drugs recently that have become available to keep the practicing physicians abreast of the times without depending entirely on the detail man and the throwaway journals.

Senator NELSON. I see. So you are thinking of a periodical.

Dr. FAULKNER. Yes.

Senator NELSON. Didn't the American Medical Association once have a periodical on new drugs?

Dr. FAULKNER. Yes, they did, and it was useful.

Senator NELSON. Have they started another?

Dr. FAULKNER. I believe they are starting one now. I haven't seen it. But I believe they are starting one.

Senator NELSON. So what you are recommending is a journal which would be available to all physicians and which would devote itself exclusively to drugs and their use.

Dr. FAULKNER. Yes, sir.

Senator NELSON. What part of that function does the Medical Letter now perform?

Dr. FAULKNER. The Medical Letter I don't think has a wide enough circulation, for one thing.

Senator NELSON. That is the issue that has been raised a number of times, something like 15,000 circulation.

Dr. FAULKNER. Yes.

Senator NELSON. Then are you referring to a journal that would go free to all physicians? This one, the Medical Letter, is subscribed to and widely praised by the medical profession, at least in the testimony before this committee over the past years. Two questions occur to me. Is there any reason to believe that a journal such as you refer to would be more widely subscribed to and, two, does the Medical Letter seek to accomplish the same purpose that you recommend a journal for?

Dr. FAULKNER. I think the Medical Letter substantially seeks the same purpose, but perhaps a journal designed to go to the practitioners of medicine across the country could be livened up and made more appealing to the perhaps casual reader. I think it would have to be subsidized in large part. It probably would be better to charge something for it, but I doubt if it could be, it would be, popular enough to be subscribed to by the majority of physicians.

The problem is that it is the ones who need it most who would not subscribe to it. Maybe it would be worthwhile to subsidize it completely, just as the so-called giveaway journals are subsidized by the pharmaceutical industry.

Senator NELSON. Do I understand that the reason for the recommendation by the Task Force, and your endorsement of it, is the belief on your part that the objective information, available to physicians on the use of drugs today, is inadequate?

Dr. FAULKNER. Yes, it is not readily enough available to them. If it came on their desks periodically, I think it would be availed of much more than it is now.

Senator NELSON. And then in the last sentence of the recommendation of the Task Force, with which you agree, was the regularly updated compendium on all prescription drugs. Could you suggest to the committee what that compendium should include, how it might be designed?

The Food and Drug Administration appeared before the committee recommending a compendium that would include all drugs. Some people have raised the question, as a matter of fact the Pharmaceutical Manufacturers Association, I believe, that that would be an unwieldy, massive document. The FDA doesn't think it would. What would you recommend about a compendium?

Dr. FAULKNER. I am not familiar enough with the field to answer that question, Senator. I don't know how large such a compendium might be. It might have to be cut down to reasonable size to make it acceptable.

Senator NELSON. You may proceed, Doctor.

Dr. FAULKNER. With these recommendations I heartily agree.

It is my opinion that medical education has failed to grasp the significance of the vast proliferation of new drugs which has taken place over the last couple of decades. When the number of effective drugs on the market was small, it was possible for a physician with a good grounding in basic pharmacology to make a reasonably intelligent choice from the drugs available in writing a prescription. Now the practicing physician finds himself obliged to choose between a bewildering array of drugs for which competing claims are made and more often than not he finds himself not only ill prepared to make correct judgments but at a loss to know where to turn for unbiased information.

A factor which has to be taken into account in any discussion of the teaching of medical therapeutics in recent years is the increased ratio of full-time teachers in the faculties of the medical schools. Relatively few are engaged in private practice except as consultants. Their skill with drug therapy is apt to be highly specialized. Perhaps the time has come to revive comprehensive medical therapeutics as a respectable part of the clinical curriculum. At the undergraduate level this might be more effectively taught by a physician whose practice was not limited to a narrow specialty.

Another factor which has entered the picture is the high cost of some of the new drug preparations. The medical student and the practitioner should have readily available to them an authoritative reference book describing all the prescription drugs and their relative costs. The compendium recommended by the task force would fill this important unmet need.

It is indeed deplorable that so much of what the medical student and the practitioner learn about drug therapy comes to them from pharmaceutical firms who are actively promoting their own products. The blame for this situation, it seems to me, must rest in large part on the failure of medical educators to interest themselves in therapeutics as such. Certainly the average medical graduate finds himself ill equipped to make informed judgments regarding the relative merits of the countless preparations available to him.

Mr. GORDON. Dr. Faulkner, may I interrupt at this point?

As it is now, very few studies are made of the relative merits of drugs. Very few drug manufacturers, as I understand it, are willing to sponsor such studies. The FDA requires a showing only of efficacy and safety, not of relative efficacy and relative safety.

How do you propose we finance such studies?

Dr. FAULKNER. I would think this is a field for research that may be financed by any funds available for valid clinical research, comparing one drug with another, and this might be financed by foundations, by NIH, or by any other neutral source of funds.

It is quite understandable that under the circumstances the drug houses would rush to fill the void in medical education by bombarding the physician with direct mail advertising, throw-away magazines, samples and detail men, not to mention supporting most of the professional medical journals.

If the drug houses have more or less preempted the area of medical education dealing with drug therapy, the appropriate approach to

the problem is for the medical educators to meet them on their own ground. If physicians have been unduly influenced by the claims of the drug houses it is not because they are particularly gullible. Physicians are trained to be critical of evidence and if they are given all of the evidence can be expected to make reasonably sound judgments. They are getting one side of the case superbly presented by the drug houses now. Thanks to the Food and Drug Administration the claims of the drug companies can now be accepted as true. However, it is not the whole truth and the practitioner must be given reliable information which will allow him to make comparative judgments of potency and price of the drugs available to him. This is a matter of continuing education for every physician in the country—a job which will require the resources of the Federal Government and the disinterestedness of the Department of Health, Education, and Welfare.

Senator NELSON. May I interrupt, sir. You say: "thanks to the Food and Drug Administration the claims of the drug companies can now be accepted as true," but not the whole truth. I assume one of the things you are getting at is that there are in the marketplace a large number of compounds all of which have about the same effect, and are used for the same purpose. The Food and Drug Administration has the authority, and attempts conscientiously to exercise it, to prohibit the specific misrepresentation of the use of the drug. So whereas a company may state truthfully what a drug does, at the same time there is no presentation to the physician that there may be a half dozen other drugs produced by a half dozen other companies that have the same effect, some of which have not only the same quality but same effect, and some of which may be much cheaper; is that what you are talking about?

Dr. FAULKNER. Yes, exactly.

Mr. Chairman, in your letter inviting me to appear before your committee you listed a number of specific ethical questions which the Monopoly Subcommittee would like to explore. With your permission, I shall present these questions and my own individual reaction to them, particularly as they involve ethical implications, possible conflicts of interest and professional responsibility in the following situations:

1. When doctors lend their names for articles and letters written by members of the pharmaceutical industry.

I regard it as dishonest for anyone to lend his name as an author to an article or letter not written by himself.

2. When doctors own stock in drug companies whose products they are evaluating.

A doctor who evaluates the drug of a company in which he owns stock cannot avoid the suspicion of bias even if the financial relationship is made known. If he does not reveal his stock ownership he is not being honest.

3. Whether ownership of stock in a drug company can influence a decision to prescribe in the first place, and what to prescribe in the second place.

I think it would almost never influence a decision to prescribe but might influence the choice of a drug and, therefore, I regard it as an undesirable practice.

4. When doctors are paid directly by a drug firm to evaluate its products.

I think my good friend, Dr. William Bean, puts it too strongly when he writes, "The physician who is in the pay of pharmaceutical manufacturers is in no position to keep public confidence in his objectivity." A physician's reputation with his peers is based on the quality and integrity of his work rather than on the source of his income. Much sound clinical research has been done by physicians in the pay of pharmaceutical houses. However, when such work is published it is desirable to include a footnote to the effect that the work has been supported in whole or in part by a drug firm. This is an honest disclosure which can alert the reader to any possible bias.

I think I can add here that this is perhaps not as simple as it sounds. So many articles have multiple authors, sometimes four or five, each of whom have a different source of support, and this becomes a little complex.

5. When influential doctors or pharmacy educators, particularly in high academic positions, are large stockholders and serve as policy-setting members of boards of drug corporations.

Since these men are in the position to mold the attitudes of other doctors and to make policy decisions in key medical and pharmaceutical organizations, might there not be a conflict of interest here? What are the implications when doctors and pharmacy educators do not make known their industry affiliations?

I can speak here only from the point of view of a medical educator to whom the principles of medical ethics apply. I cannot speak for the pharmacy educators. I share the view of many but not all members of the medical profession in feeling that it is unethical for a physician to take out a patent on a new drug for his own benefit. A logical extension of this principle makes it unethical for a physician who is prescribing drugs to profit from the sale of drugs patented by others. It is, therefore, in my view particularly undesirable for a medical educator who should exemplify the highest standards of medical ethics to be getting a significant portion of his income from the profits of drug companies. It is positively reprehensible if such a financial dependency on the drug industry is not made known.

6. When prominent professors receive regular retainer fees from the drug industry for consultation while simultaneously advising Government or private agencies on matters of policy which can severely affect drug firms' products.

I believe that collaboration between drug houses and medical professors has not infrequently resulted in important advances in medicine. I would not condemn, out of hand, the practice of drug houses paying retainer fees to medical professors if the relationship is made public including the nature and amount of services rendered.

A medical professor is on safer ethical ground if his financial relationship to the drug house is in the form of recompense for specific services rendered in the form of consultation or research.

7. When medical organizations and publications—national, local, and student—are largely dependent on income from industry advertising.

No organization which purports to represent the medical profession should allow itself to get into the position of being largely dependent

on income from drug advertising. It is difficult for an organization in this position not to allow its policy to be influenced by considerations which may not be in the long-term interest of the public and the medical profession.

The medical publications of this country show a complete spectrum of dependency on drug advertising, ranging all the way from the throwaway journals some of which include well-edited text of high quality, to strictly scientific journals containing no advertising whatsoever.

There has also been a wide discrepancy in the quality of the advertising in the different journals. The best journals screened their advertising for accuracy long before the Food and Drug Administration began to enforce their standards on all, and one could make a judgment as to the quality of a journal by the reliability of its advertising claims. Now, the better journals which do accept advertising tend to limit it in amount, to restrict it to the front and back sections, never interleaving it with the body of the text and to adhere to certain standards of good taste.

It is undoubtedly true that just as there is a complete spectrum of dependency on drug advertising among the medical journals, there is also a spectrum of reliability on their textual matter. There is a general correlation between the two, but not an exact one.

Senator NELSON. May I ask a question here?

On page 6, at the beginning of your statement on advertising, you state that no organization which purports to represent the medical profession should allow itself to get into a position of being largely dependent on income from drug advertising. I don't have the figures but I believe that some years back it was disclosed that the Journal of the American Medical Association received some 50 percent of its income from advertising. Do you include them—is your statement here critical of that amount? Would you term that being largely dependent on the income from drug advertising?

Dr. FAULKNER. Your statement is that the American Medical Association itself got 50 percent of its income?

Senator NELSON. I believe the JAMA.

Mr. Gordon says that it is the American Medical Association which derives about 50 percent of its income from drug advertising.

Dr. FAULKNER. This gives me great concern.

Senator NELSON. Mr. Gordon thinks it is about 50 percent, in any event. We will want to recheck to be positive about it and correct the record if that is not correct, but he states that that is his information, that it is about 50 percent of the support of the whole AMA itself, not just the publication of the JAMA.

Dr. FAULKNER. In my opinion, this is a highly undesirable situation.

Senator NELSON. What about the journals which are sometimes called throwaways, those which are totally dependent upon advertising—in other words, there is no subscription price paid. They go to all members of the profession. They depend solely upon advertising. I believe it was Dr. O'Brien, who said in evaluating this situation, that the entire contents of the throwaways ought to be considered advertising. The significance of that, of course, is that if it is considered advertising it would be subject to the control of the FDA.

Do you have any opinion about those which are totally dependent upon advertising?

Dr. FAULKNER. I would agree that the entire content of such journals should be subject to the same regulations that apply to the overt advertising matter in these journals.

Senator NELSON. In other words, all the written material, whether it is in the nature of an ad or an article, should be considered advertising, is that what you are saying?

Dr. FAULKNER. From the point of view of making claims for drugs, yes.

Senator NELSON. Go ahead, Doctor.

Dr. FAULKNER. Rather than to attempt to impose restrictions on the amount of advertising, I would favor taking positive steps to provide the practitioner with up-to-date information about drugs which would act as a counterpoise to the limited and strongly biased literature put out by the drug companies. I believe the doctor should be given the opportunity to form his own judgments about drugs on the basis of all the evidence. On the other hand, I don't think advertising should be permitted to hide behind a cloak of pretended objective presentation. A most nefarious practice utilized by some of the purely advertising journals is to plant articles which purport to be scientific evaluations of new drugs and which are, in fact, promotion. Claims made in such articles are not subject to the control which the Food and Drug Administration has over straightforward advertising matter. I hope action can be taken to bring such surreptitious advertising under control.

8. The implications for the medical profession and the public when the so-called independent giveaway sheets and journals, which are easy to read and subsist entirely on drug advertising, are becoming a factor of some importance in the physicians' education.

I regard it as deplorable that practitioners of medicine receive so much of their information regarding new drugs from the giveaway journals. The drug companies have simply moved into a vacuum here and the busy doctor seldom has available an alternate source of information. Every effort must be made to get good reliable up-to-date information on all new drugs to the doctors in their offices. It may not be as eye appealing as some of the drug handouts, but I think it will be well received.

9. When many physicians accept fellowships, salaries, and research support directly from the drug industry.

I do not see anything inherently improper in such arrangements as long as they are carried out openly. A good deal of excellent research has been carried out in medical schools with drug industry support. Ideally, research supported entirely or in part by drug company funds should have an acknowledgment to that effect attached to the published articles resulting from the research.

10. When many physicians base their prescribing practices, to a large extent, on information supplied them by industry salesmen, detail men and other commercial sources.

Senator NELSON. Doctor, may I interrupt for a moment?

From 1947 to 1955, from your biographical sketch, you were dean of the Boston University School of Medicine and from 1955 to 1960 medical director of the Massachusetts Institute of Technology, then

one of the directors of the National Fund for Medical Education since 1959.

We had testimony yesterday from Dr. Lowinger of Wayne State University Medical School in which he discussed the same subject matter and responded to the same question. We raised the issue of what cost, what percentage of the cost of research did the pharmaceutical companies pay in the research that he did, and he responded that they did not pay the cost of his salary, did not pay the so-called overhead cost for use of the facility. They did pay some other costs, including the technicians, and so forth. I am contrasting this with the research costs assumed by NIH for research done for them in graduate schools, or the National Science Foundation for research done by them for the military, in which they cover costs of the time invested by the researcher, overhead cost of the facility, and so forth.

In any event, the situation that Dr. Lowinger presented is one in which it appeared that the school itself was, in fact, not receiving full cost of the research they did, which ended up in a situation in which the university was in fact subsidizing the cost of the research. The company was getting the research without paying the full cost. It that a typical circumstance? Do I state the question clearly enough?

Dr. FAULKNER. Yes. I haven't had enough recent experience in this problem as it affects a medical school. My previous experience has been a good deal the same as the doctor from Wayne State. The support has been partial. It was paying a salary for a technician and not often in the form of comprehensive grants that covered all expenses.

However, often it was work that would have needed to be done. It wasn't particularly—it might have interested the pharmaceutical company but was not initiated by them.

In general, I have not been impressed with the largesse of the pharmaceutical companies in supporting research in the medical schools.

Senator NELSON. From observations I made at our university when I was Governor, it seems that all the larger universities were very pleased to have the opportunity of a research contract with NIH or the National Science Foundation or HEW. One, of course, because they would be interested in the subject matter and it would help induce scholarships at the universities, and, two, because the total cost was paid by the contracting agency, including the overhead costs of the institution.

What is the explanation, in your judgment, of this relationship that Dr. Lowinger referred to from his relatively recent experience, I think through 1966, or thereabouts, and your own. What is the explanation of this relationship, how did it develop this way instead of the way the National Science Foundation, NIH, and so forth, may deal with the universities?

Dr. FAULKNER. Well, my impression is that the drug companies have been interested in really supporting studies which had a practical bearing on their own problems, and were less interested in giving broad support to basic research, although I think there is a great deal of variation.

I know of one drug company which supported the complete salary of a man who was in a local hospital in Boston, attached to one of the medical schools over quite a period of years, absolutely no restrictions whatsoever on what he did.

Senator NELSON. Just any kind of research he desired in the pharmaceutical or drug field?

Dr. FAULKNER. Yes. He was a biochemist.

Senator NELSON. Did he have any relationship in reporting results directly to the company?

Dr. FAULKNER. He sent copies of his reprints to the company.

Senator NELSON. His research was public information?

Dr. FAULKNER. Yes.

Senator NELSON. Go ahead, Doctor.

Dr. FAULKNER. The problem posed by the growing dependence of the medical practitioner on the itinerant drug salesman for information on the new drugs is to offer more complete and more reliable information to all practicing physicians. This could be accomplished by distribution of a Journal of Prescribing and the periodic issuance of a compendium of drugs as recommended by the task force.

11. When many physicians prescribe dangerous drugs for nonindicated purposes.

For example, during the past year a highly dangerous drug was prescribed by doctors for 3.5 to 4 million people. Yet, testimony from eminent medical authorities who appeared before the subcommittee indicated that no more than 10,000 people in the United States should have received it. What explanation can be found for this?

It is a sad reflection on the medical profession that this drug, presumably chloramphenicol, continues to be prescribed for a wide variety of minor infections in spite of the widely advertised risk of serious blood dyscrasias resulting from its administration. It apparently achieved great popularity before its dangers were appreciated and practitioners who have not had direct experience with its toxic effects have not been sufficiently impressed by the statistics which came out later. Certainly there has been no dearth of literature on the subject. Perhaps the time has come for hospital staffs to put this drug on a restricted list to be prescribed only after consultation with an internist and a justification for its use written into the hospital records.

12. When doctors, acting as purchasing agents for the consumer, prescribe drugs without adequate knowledge of the cost of these drugs relative to other drugs which have the same action.

I am afraid that medical educators have generally ignored this subject as too mundane for their consideration. Certainly medical students should be made aware that there are discrepancies in prices that need to be taken into account and it would be highly desirable for every physician to have at his elbow a compendium of all available drugs with their prices.

Mr. Chairman, your committee has accumulated plenty of evidence that the present system of evaluating the effectiveness of new drugs is unsatisfactory. Claims are made based on subjective evidence, on uncontrolled experiments, and often by biased investigators. The Food and Drug Administration with its limited staff has difficulty in making prompt judgments in some instances where there may be a wealth of published material but a dearth of well controlled data. Perhaps confusion could be avoided if the clinical testing of all new drugs were made the responsibility of a top level group of experts representing both the Government and the pharmaceutical industry. The group

would establish procedure for testing, select panels of qualified individuals to evaluate new drugs on a completely objective basis and make appropriate recommendations. The operation would be funded by the pharmaceutical industry on a cost basis.

Such an arrangement would go far toward insuring an accurate appraisal of new drugs in the beginning and make unnecessary much of the reappraisal of drugs which has proved both costly and confusing.

Senator NELSON. Thank you very much, Dr. Faulkner for your most thoughtful statement.

I wonder if Dr. Baehr would like to come to the witness table at this time. Dr. Faulkner, if you would not mind staying where you are, perhaps you both may wish to comment on some of the questions that are raised.

Dr. Baehr?

STATEMENT OF DR. GEORGE BAEHR, CHAIRMAN, PUBLIC HEALTH COUNCIL OF THE STATE OF NEW YORK, AND DISTINGUISHED SERVICE PROFESSOR, MOUNT SINAI SCHOOL OF MEDICINE, CITY UNIVERSITY OF NEW YORK

Dr. BAEHR. Senator, I shall skip the biographical data with which you are familiar, because it is included in the statement that I submitted.[1]

Senator NELSON. Doctor, I think we will just take a 3- or 4-minute break to allow the reporter a little time, if you don't mind.

(Brief recess.)

Senator NELSON. Our next witness is Dr. George Baehr, chairman of the Public Health Council of the State of New York, a member of the Board of Hospitals of the City of New York, and distinguished service professor at the Mount Sinai School of Medicine of the City University of New York.

Dr. Baehr, the committee appreciates very much your taking the time to come here today. Your statement as well as the biographical sketch will be printed in toto in the record, and you may proceed to present your statement as you desire.

If you wish to extemporize from it, elaborate on it at any stage, feel free to do so.

Dr. BAEHR. I should like to read the statement and then from time to time with your permission introduce some exhibits to support some of the statements that I may make.

Senator NELSON. Fine.

Dr. BAEHR. I shall begin by saying that during many years of practice, I have served as consultant to many local physicians and have been bewildered by the enormous number and variety of brand-named drugs which they prescribe. It is what has been derisively called polypharmacy and today this practice has become almost the rule.

For example, a few days ago I was consulted by a patient who took out of her bag eight different medicines that she was taking, not one of which was indicated.

[1] See statement beginning at p. 4070, infra.

Senator NELSON. Not one of which was indicated?

Dr. BAEHR. Yes. She had had the Hong Kong flu, mild type, and her doctor had started to treat each symptom with a different medicine, including a drug which is totally ineffective in controlling a viral infection; namely, tetracycline, an antibiotic which has no effect upon virus infections.

The result was that the disease from which she was suffering at the time she consulted me was caused by the medication she had been taking. She had what is called aphthous stomatitis, ulcerative lesion in the mouth, and lesions in the colon giving her distressing bowel disturbances. It may take months before she recovers from the effects of the drug which wasn't indicated.

Senator NELSON. Is this, in your experience, a common occurrence?

Dr. BAEHR. Exceedingly common.

Senator NELSON. Exceedingly common?

Dr. BAEHR. Exceedingly common.

The prescribing of expensive brand-named drugs to the exclusion of their generic equivalents has been fostered by the pharmaceutical industry through its 15,000 or more detail men who visit physicians' offices and also by retail pharmacists themselves. Both have been spreading the false gospel that generic preparations are universally unreliable and that brand names are a guarantee of reliability.

There are retail druggists in New York City who do not stock any generic drugs on the excuse that they are generally unreliable. A New York State law, quite properly, forbids a druggist to dispense a generic equivalent when the physician specifies a brand-named preparation. Paradoxically, however, the State law permits a druggist to substitute a brand-named drug when a generic drug is specifically prescribed by the physician—although it may mean 10 times the retail price and 10 times the markup profit to the druggist. When the physician specifies a generic drug, neither he nor his patient is protected from substitution.

The consultant experts of the Medical Letter have made a comparative study of some of the most frequently used drugs purchased by them in the marketplace under their brand names and, also, under their generic equivalents. They found that the brand name is not a guarantee that the preparation meets required U.S. Pharmacopeia standards.

Senator NELSON. Doctor, I notice that you were formerly director of medicine and clinical research at the Mount Sinai Hospital in New York and clinical professor of medicine at the College of Physicians and Surgeons, Columbia University. In Mount Sinai Hospital, were generic drugs used?

Dr. BAEHR. They have been for some years. A formulary containing a list of generic drugs and brand-name drugs that are considered reliable from the evidence within the hospital and from evidence of other reputable institutions are listed in the hospital's drug formulary, and corrected, kept up to date, from month to month. The medical staff of the hospital has agreed that if they can only remember a brand name but have no objection to the dispensing of a generic equivalent, the hospital's pharmacist has the right to dispense the latter. If they want a brand-name drug for some special purpose they can have it.

They are not denied the use of it, but unless they specify that they want it, a generic equivalent is dispensed.

This is the practice in many good teaching hospitals. I think New York Hospital in our city was the first to adopt a hospital formulary. Hospitals have saved at least 50 percent of the cost of drugs used in the hospital and in their outpatient services. The hospital staffs have been encouraged to distinguish between effective generic preparations which are purchasable at lower cost, and those brand-name drugs which must be used. They also learn to appreciate that the brand name alone is not a guarantee of reliability, but is a guarantee of much higher cost.

Senator NELSON. Do you have any knowledge of what percentage of the drugs dispensed at Mount Sinai, while you were there, were generic drugs?

Dr. BAEHR. I cannot answer your question. In my early days, the profits of the pharmaceutical industry were made largely through the over-the-counter sale of patent medicines, but in recent years the major share of the profits of the pharmaceutical industry is derived from indoctrination of the medical profession in regard to the prescribing of brand-named preparations.

Most teaching hospitals have a drug formulary of their own, and compare it with the formularies of other hospitals. They usually have a committee on pharmacy and therapeutics which determines the drugs included in the formulary. This assures the medical staff that the quality of a generic drug included in the hospital's formulary has been passed upon by the committee on pharmacy and therapeutics of the hospital.

Senator NELSON. Does Mount Sinai purchase its own drugs direct or does it have another purchaser who purchases for it?

Dr. BAEHR. Some are purchased directly from the manufacturers and some through an intermediary distributor. I think that is the case in most hospitals.

Senator NELSON. How does the pharmacy and the formulary committee assure itself that the drugs being dispensed meet USP standards and N.F. standards, do they assay these drugs to see from time to time that they do meet the standards?

Dr. BAEHR. In part they depend upon an assurance from the distributor or from the drug firm that they meet USP standards. But they also rely upon a constant survey of the literature by the hospital's committee on drugs, upon the Food and Drug Administration, and upon the Medical Letter. The Medical Letter has played a very important role in guiding institutions and individual physicians in the use of drugs that are dependable and, if possible, of low cost.

Senator NELSON. I take it then that the experience of a hospital and the physicians in the hospital have been as satisfactory with generic drugs as with brand-name drugs?

Dr. BAEHR. I can reply affirmatively with a few reservations. There are some generic preparations that are not purchased because they may not be packaged in a form regarded by the committee as reliable as the brand-named equivalent.

The staff experience with all drugs is watched by the committee. Any untoward effects must, by rules of the medical board of the hospital, be reported promptly to the committee for investigation.

From month to month drugs in the formulary may be eliminated and new ones added as they prove to be reliable in the experience of the institution. The chairman of any departmental specialty may also request the inclusion of a new drug for temporary trial by the staff of his clinical department.

Senator NELSON. Did I understand you to say that by the use of generics the hospital has been able to reduce its drug costs by about 50 percent?

Dr. BAEHR. Yes; I think that is true of most hospitals that have adopted a drug formulary.

Senator NELSON. Thank you.

Dr. BAEHR. May I say that the Medical Letter has proved to be exceedingly valuable in the education of physicians who have used it. When its publication was started without subsidy by the pharmaceutical houses or advertising, I considered it to be so important that I subscribed through my organization—Health Insurance Plan—to a thousand subscriptions. The Medical Letter has been distributed since that time to a thousand physicians who provide medical services to 780,000 New Yorkers enrolled in the Health Insurance Plan of Greater New York.

Now subscriptions to the Medical Letter have risen to about 20,000, but it still does not reach the vast majority of the medical profession who could profit by it.

Incidentally, I would like to call your attention to the fact that it has been reprinted in several foreign countries, such as England and Holland, where it has been distributd free by the government.

Senator NELSON. Some time earlier when Dr. Faulkner was testifying, I said the circulation was about 15,000.

Counsel corrects me and says that the circulation of the Medical Letter, as he understands it, is now about 35,000 to 40,000.

Dr. BAEHR. The unnecessary prescribing of brand name drugs is fostered by the distribution to physicians of free samples and persuasive literature through thousands of detail men and by hundreds of free magazines published by pharmaceutical firms to encourage the use of their innumerable products. Their use is also encouraged by voluminous advertising in virtually all reputable medical journals. A recent issue of the weekly Journal of the American Medical Association devotes 85 pages to text and 186 pages to such advertisements.

I would like at this point to introduce an exhibit, the Journal of the American Medical Association, November 18, 1968. The lead article, the most conspicuous place in the journal, is given to a paper entitled "The Generic Inequivalence of Drugs." [1]

The drug tolbutamide, which is used in the treatment of diabetes and is sold under the name of Orinase by the Upjohn Co., was tested by an employee of the company. In this article the results of a test on 20 prisoners is reported, which revealed that tolbutamide in the way it is ordinarily sold by the Upjohn Co., is compounded with a gum like substance, so that it holds its form, but also acts as a dispersing agent, so after it reaches the upper gastrointestinal tract it is liberated and can be promptly absorbed.

[1] See article beginning at p. 4071, infra.

When they reduced the gumlike substance, which is inert, to half that amount, the tolbutamide was not dispersed as promptly, and its effect upon the blood sugar of normal prisoners was not as good as with the commercial preparation.

The article is given conspicuous place as the lead article, although it concluded with the statement:

> The ideal criterion for establishment of therapeutic equivalence is trial of comparative efficacy in appropriately disease-afflicted patients. Yet they did not try it in a disease-afflicted patient, but only on 10 normal prisoners. They then admit: This is a concept probably not feasible in the context of today's clinical research methodology and standards of ethical medical research. The medical world is left with drug availability as the present most sensible and feasible way of establishing generic equivalence of drugs.

This article is obviously designed to foster in physician's minds the belief that they cannot depend on generic drugs. In the same issue of the Journal of the American Medical Association there follows an editorial comment on the article by the Upjohn Co., entitled "Generic Drugs and Therapeutic Equivalence." [1] In other words, from this one instance of pseudo scientific research on normal persons, the editorial takes the liberty to generalize about generic drugs and their therapeutic equivalence, and says, "factors which may influence the therapeutic usefulness of a drug even though the preparation contained the stated amount of the active ingredient.

"Unless a preparation has been proven to be as effective as the standardized preparation"—by "standard" they are implying, I believe, a brand-name drug, although it is not so stated. By the use of this form of obscurantism, the idea is being fixed in the practitioner's mind that he better not prescribe generic drugs because they may be unreliable.

The Medical Letter has demonstrated that both kinds of drugs, the brand named and the generic may at times be unreliable due to the method of compounding. It is up to some official agency to determine that all drugs, whether brand name or generic, meet standards of reliability and therapeutic efficiency.

Senator NELSON. I read that article, and I thought it was a most unscientific procedure to write an editorial based on one article.

There are of course, several thousand drugs in the marketplace, and as one doctor commented after reading the article—it was mighty strange that in order to find a case of therapeutic inequivalence, generic inequivalence, they had to manufacture it.

Tolbutamide is in the marketplace under only one name, Orinase. There is no generic, there is no other brand name in the marketplace. So instead of finding one of the thousands of drugs in the marketplace where they could show a drug meeting USP standards that was not equivalent, they had to manufacture an example.

The testimony before this committee by USP and the National Formulary and others is that there are—at the outside—only a half dozen or so proven cases of generic inequivalence when the two drugs compared both met USP standards or National Formulary standards.

Dr. BAEHR. What I also object to is that the employees of Upjohn must have known in advance what they were going to find. The reason

[1] See editorial beginning at p. 4077, infra.

that this inert gum was used in the first place was to get dispersal and prompt release into the gastrointestinal tract and prompt effect on the blood sugar. They must have known in advance what the effect of eliminating the gum substance would be. An editorial to emphasize the general unreliability of generic drugs based on such unscientific research is to be condemned.

Senator NELSON The article and the editorial will be printed at the appropriate place in the record.

Mr. GORDON. Dr. Baehr, may I interrupt here? Isn't this really an illustration of what Dr. Faulkner said before about the danger, possible danger, of relying so heavily on financing by the drug industry? Do you think that this kind of article, this kind of an editorial, would have been written if the American Medical Association had not been so heavily dependent on the drug industry?

Dr. BAEHR. You are right. To be charitable, the least I could say about it, is that it may have been influenced by subconscious bias.

Senator NELSON. Thank you.

Dr. BAEHR. Could I introduce another exhibit at this moment? This is an editorial in the New England Journal of Medicine,[1] which I and many others in our profession regard as one of the most reliable journals published in this country.

It states that:

About 5 percent of all inpatients suffer adverse drug reactions severe enough to cause marked morbidity, prolonged hospitalization, result in permanent sequelae or contribute to a fatal outcome. The risks for outpatients are also considerable, and three to four percent of all admissions to medical service are for pathologic states resulting from drug therapy.

All of us have seen much too serious illness from drugs for which the patient had no real need.

Senator NELSON. Pardon, I did not hear the last sentence.

Dr. BAEHR (reading):

All of us have seen too much serious illness from drugs for which the patient had no real need.

This form of polypharmaceutical prescribing is fostered by advertising through throwaway journals, through articles in these commercial journals, and through wholesale and retail distributors to the medical profession.

Senator NELSON. Yes, sir.

Dr. Frederick Wolff, who is director of research, Washington Hospital Center, and professor of medicine, George Washington University School of Medicine—in his testimony before us, estimated that out of every $10 spent on drugs, in his judgment, $6 was unnecessarily spent.

What, in your experience, would your judgment be as to this statement of Dr. Wolff's or what is your own guess?

Dr. BAEHR. From my own experience with doctors generally, I would say that that is a conservative statement. In the treatment of ambulatory patients outside of a hospital by physicians, the cost of unnecessarily prescribed drugs is probably more than 60 percent.

Senator NELSON. Thank you, Doctor.

Dr. BAEHR. May I continue?

Senator NELSON. Yes, sir.

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[1] See editorial beginning at p. 4078, infra.

Dr. BAEHR. It would be of interest to you to know that some years ago I was approached by the head of a pharmaceutical drug-testing institute with an offer of an appointment as editor in chief of a new journal designed to enable physicians testing new drugs to secure prompt publication of reports of their therapeutic experiences. I was to receive 15 percent of the profit for the use of my name and two associate editors were each to receive 10 percent in return for doing all the editorial work. The new journal, I was told, would take no advertising and would not receive any subsidy from the pharmaceutical industry. I was assured that the venture would nevertheless be extremely profitable and I could expect a substantial income.

Upon inquiring about the mysterious source of such income, I was informed it would come from the purchase of reprints by firms whose drugs were favorably mentioned in the published articles. There was much money to be made from the sale of reprints by the hundreds of thousands for mailing by the drug manufacturers to physicians throughout the country. I rejected the humiliating proposal and the new journal never saw the light of day.

The New England Journal of Medicine, and some of the house journals published by good teaching hospitals, will not sell more than a limited number of reprints for distribution by the authors to scientists and physicians who ask for them. They reject orders from pharmaceutical firms for tens or hundreds of thousands of reprints because it is obvious that this is intended to promote the commercial sale of the product.

Mr. GORDON. Dr. Baehr, may I ask one question here? I noticed that several of the throwaways have names of well-known physicians on the masthead "as members of their advisory boards." I put this in quotation marks.

Is it your impression that these names are used for purposes of impressing the readers or do these people on the advisory board perform a real service?

Dr. BAEHR. To some extent. I think most members of the editorial board wish to keep the text educationally useful. They have as little to do with the advertising material in such throwaways as with the advertisements accepted by the reputable scientific journals. They scrutinize the text in their various special fields of expertise so as to make it as far as possible a valuable educational publication.

I would like to introduce at this point a letter which I addressed to Dr. Philip R. Lee on November 27, 1968, in response to his inquiry, which was also commented upon by Dr. Faulkner. The letter may be of interest to the Senate Committee.

Senator NELSON. That letter will be printed in full in the record.[1]

Dr. BAEHR. In that letter I point out the experience of the Health Insurance Plan of Greater New York, which is one of the questions that you wished me to comment upon. Could I read that part of the letter?

Senator NELSON. Yes, sir.

Dr. BAEHR (reading):

The Health Insurance Plan of Greater New York has included prescription drugs as a benefit since January 1, 1967, in the form of a rider to its basic con-

[1] See letter beginning at p. 4079, infra.

tract. Approximately 120,000 persons out of our total enrollment of 780,000 are presently covered by the drug rider. Covered enrollees may have their prescriptions filled in any licensed community pharmacy, in which case they are subject to a $25 annual deductible and 20 percent coinsurance, or they may have their prescriptions filled by mail through a nonprofit HIP-operated pharmacy, in which case there is no charge whatever.

The drugs dispensed by the central pharmacy are purchased either directly from manufacturers or through intermediary distributors and their efficacy and reliability are passed upon by a committee of experts in pharmacology and therapeutics.

About one-third of the subscribers have thus far used the mail-order route. The monthly premium for the drug rider is $0.98 for a single person, $1.96 for a couple, and $2.94 for a family of three or more persons. The premium would be much less if all prescriptions were dispensed by our own local outlets.

This cannot be done without the cooperation of local pharmacists. and they will not cooperate in this manner.

A prepaid drug benefit is especially important for the medicare population. As your Department has observed, annual expenditures per person for prescribed drugs for persons 65 and over, amount to over $40, compared to about $15 per persons of all ages. (U.S. Department of Health, Education, and Welfare, National Center for Health Statistics, series 10, No. 39.)

Because drug costs for the elderly are so high, it is imperative to take full advantage of all possible means to keep costs to a minimum while maintaining control over quality. Based on our experience, which admittedly is as yet relatively limited, the following suggestions are offered for your consideration——

Do you wish me to read this or should we leave it for the record?

Senator NELSON. Whichever you desire. It will be printed in the record in full. If there is something you wish to emphasize in it you may proceed to do so.

Dr. BAEHR. The only thing that I would like to emphasize is what has already been stated by Dr. Faulkner.

As in many hospitals, the use of a formulary which emphasizes the prescribing of generic drugs is, of course, the major means of reducing costs. Also central pharmacies can assure the physician of quality controls of generic as well as brand-name products.

For the mail-order delivery, special prescription blanks may be supplied on which the doctor may indicate by a checkmark or initial that the dispensing of a reliable generic equivalent is permissible. This has been done through mail order by the Association of Retired Persons in Washington, D.C., for quite a long time. They have been filling prescriptions for years for retired persons living all over the United States, and the distribution would, under different circumstances with local distributors, be feasible for all medicare and medicaid beneficiaries if regional facilities were used.

This suggestion is offered for reducing the cost and maintaining standards of quality under the medicare and medicaid programs.

A statewide association of retail pharmacists in New York endeavored to interfere with the HIP drug program described in the letter to Dr. Lee by having a bill introduced in the 1968 session of the New York State Legislature which would amend article IX–C of the State insurance law governing the operation of nonprofit health insurance plans. The amendment would remove a provision of the law which had, for more than 20 years, authorized a nonprofit, comprehensive prepayment plan to include drugs as a benefit in its comprehensive health insurance coverage. In spite of the efforts of a powerful lobby of the

retail pharmacists, the bill failed to pass. The pharmacists then sought an injunction which was denied by the courts. Efforts to eliminate HIP's endeavors to control the quality and the cost of prescription drugs required by its beneficiaries will probably be renewed when the State legislature reconvenes next month.

Senator NELSON. Thank you, Doctor.

I neglected a few moments back, when you were commenting on the use of generic drugs in the hospital formulary, to ask Dr. Faulkner to comment on that.

Dr. Faulkner, you were dean at Boston University—with what hospital is Boston University associated?

Dr. FAULKNER. It is now called the University Hospital. We have our own formulary there with a pharmacy committee very much like the setup which Dr. Baehr described.

Senator NELSON. Historically, when did hospitals in this country begin establishing formulary committees which initiated this practice of using both brand- and generic-name drugs? How recent is that?

Dr. BAEHR. I should say it is about 8 or 10 years. I think as far as I recall perhaps the first one was the New York Hospital at Cornell University, and then other hospitals followed along, good teaching hospitals—and controls over quality and great savings in cost.

Senator NELSON. What is your experience in the hospitals you have been in on this issue, Dr. Faulkner?

Dr. FAULKNER. Well, I think the Massachusetts General Hospital, where I had my internship, already had a formulary there. But, as Dr. Baehr pointed out, in those days there were not very many brand name drugs. It was mostly digitalis, and we generally, naturally, used generic drugs and very seldom prescribed a brand name.

Senator NELSON. What has been your experience in recent years with the use of generic drugs in the hospital formularies in the hospitals with which you have been associated?

Dr. FAULKNER. Well, actually I have not been closely associated with the clinical aspects of hospitals enough to really be able to answer that question.

Mr. GORDON. I would like to ask you about throwaways once again.

Do you consider that these throwaways we were discussing constitute a threat to the circulation of distinguished educational journals such as the New England Journal of Medicine?

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

Mr. GORDON. Do you think that these throwaways are really important in influencing the average practicing physician?

Dr. FAULKNER. Yes, I think they do. I think it partly is because there is not any counterpoise of factual information about new drugs to balance out the information they get through the throwaway journals.

Senator NELSON. I want to thank you, Dr. Baehr, and you, Dr. Faulkner, for your very thoughtful and useful contribution to these hearings. The committee appreciates your taking the time to come here very much.

We will adjourn until sometime in January.

(The complete prepared statement and supplemental information submitted by Dr. Baehr follows:)

STATEMENT OF DR. GEORGE BAEHR

I am Dr. George Baehr of New York, a physician engaged in the practice of medicine and medical education. I am Chairman of the Public Health Council of the State of New York, a member of the Board of Hospitals of the City of New York, and hold the rank of Distinguished Service Professor at the Mount Sinai School of Medicine of the City University of New York. I have formerly been President of the New York Academy of Medicine, Vice President of the American Public Health Association, Director of Medicine and of Clinical Research at the Mount Sinai Hospital, New York, and Clinical Professor of Medicine at the College of Physicians and Surgeons of Columbia University. I was at one time President and Medical Director of the Health Insurance Plan of Greater New York, now providing more than 780,000 persons in the New York area with prepaid comprehensive medical care.

I should like to emphasize that I am testifying as an individual and not as a representative of any of the organizations or agencies with which I am or have been associated.

During many years of practice, I have served as consultant to many local physicians and have been bewildered by the enormous number and variety of brand-named drugs which they prescribe. What has been derisively called polypharmacy is almost the rule.

The prescribing of expensive brand-named drugs to the exclusion of their generic equivalents has been fostered by the pharmaceutical industry through its 15,000 or more detail men who visit physicians' offices and by retail pharmacists. Both have been spreading the false gospel that generic preparations are unreliable and that brand names are a guarantee of reliability.

There are retail druggists in New York who do not stock any generic drugs on the excuse that they are unreliable. A New York State law, quite properly, forbids a druggist to dispense a generic equivalent when the physician specifies a brand-named preparation. Paradoxically, however, the State law permits a druggist to substitute a brand-named drug when a generic drug is specifically prescribed by the physician—although it may mean ten times the retail price and ten times the mark-up profit to the druggist. When the physician specifies a generic drug, neither he nor his patient is protected from substitution.

Actually, the consultant experts of *The Medical Letter* have made a comparative study of some of the most frequently used drugs purchased under their brand names and under their generic equivalents. They found that the brand name is not a guarantee that the preparation meets required U.S. Pharmacopeial standards.

The unnecessary prescribing of brand-named drugs is fostered by the distribution to physicians of free samples and persuasive literature through thousands of detail men and by hundreds of free magazines published by pharmaceutical firms to encourage the use of their innumerable products. Their use is also encouraged by voluminous advertising in virtually all reputable medical journals. A recent issue of the weekly *Journal of the American Medical Association* devotes 85 pages to text and 186 pages to such advertisements.

Some years ago, I was approached by the head of a pharmaceutical drug-testing institute with an offer of the editor-in-chief of a new journal designed to enable physicians testing new drugs to secure prompt publication of reports of their therapeutic experiences. I was to receive 15 per cent of the profit for the use of my name and two associate editors were each to receive 10 per cent in return for doing all the editorial work. The new journal would take no advertising and would not receive any subsidy from the pharmaceutical industry. I was assured that the venture would nevertheless be extremely profitable and I could expect a substantial income.

Upon inquiring about the mysterious source of such income, I was informed it would come from the purchase of reprints by firms whose drugs were favorably mentioned in the published articles. There was much money to be made from the sale of reprints by the hundreds of thousands for mailing by drug manufacturers to physicians throughout the country. I rejected the humiliating proposal and the new journal never saw the light of day.

Herewith is a letter which I addressed to Dr. Philip H. Lee on November 27, 1968, in response to his query. It may be of interest to the Senate Committee.

A State-wide association of retail pharmacists endeavored to interfere with the HIP drug program described in the letter to Dr. Lee by having a bill introduced in the 1968 session of the New York State Legislature which would amend

Article IX–C of the State Insurance Law governing the operation of nonprofit health insurance plans. The amendment would remove a provision of the law which had, for more than 20 years, authorized a nonprofit, comprehensive prepayment plan to include drugs as a benefit in its comprehensive health insurance coverage. In spite of the efforts of a powerful lobby of the retail pharmacists, the bill failed to pass. The pharmacists then sought an injunction which was denied by the courts. The threat to HIP endeavor's to control the quality and the cost of prescription drugs required by its beneficiaries will probably be renewed when the State Legislature reconvenes next month.

As members of the Senate Committee are aware, most good hospitals have adopted a hospital drug formulary and have entered into an agreement with their medical staff to prescribe under the generic terminology as far as reasonably possible. The agreement permits the hospital pharmacy to dispense equivalent generic preparations if a physician can only remember a brand name, provided the generic equivalent meets the required standards of the U.S. Pharmacopeia and of the hospital's own committee on drugs. If a staff physician actually wishes the brand-named preparation to be dispensed, it is provided without question. In this manner, hospitals have reduced their annual drug bills 50 per cent and have exercised control over quality standards.

[From the Journal of the American Medical Association, vol. 206, No. 8, Nov. 18, 1968]

THE GENERIC INEQUIVALENCE OF DRUGS

(By Alan B. Varley, M.D.*)

Generic equivalence of drugs is a semantically muddled concept. To be meaningful, the criteria for equivalence must be stated. In this simple study, two different formulations of tolbutamide, both generally equivalent in terms of chemical content and specifications of the *United States Pharamacopeia*, were found to be clearly not equivalent as measured by availability of drug to the patient (serum drug levels or therapeutic efficacy (hypoglycemic response. Clarity in pronouncements on this subject should be established so that confusion in terminology and meaning does not lead to "generic inequivalence" of therapeutic response.

In the past several years, much has been written both in the lay and the technical press regarding the concept of generic equivalence of drugs. The purpose of reporting this simple but tightly controlled clinical study is to illustrate the belief that just as some drug formulations are generically "equivalent," some are also generically "inequivalent" and, thus, the term "generic equivalence" badly needs better definition or abandonment.

The physician's researchers, or lawmaker's usual reference to generically equivalent drugs is in terms of expected pharmacologic or therapeutic effect in the human patient. The usual criterion for establishing this equivalence, however, is the amount of bulk chemical in the commercial drug or the specifications of the *United States Pharmacopeia* (USP) for the chemical and physical characteristics of the formulation or both.

It is the purpose of this study to demonstrate that this simplistic notion is *not* satisfactory for establishing criteria for generically equivalent drugs if equivalent therapeutic results are intended and expected.

For the purposes of this communication, three different types of genric equivalence are discussed:

1. Chemical Equivalence.—Drugs considered chemically equivalent have the prescribed amount of drug chemical in a prescribed stable condition and meet USP specifications for chemical and physical characteristics.

2. Availability Equivalence.—In addition to being chemically or USP-equivalent, the formulation must also insure that equivalent amounts of the drugs are delivered *to the patient*, as measured most frequently by serum drug levels. Availability equivalence presumes that equal amounts of drug absorbed from the site of administration to the circulating blood (as demonstrated by serum levels) will indeed have similar or identical therapeutic effects.

3. Therapeutic Equivalence.—Criteria for this level of equivalence require that therapeutic or clinical effects of the drug, as seen and measured in the human

*From the Department of Clinical Pharmacology, the Upjohn Co., Kalamazoo, Mich. Reprint requests to 7171 Portage Rd., Kalamazoo, Mich. 49001 (Dr. Varley).

patient, are also equivalent. This is obviously the acid test of drug equivalence and one which, though ideal, is not generally easy to quickly establish, considering our presnt clinical tools for measuremnt of therapeutic effectiveness and the ethical constraints in establishing such proof in sick human patients.

It is the contention of this communication that chemically equivalent drugs are not necessarily equally available to the patient or therapeutically equivalent in the patient.

MATERIALS AND METHODS

Inasmuch as therapeutic effectiveness is the most difficult aspect to simply and accurately monitor, it was decided to test this hypothesis with use of an orally administered hypoglycemic agent as the test drug variable and to accept laboratory demonstration of chemical hypoglycemia as evidence of clinical "therapeutic" efficacy. It is our belief that hypoglycemia is generally accepted by physicians as evidence of therapeutic effect. Inasmuch as a dependable and accurate assay method is available for measurement of tolbutamide serum levels (drug availability) and a historical experience in pharmacy technique has been developed with this agent, tolbutamide (Orinase) was selected as the particular test drug.

In this study, we have considered only this question: Does "generic" chemical equivalence guarantee simultaneous availability and therapeutic equivalence?

Our pharmacy department was asked to prepare two lots of tolbutamide tablets, both containing 0.5 gm of the chemical and both meeting USP specifications but which, based upon past pharmacy formulation experience, might be expected to behave very differently in the human patient. Two formulations were delivered: one taken from a commercial production lot (Orinase) and the other identical in all composition and manufacturing respects except for a halving of the amount of the disintegrant (Vee Gum). This single and seemingly minor pharmacy change did effect an increase in both the disintegration time (commercial, two minutes; experimental 7.6 minutes) and dissolution rate (commercial, 3.8 minutes; experimental, 103 minutes) of the tablets, although blood formulations meet completely the tolbutamide specifications of the USP and, therefore, meet our criteria for *chemical* equivalence.

A double-blind, crossover clinical study was arranged in which ten healthy, nondiabetic, volunteer subjects at the Southern Michigan State Prison at Jackson received both formulations of drug. The group of ten was randomly assigned into two groups of five subjects each. After prestudy physical examination and laboratory work-up demonstrated absence of disease and suitability for study, a zero-hour blood sample was drawn and each subject in each group received 1 gm (two 0.5-gm tablets) of one of the two test medications. Blood samples for glucose and drug assay were drawn at 1½, 3, 5, and 8 hours after drug administration. All subjects remained fasting from midnight preceding drug ingestion until the collection of the last eight-hour blood sample. The study was repeated one week later under identical conditions with the test medication crossed over and assigned to the opposite group. All subjects, therefore, received both test medications in a blind, randomly assigned, crossover fashion over the eight-day study period.

A 15-cc sample of blood was drawn at the indicated times after drug administration. The specimen was promptly centrifuged, and the serum separated into two aliquots and frozen immediately. One aliquot was sent to our Clinical Research Laboratory in Kalamazoo, Mich., for determination of blood glucose values by the Somogyi-Nelson method.[1] The second frozen aliquot was sent to the Huffman Laboratories, Inc., in Wheatridge, Colo., for determination of serum tolbutamide levels by the Toolan-Wagner method.[2] Results were submitted to me under code label, and the data were analyzed before the formulation identification was decoded.

RESULTS

The study was completed as described. The serum glucose and drug levels after medication are presented in Tables 1 and 2 and summarized graphically in Figs. 1 and 2.

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[1] Hoffman, W. S.: Rapid Photoelectric Method for Determination of Glucose in Blood and Urine, *J. Biol. Chem.* 120:51–55 (Aug.) 1937.

[2] Toolan, T. J., and Wagner, R. L., Jr.: The Physical Properties of Chlorpropamide and Its Determination in Human Serum, *Ann. N.Y. Acad. Sci.* 74:449–458 (March 30) 1959.

1. Serum tolbutamide levels after administration of commercial tolbutamide (Orinase) and experimental drug. Results were achieved in a carefully controlled, two-way crossover study in ten normal adult volunteers.

2. Serum glucose levels after administration of commercial tolbutamide (Orinase; drug A) and experimental drug (B). Results were achieved in a carefully controlled, two-way crossover study in ten normal adult volunteers.

TABLE 1.—SERUM GLUCOSE LEVELS (MG./100 ML.)

Subject No.	Day	Hour 0	1½	3	5	8
Group 73–BA: Experimental formulation:						
1	1	82.0	82.0	82.0	72.0	75.0
5	1	72.0	74.0	75.0	64.0	72.0
6	1	73.0	75.0	75.0	70.0	76.0
7	1	76.0	81.0	82.0	75.0	82.0
9	1	82.0	84.0	81.0	74.0	78.0
2	8	83.0	72.0	75.0	78.0	78.0
3	8	78.0	67.0	71.0	78.0	81.0
4	8	83.0	74.0	74.0	81.0	85.0
8	8	85.0	77.0	76.0	80.0	81.0
10	8	77.0	70.0	70.0	75.0	71.0
Average		79.1	75.6	76.1	74.7	77.9
Group 74–BA: Commercial tolbutamide (Orinase):						
2	1	73.0	61.0	75.0	68.0	73.0
3	1	75.0	70.0	75.0	73.0	76.0
4	1	81.0	79.0	77.0	72.0	80.0
8	1	81.0	78.0	80.0	91.0	85.0
10	1	70.0	65.0	70.0	68.0	69.0
1	8	83.0	66.0	64.0	73.0	77.0
5	8	74.0	54.0	61.0	68.0	76.0
6	8	82.0	52.0	60.0	77.0	79.0
7	8	82.0	64.0	71.0	78.0	87.0
9	8	86.0	62.0	69.0	80.0	83.0
Average		78.7	65.1	70.2	74.8	78.5

TABLE 2.—SERUM TOLBUTAMIDE LEVELS (MG./ML.)

Subject No.	Day	Hour 1½	3	5	8
Group 73–BA: Experimental formulation:					
1	1	0.017	0.011	0.027	0.033
5	1	.006	.005	.010	.017
6	1	.019	.024	.027	.027
7	1	.011	.018	.021	.020
9	1	.009	.016	.019	.016
2	8	.009	.012	.016	.019
3	8	.008	.014	.014	.018
4	8	.013	.023	.025	.031
8	8	.019	.027	.032	.031
10	8	.006	.013	.010	.031
Average		.0117	.0163	.0201	.0243
Group 74–BA: Commercial tolbutamide (Orinase):					
2	1	.070	.074	.070	.064
3	1	.074	.060	.088	.035
4	1	.013	.057	.110	.083
8	1	.062	.083	.064	.051
10	1	.053	.065	.060	.945
1	8	.051	.071	.062	.059
5	8	.060	.058	.050	.037
6	8	.078	.094	.067	.059
7	8	.067	.063	.054	.042
9	8	.073	.089	.077	.064
Average		.0601	.0714	.0702	.0539

Inspection of the data makes it quickly apparent that significant differences are present both in terms of drug availability (as measured by serum drug levels) and efficacy (as measured by serum glucose levels). The experimental formulation, which as stated before, contains an identical amount of drug and meets all USP specifications, is statistically (and perhaps even more important, clinically) inferior to commercial tolbutamide measured both as drug available and by hypoglycemic effect. (In reviewing the hypoglycemic response, it is important to keep in mind that these subjects are nondiabetic, presumably normal adults with mean control glucose levels of 78.7 and 79.1 mg per 100 ml after fasting. The magnitude of hypoglycemic response cannot be expected to parallel results

obtained in hyperglycemic patients, though, as can be seen, it is a valuable method in distinguishing the hypoglycemia-inducing potency of two or more drugs.)

Serum Tolbutamide Levels.—Every subject, at each sampling time, had a higher serum drug level after receiving the commercial lot of tolbutamide than after receiving the experimentally contrived, but USP-equivalent, formulation.

At each sampling time, the group difference between average serum tolbutamide levels was highly significant ($P < 0.001$, based upon analysis of variance for crossover design).

The area under the average serum drug curves over the eight-hour period was 3.57 times greater with commercial tolbutamide than with the experimental formulation, as follows:

$$\frac{47.1}{13.2} = 3.57.$$

Serum Glucose Levels.—The average zero-hour blood glucose levels after fasting for the two groups were 78.7 and 79.1 mg per 100 ml. These averages do not differ statistically ($P > 0.25$).

The differences between the average serum glucose levels at the five-hour (74.8 and 74.7 mg per 100 ml) and the eight-hour (78.5 and 77.9 mg per 100 ml) sampling times also are not different statistically ($P > 0.25$).

However, at the 1½- and 3-hour sampling intervals, the difference between average serum glucose levels with the two formulations differed markedly. At 1½ hours (65.1 and 75.6 mg per 100 ml) and at 3 hours (70.2 and 76.1 mg per 100 ml) differences between average serum glucose levels of commercial tolbutamide and the experimental formulation were highly significant ($P < 0.001$, based upon analysis of variance for crossover design).

The area under the curve for the average serum glucose level over the eight-hour period was 2.09 times higher (less glucose) for commercial tolbutamide than for the experimental formulation, as follows:

$$\frac{45.0}{21.5} = 2.09.$$

COMMENT

Statements such as the following have been made with some regularity of late: "There have been probably fewer than five well-conducted, clinically acceptable studies which have demonstrated significant difference between two or more products clinically where they have met all the chemical and physical standards as provided by the official compendia."

It is believed that the presented data will help establish the error in the implication that clinical differences between generically equivalent drugs are, therefore, rare and not important. Criticisms of this study can be raised insisting that the experimental formulation was not a "product," that clinical differences cannot be established in nondiseased patients, that the study was not large or small enough, or is not in one way or another completely acceptable to the objector. The fact remains that it *is* clearly possible to produce considerable differences in both availability of drug to the human patient and in eventual therapeutic usefulness by making tiny changes in the formulation which are clearly within present USP chemical equivalence standards.

It is not my contention that generic, therapeutically equivalent drugs cannot be formulated. Quite to the contrary. It is my contention that criteria for establishment of equivalence cannot be made by chemical and physical standards as they are now established in the USP, unless one is not interested in the patient's therapeutic response which concerns most physicians.

Without question, the ideal criterion for establishment of therapeutic equivalence is trial of comparative efficacy in appropriately disease-afflicted patients. While not within the scope of data presented in this communication, this is a concept probably not feasible in the context of today's clinical research methodology and standards of ethical medical research. Inasmuch as chemical or USP-type specifications are clearly not a satisfactory answer, the medical world is left with drug availability as the present most sensible and feasible way of establishing generic equivalence of drugs.

GENERIC AND TRADE NAMES OF DRUG

Tolbutamide—*Orinase.*

[From the Journal of the American Medical Association, vol. 206, No. 8, Nov. 18, 1968]
(Editorial)

Generic Drugs and Therapeutic Equivalence

In recent years, there has developed the belief that nonproprietary or generic drugs are much cheaper than, and as effective as, trade-named items. This belief has led to a widespread demand that prescribing and use of generic drugs be encouraged. Studies conducted by impartial groups such as the *Medical Letter on Drugs and Therapeutics* have applied United States Pharmacopeial methods to assay certain drugs prepared by many different manufacturers.[1-3] These analyses have shown that, generally, these preparations are chemically equivalent in that they contain the amount of drug claimed. These findings have led many to the conclusion that drugs prepared by various manufacturers should be equally effective in therapy. While this seems to be true in many instances, there are situations where this is not so.

For some time, workers in the pharmaceutical field have been compiling a list of factors which may influence the therapeutic usefulness of a drug even though the preparation contained the stated amount of the active ingredient. The list includes appearance, taste, availability for absorption, solubility of the dosage form, effect of other ingredients, binders, pH, particle size, stability, age of the preparation, compression of the tablet, and thickness and type of enteric coating. All these factors have been shown to influence the therapeutic efficacy of drugs.

Recently interest has focused on the purity of drugs. For example, even a "pure" commercially available preparation of penicillin G was found to harbor impurities capable of causing allergic reactions. When the preparation was further purified it could be given to some individuals who were previously allergic to it.[4] Apparently, the allergen came from the fermentation process, and minute traces remained with the penicillin. This information raises questions about the present method of handling penicillin. For example, the United States Pharmacopeia requires penicillin G preparations to contain at least 85% of penicillin G. Commercially available penicillin G from reputable manufacturers contain 98% or more of penicillin G. It is reasonable to suspect that the less-pure preparation may contain more of these sensitizing allergens and that some reactions thought to be caused by the penicillin molecule may actually be caused by contaminating allergens. Thus a cheaper, less-pure penicillin may not be cheaper as far as the patient is concerned, should he manifest a serious reaction to the contaminant. How extensive this problem may be remains to be seen. Certainly, it points out the desirability of etting as pure a preparation of penicillin as possible.

A communication by Varley (p 1745) stresses the importance of the slightest alteration in ingredients in affecting the therapeutic efficacy of the drug. The halving of an inert binding gum in tolbutamide tablets, prepared to contain the same amount of tolbutamide as the commercially available tablet, resulted in a serious lowering in the level of the drug absorbed and in a consequent reduced ability to lower blood glucose. This points out the necessity by making sure by measuring patients' blood levels or by adequate therapeutic testing that a drug preparation varying in any way from one performing satisfactorily is also capable of doing what is claimed for it.

It is important that we demand the highest purity for our drugs. Unless a preparation has been proven to be as effective as the standardized preparation, it should be considered as a possible source of therapeutic nonequivalence. Where a drug may be critical to the proper treatment of a disease, physicians should make certain that it has not only chemical equivalence but also therapeutic or at least blood-level equivalence.

Dale G. Friend, M.D.,
Boston.

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[1] Tests of Diethylstilbestrol Tablets, Med Lett Drugs Ther 4:15–16 (Feb 16) 1962.
[2] Chlorpheniramine Maleate Tablets, *Med Lett Drugs Ther* 7:18–19 (Feb 26) 1965.
[3] Tests of Prednisone Tablets, *Med Lett Drugs Ther* 9:41–43 (June 2) 1967.
[4] Stewart, G. T.: Allergenic Residues in Penicillin, *Lancet* 1:1177–1183 (June 3) 1967.

[From the New England Journal of Medicine, vol. 279, No. 23, Dec. 5, 1968]

(Editorial)

Disease Drugs Cause

Three articles in this issue of the *Journal** describing noxious effects of therapeutic or diagnostic chemicals once again point up this vexing problem. Although most of the sick benefit from their contact with the treasure chest of modern pharmacotherapy, the experience is unhappy for too many. Several recent studies have quantitated drug-related morbidity, sequelae and mortality in hospitalized patients.[1-3] About 5 percent of all inpatients suffer adverse drug reactions severe enough to cause marked morbidity, prolong hospitalization, result in permanent sequelae or contribute to a fatal outcome. The risks for outpatients are also considerable, and 3 to 4 percent of all admissions to a medical service are for pathologic states resulting from drug therapy.

No matter how skillfully used, a drug that helps anyone will occasionally harm someone. Some adverse reactions to drugs are the price of progress in effective drug therapy. Regrettably, however, today's sum total of drug-induced disease greatly exceeds the irreducible minimum. Many untoward consequences of drug therapy could easily be avoided, and others would become evitable if carefully studied and reported. The challenge to the medical profession is pressing. Adverse drug reactions can and must be minimized through improved recognition, investigation and awareness of these events.

It is not easy to recognize a previously unsuspected causal relation between a drug and an untoward change in a patient's course. The difficulty is compounded when the drug rarely causes the adverse reaction and when the reaction is a common clinical event usually occurring from nondrug causes. The adverse reactions related to pharmacologic actions of drugs can generally be predicted from animal testing, but such testing is unrevealing about the most important reactions that have immunologic or idiosyncratic mechanisms specific to man. Much of the adverse potential of a drug in man can be defined during its early clinical testing, but the number of subjects exposed is small and only a happy accident would lead to the discovery of a rare reaction. The same problem is encountered by studies prospectively surveying limited populations for adverse reactions to widely used drugs.

Only the population at risk during general clinical use is large enough for uncommon drug-induced diseases to display themselves. Thus, the practicing physician becomes a key figure.[4] Knowledge of new drug-induced diseases has always come primarily from practitioners who observed their patients with a discerning and open mind and who were willing to report their observations. Unfortunately, some suppress their suspicions by asking an inapt question ("Has this drug caused such trouble before?") instead of relying on their clinical judgment and realizing that some report must always be the first. Others fear that a patient's drug-induced disease reflects unfavorably on his physician—an unreasonable concern if the drug was prescribed appropriately.

Most initial reports of a suspicious association between drug and disease cannot prove a causal relation. Repeated reports are required to harden the suspicion. Suspected new adverse reactions of clinical importance should be described promptly in the medical literature to alert other physicians and to induce them to report their observations. Other reports can be directed to hospital drug committees, medical associations, drug manufacturers or the Food and Drug Administration. Systematic nationwide and international collation of such communications is essential to translate them quickly into effective warnings and is now being attempted. Such programs must not be clogged by myriad meaningless reports of well known, minor, accepted side effects of drug therapy.[5]

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*Articles appear as appendixes I, II, and III, pp. 4174B–94, infra.

[1] MacDonald, M. G., and MacKay, R. R. Adverse drug reactions: experience of Mary Fletcher Hospital during 1962. *J.A.M.A.* 190:1071–1074, 1964.

[2] Seidl, L. G., Thornton, G. F., Smith, J. W., and Cluff, L. E. Studies on epidemiology of adverse drug reactions. III. Reactions in patients on general medical service. *Bull. Johns Hopkins Hosp.* 119:299–315, 1966.

[3] Ogilvie, R. I., and Ruedy, J. Adverse drug reactions during hospitalization. *Canad. M.A.J.* 97:1450–1457, 1967.

[4] Koch-Weser, J., Sidel, V. W., Sweet, R., Kanarek, P., and Eaton, A. Factors determining physician reporting of adverse reactions. *New Eng. J. Med.* (in press).

[5] Koch-Weser, J. Definition and classification of adverse drug reactions. *Drug Information Bull.* 2:72–78, 1968.

Qualitative and quantitative investigation of drug-induced disease is also urgently needed. Since experimental reproduction of serious drug reactions is rarely feasible, each such event deserves careful study with all appropriate technics to elucidate its mechanism and all contributing factors. Much remains to be learned about the prevalence of adverse reactions to individual drugs. Such quantitative knowledge of specific risks is one prerequisite of proficient pharmacotherapy. Risk figures should take into account such factors as age, sex, genetic characteristics, pathologic states and concomitant therapy with other drugs. All this requires carefully planned studies relating drug reactions to drug usage and characterizing the populations studied.

Most importantly we should be more constantly aware of the noxious potential of drugs. Drug usage and adverse reactions would surely decrease if every drug not clearly indicated were to be considered contraindicated. Before prescribing any drug, we should weigh the need for pharmacotherapy and consider the benefit-risk ratio of the drug in question and of therapeutically equivalent agents. All of us have seen too much serious illness from drugs for which the patient had no real need. Another urgent task is the creation of a foolproof system warning physicians of serious drug reactions suffered by their patients in the past. Finally, medical-school and postgraduate education in clinical pharmacology must be expanded. Much disease caused by drugs could be prevented if all physicians were conversant with factors influencing the metabolic disposition of drugs, with modification of drug action by disease and with dangerous interactions between drugs. Greater familiarity with all features of drug-induced syndromes would make for more timely diagnosis. Nobody can remember all important information about all of today's drugs, but each of us should know every drug he prescribes.

NOVEMBER 27, 1968.

Dr. PHILIP R. LEE,
Assistant Secretary for Health and Scientific Affairs, Department of Health, Education, and Welfare, Washington, D.C.

DEAR DR. LEE: This is in respect to your letter of November 7, 1968 referring to the Task Force established in May, 1967 to examine the possibility of including the cost of out-of-hospital prescription drugs as a Medicare benefit.

The Health Insurance Plan of Greater New York has included prescription drugs as a benefit since January 1, 1967 in the form of a rider to its basic contract. Approximately 120,000 persons out of our total enrollment of 780,000 are presently covered by the drug rider. Covered enrollees may have their prescriptions filled in any licensed community pharmacy, in which case they are subject to a $25.00 annual deductible and 20% co-insurance, or they may have their prescriptions filled by mail through an HIP operated pharmacy, in which case there is no charge. About one-third have thus far used the mail order route. The monthly premium for the drug rider is $.98 for a single person, $1.96 for a couple and $2.94 for a family of three or more persons. The premium would be much less if all prescriptions were dispensed by our own local outlets.

A prepaid drug benefit is important for the Medicare population. As your Department has observed, annual expenditures per person for prescribed drugs for persons 65 and over, amount to over $40.00, compared to about $15.00 for persons of all ages. (U.S. Department of Health, Education, and Welfare, National Center for Health Statistics, Series 10, Number 39.)

Because drug costs for the elderly are so high, it is imperative to take full advantage of all possible means to keep costs to a minimum while maintaining control over quality. Based on our experience, which admittedly is as yet relatively limited, the following suggestions are offered for your consideration:

1. In addition to community pharmacies, use regional mail order facilities as a yardstick with which to control costs and quality. As you doubtless know, the Association for Retired Persons in Washington, D. C. has been filling prescriptions for years for retired persons living all over the United States. This method of distribution would be feasible for all Medicare and Medicaid beneficiaries if regional facilities were used. As you are well aware, a regional mail order facility offers substantial economies because it permits mass purchasing and quality standards.

2. A substantial proportion of the prescription drugs required by persons over 65 are maintenance drugs which lend themselves very well to a mail order

operation. Regional mail order facilities should take care of a much larger share of prescription drugs required by Medicare recipients than by HIP's overall New York City experience with a population of all ages.

3. Some restrictions should be placed upon the quantities of drugs dispensed at one filling. In our experience, doctors tend to write for larger quantities when there is no cost to the patients. This seems to be particularly true when prescriptions are to be filled by mail. For this reason, Medicare prescriptions should not be honored for more than a 30-day supply, whether filled in a community pharmacy or through a mail order facility, with a few specified exceptions.

4. As in many hospitals, the use of a formulary which emphasizes the prescribing of generic drugs is, of course, a major means of reducing costs. Also, use of central pharmacies can assure the physicians of quality controls of generic as well as of brand-named products.

5. For mail order delivery, special prescription blanks may be supplied on which the doctor may indicate, by a check mark or initial, that the dispensing of a reliable generic equivalent is permissible.

Sincerely,

GEORGE BAEHR, M.D.

(Whereupon at 11:45 a.m., the committee adjourned, subject to the call of the Chair.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

THURSDAY, JANUARY 23, 1969

U. S. SENATE,
MONOPOLY SUBCOMMITTEE OF THE
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C.

The subcommittee met, pursuant to notice, at 10 a.m., in the caucus room, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senators Nelson and Hatfield.

Also present: Chester H. Smith, staff director and general counsel; Benjamin Gordon, staff economist; and Elaine C. Dye, research assistant.

Senator NELSON. We will resume the hearings of the Monopoly Subcommittee. Our two distinguished witnesses this morning are Dr. Frank J. Ayd, Jr., psychiatrist in private practice in Baltimore, Md., and Dr. Clinton S. McGill, internist in private practice in Portland, Oreg.

There is on the floor of the Senate an agreed time limitation for debate on the appointment of the Secretary of the Interior which starts at 11 o'clock. At some stage thereafter I may have to recess to go to the floor to make some remarks. I would hope that we would be able to finish with our two witnesses before then.

The two witnesses this morning are physicians in private practice, both of whom have requested the opportunity to come before the subcommittee. Repeatedly these hearings have been attacked by the Pharmaceutical Manufacturers Association, and by others, on the grounds that they are not balanced hearings.

I would like to state the policy that we have pursued from the beginning. Since there are almost unlimited numbers of witnesses who would like to be heard and since it is not possible to hear all the witnesses at once, we have attempted to establish a policy, which I think is fair.

First, it is the policy of the committee to hear every viewpoint on any of the matters that are raised before this committee.

It is the policy of the hearings to give the first opportunity to the drug industry itself, since it is the industry whose business is being discussed here. We have stated publicly on numerous occasions that our first priority is to the industry. I do not know of anybody who would think that that is unfair, unless some of the critics of the industry might consider it unfair. We have invited all the major drug companies to appear before the committee.

Secondly, whenever any drug company is criticized before this committee, we forthwith give them the opportunity to respond, with priority over anyone else. We have always done that.

81-280—69—pt. 10——12

We have already heard from the Pharmaceutical Manufacturers Association on three occasions and have offered to have them back. In listening to the speeches of Mr. Stetler—which I suppose many doctors around the country have done—one would get quite a different impression.

We have made it a policy to give the representatives of the major medical organizations an opportunity to appear. Incidentally, we have been trying to get the AMA for the past year without success. And we invited them again in the latter part of last year.

We then have heard from Government witnesses—the Federal Trade Commission, Bureau of Labor Statistics, FDA, and so forth.

After that in priority—last and properly so—would be individual witnesses representing solely themselves, although we have had such individuals already.

I asked the staff to go through the hearings so that we could just summarize what the breakdown has been. The largest single group of witnesses represented before this committee has been the members of the pharmaceutical industry and people representing the industry. There would have been more if all of them had accepted my invitation to appear. Only a half dozen companies have volunteered, perhaps fewer than that.

There have been a total of 114 witnesses before the committee. Some of them appeared more than once, particularly Government witnesses. The largest single group represented in testimony before the subcommittee constitutes members of the pharmaceutical industry and people representing the industry. There have been 44 witnesses from the drug industry, far and away the largest single group. We have had 27 eminent medical authorities from the academic field, men who are nationally and internationally known; 27 from the Federal Government; five or more physicians devoted exclusively to private practice; and the breakdown continues, to include a couple from State and local government, four from consumer groups, and two from the area of research, and the representatives of the highly regarded National Formulary and the U.S. Pharmacopeia.

Thus, considering that we have not begun to hear from all the people who will be heard, I think the balance, despite Mr. Stetler's criticism, has been strongly biased in favor of the industry.

Our first witness this morning is Dr. Clinton McGill. Doctor, you have submitted a biographical sketch which will be printed in the record.

(The biographical sketch of Dr. McGill follows:)

BIOGRAPHICAL DATA—CLINTON S. MCGILL, M.D.

Born in Long Beach, California, June 27, 1921. Moved to Portland, Oregon in early childhood. Father—Clinton S. McGill, Sr., electrical engineer, mother—Ada McGill, one brother—Robert, three years older.

Attended public schools in Portland, graduated from Grant High School. Earned letters in three sports—football, soccer, and track (shot and discus). High school activities included student government, debate, drama, creative writing and scholastic honor society.

Attended University of Oregon, majored in Psychology. Joined Phi Gamma Delta, social fraternity. Elected to Skull and Dagger, sophomore honor club.

Junior year elected to Asklepiads, pre-medical honorary. Senior year elected to Phi Beta Kappa, national scholastic honorary. Graduated with Honors (B.A.). Other college activities included athletics—earned letters in football and swimming, student government. Editorial staff, Oregana (college annual), three years.

Attended University of Oregon Medical School. Fulfilled academic requirements for Master's degree in Physiology. Junior year elected to Alpha Omego Alpha (national scholastic honorary). Graduated with Honors—thesis in pulmonary physiology. Academic rank—second in a class of seventy two. Social fraternity—Nu Sigma Nu.

Internship and Residency in Internal Medicine at Henry Ford Hospital, Detroit, Michigan.

Served in the Army Medical Corps. Stationed at Bruns General Hospital, Santa Fe, New Mexico; Brooke Army Medical Center, San Antonio, Texas; Beaumont General Hospital, El Paso, Texas; and Madigan General Hospital, Tacoma, Washington. Discharged with rank of Captain.

Entered private practice in Portland, Oregon, in association with Dr. Leon A. Goldsmith, Internist and Cardiologist. Appointed Instructor in Physiology at Oregon Medical School (part time). Taught Physiology one year at Portland State College. 1950 (following death of Dr. Goldsmith) appointed Medical Director of the State Public Welfare Commission (part time). Served in that position ten years, at which time a full-time Director was appointed. During this period co-authored the nation's first Permanent and Total Disability program and served as a consultant for the Federal APTD program. Also served as consultant for the Social Security Department in the development of the disability benefit program.

Appointed Attending Physician, Good Samaritan Hospital. Served on various committees including Chairman of the Internship and Residency program (five years) and Executive Committee (three years).

Married, wife—Trudie, four children (ages 15 through 24). Hobbies include—hunting, fishing, skiing, swimming, gardening.

Civic Activities:

Medical Director, Oregon School Activities Association (10 years).
Portland Boxing Commission (10 years–Chrm. 2 years).
Board of Directors, Community Child Guidance Clinic (3 years).
Board of Directors, Oregon Cancer Society (3 years).
Board of Directors, Oregon Heart Association (3 years).
Junior Chamber of Commerce (Legislative Committee and Health Affairs Comm.).
Senior Chamber of Commerce (Legislative Committee.)
Board of Directors, Consumer Credit Counseling Service (at present).
Lecturer, Division of Continuing Education, Oregon State Board of Higher Education (at present).
Lecturer, Portland State College (at present).
Lecturer, Portland School District No. 1 (at present).

Multnomah County Medical Society:

Immediate Past-President (present position).
President (one term).
Vice President (one term).
Board of Trustees (two terms).
Delegate to House of Delegates (16 years).
Chrm. Public Relations and Public Policy.
Various Committees.
Speakers Bureau.

Oregon Medical Association:

Speaker of the House of Delegates (3 years).
Board of Trustees (6 years).
Executive Committee (3 years).
Public Policy Committee (Legislative Comm.)–(10 years; Chrm. 5 years).
Charitable Medical Care (5 years; Chrm. 2 years).
Ethics Committee (Chrm. 3 years).
"Operation Hometown"—Co-chairman (Medicare campaign).
Committee on Title XIX Legislation.
Committee on Public Law 89–749.
Various other committees.
Speakers Bureau.

American Medical Association:
Delegate, Western Conference of National Commission on Community Health Services.
Delegate, AMA Kerr-Mills Conference.
Delegate, AMA National Conference on Ethics.
Delegate, AMA National Conference on Socio-Economics.
Member of Speakers Bureau.
Delegate, House of Delegates.
AMPAC–OMPAC Activities:
Board of Directors (4 years).
Steering Committee (3 years).
Chrm. Oregon Conference on Good Government (Co-author, handbook on State Government).
Delegate, National AMPAC Workohop, Washington, D.C. (4 years).
American Society of Internal Medicine:
Charter Member, Oregon Chapter.
Board of Trustees (2 years).

Senator NELSON. The committee certainly appreciates your taking time to come here. I defer to my distinguished colleague, Senator Hatfield from Oregon, who will introduce the witness.

Senator HATFIELD. Mr. Chairman, I am proud to present to the committee this morning Dr. Clinton McGill, who is a product of the Oregon schools, the University of Oregon Medical School, with internship and residency in internal medicine at Henry Ford Hospital in Detroit, Mich. He has been a teacher. He has been a practitioner. He has been a public servant working in the State public welfare commission as the medical director. He has been very active in his professional life, in the activities of the Multnomah County Medical Society, American Medical Association.

I would not attempt to list all of the honors and all of the distinctions that have been bestowed upon him for his professional and civic activity, but I think they speak for themselves and I think you will find him to be a very direct, frank witness and able to take care of himself.

Senator NELSON. Thank you, Senator Hatfield.

Doctor, you may proceed to present your testimony in any manner that you wish. You may read it directly, and if you wish to depart from your prepared testimony and discourse at greater length on points you have raised, the committee certainly will be pleased to have you do so.

I trust you have no objection to questions as you proceed.

Dr. MCGILL. None whatever, Senator.

Senator NELSON. Thank you, Doctor. Go ahead.

STATEMENT OF DR. CLINTON S. McGILL, PRIVATE PHYSICIAN, PORTLAND, OREG.

Dr. MCGILL. Senator, if I may just start by pointing out something which has come up since I submitted my testimony, and I point to the article in U.S. Medicine, the copy of January 1, 1969, that was an interview with your counsel, Mr. Gordon, seated on your right, in which he chose the opportunity to make a personal attack on me. I resent this attack and I would like to set the record straight right now about the facts in this case, if you will allow me.

Senator NELSON. Yes. I was not familiar with the article.

Dr. McGILL. In this article, and I shall quote only a few lines from it, Mr. Gordon made the comment charging the drug trade association with promoting a physician for these hearings. The disparaging comment that individual witnesses are a dime a dozen, which I resent, that I have had communication with the PMA regarding the testimony that I would give before the subcommittee. He said the subcommittee knows of several instances in which the PMA has promoted individual witnesses and in some instances PMA will even write their statements.

Now, I would like to make this perfectly clear. The statement I submitted today is my own and has not—was never seen by the PMA until after it was submitted to this committee. I wrote every line of it and the views are my own.

And the comment, Mr. Gordon, that what happens in these hearings is completely irrelevant to us I think is a little unfair. The hearings are relevant to us. We are the ones that practice medicine in this country. What possible purpose would be served by having my statement copied and sent to other physicians? That would serve no one's purpose.[1]

But I would like to set the record straight right now. I have never been employed by the pharmaceutical industry. I do not own stock in any drug company nor have I ever. I have never received an honorarium, stipend, gift, or fee of any kind from the pharmaceutical industry and I would like the record to show that.

With that point clear, I will proceed.

The first paragraph of my testimony included some of the biographical data that Senator Hatfield has already covered. I would like to point out that from 1940 to 1959, a period of 10 years, I did serve as the part-time medical director of Oregon State Public Welfare Commission. During that period I was called as a consultant for the Federal Government in the development of the permanent and total disability program under the Department of Public Assistance. On another occasion I was called as a consultant to the Federal Government when the disability amendments were added to the Social Security Act. I have included this information to establish my familiarity with the problems involved in purchasing necessary medications for low-income families and welfare recipients.

I have followed with great interest the hearings of this committee for the past 20 months. I felt a growing concern that no one from the private sector of medicine had been heard.

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[1] (Subsequent information follows:)

MEMORANDUM

April 15, 1969

TO: Senator Gaylord Nelson
Chairman, Monopoly Subcommittee

FROM: Benjamin Gordon, Staff Economist

RE: DR. McGILL'S TESTIMONY

During the course of Dr. McGill's testimony before our Monopoly Subcommittee, the witness stated:

"And the comment, Mr. Gordon, that what happens in these hearings is completely irrelevant to us I think is a little unfair. The hearings are relevant to us. We are the ones that practice medicine in this country. What possible purpose would be served by having my statement copied and sent to other physicians? That would serve no one's purpose."

In the February 10 issue of the AMA News, which goes to every physician in the country whether he is a member of the AMA or not, two-thirds of the editorial page is devoted to excerpts of Dr. McGill's prepared statement which he submitted to the Committee.

Not a single word is mentioned about the proceedings in the hearing room.

Senator NELSON. May I interrupt just a moment?

Dr. MCGILL. Surely.

Senator NELSON. Have you read the testimony of the hearings?

Dr. MCGILL. I have read a great deal of the testimony, Senator Nelson.

Senator NELSON. Yesterday I glanced through the record after reading your statement and I notice that there have been several from private practice who have appeared before the subcommittee. The record shows that Dr. Albe Watkins appeared, Dr. Franklin Farman, Dr. Richard Burack, Congressman Durward Hall——

Dr. MCGILL. Dr. Hall and Dr. Burack, neither one represents private practitioners. Understand, I know Dr. Hall, Durward Hall, and have great respect for him but he is a U.S. Congressman. Dr. Burack is a professor of pharmacology at Harvard.

Senator NELSON. He is in private practice.

Dr. MCGILL. There is a difference between the academically oriented practitioner of pharmacology and the private practitioner.

Senator NELSON. He is from private practice but in any event your statement is that none have appeared, and the record shows otherwise.

Dr. MCGILL. All right.

Senator NELSON. Incidentally, Dr. Hall practiced in Missouri for 25 years. I suppose he did not lose his experience as a private practitioner when he became a Congressman. He was appearing against the hearings. He has your viewpoint.

Dr. MCGILL. I have seen his testimony.

Senator NELSON. Dr. James Faulkner, now retired, was in private practice of internal medicine and Dr. George Baehr of New York is in private practice. I just wanted to point out that there have been at least five witnesses who have had an extensive private practice. There may be 500 more private practitioners who want to appear. We have had to establish a policy, as I stated earlier, of hearing from the drug companies and organizations and others before we get to the private practitioner. We have not even had the Academy of General Practice before us yet, and I would think you might agree that the spokesman for the Academy of General Practice would have some priority generally, over individual practitioners, but we will get to the practitioners and that is what we are doing this morning.

Dr. MCGILL. I would certainly agree and I am also aware of the fact that the American Academy of General Practice has made the request many months ago to be heard before this committee.

Senator NELSON. Yes. As I told Mr. Stetler when he was here, if we followed his theory we would have to hold the hearings all at once in the stadium and everybody testify at the same time. We have to have some order in which to present witnesses.

Dr. MCGILL. I realize that.

Senator NELSON. The Academy of General Practice has been invited. The AMA was invited a year ago, and again last December. It seems to me that a large share of the information concerning witnesses who have been invited to appear before the subcommittee has come from the PMA rather than the subcommittee. We would be glad to let you have this information, and we invite you to examine our files so that you might have firsthand knowledge of the persons we have in-

vited, those who have declined, those who have not given any indications as to their intentions and, of course, those who have accepted our invitation.

Dr. McGILL. The only reason I even raise the point is the fact that many of the witnesses that this committee has already heard have made some very serious charges which I think we should be allowed the privilege of answering, not many months later but as soon as the charge is made. This is my concern, that somebody be able to answer the charges that have been made I think I will answer them in my testimony.

Senator NELSON. Please go ahead.

Dr. McGILL. As I mentioned, on March 28 of last year I wrote to Senator Nelson and Senator Hatfield volunteering my services, hoping my testimony might add a useful dimension to these hearings. In the final analysis we are the ones who prescribe the medicines and must evaluate their worth on a day-by-day basis. We are also the ones toward whom the pressures and promotions of the drug companies are directed. I should add that we carry the moral, medical, and legal responsibility for the effects of those drugs on our patients.

I am grateful to the committee for inviting me to testify. From the outset I would like to make my position clear as I have tried to do. I am here today representing no vested interest except the health of the American public. My interest in your proceedings stems solely from my concern for the welfare of my patients and for our health care system. The views that I am expressing today are strictly my own.

A number of very strong opinions have been voiced before this committee. Although I agree with some, I take strong exception to others. These committee hearings, I think, have the potential for accomplishing much that is good and I sincerely hope this will be the case. But, I would submit that this committee also has the potential for creating a great deal of mischief, and this is my greatest concern.

Senator NELSON. Did you document the mischief?

Dr. McGILL. Yes. I think it will be pointed out, Senator.

I would like to direct my attention to several areas that I think need to be clarified from the point of view of a practicing physician.

First, I would like to briefly point to the great strides that have been made in medicine during the 20 years of my private practice. In this period we have been given more effective therapeutic agents than were produced in the entire history of medicine before that time. In these few years, the progress of our science has achieved a "health miracle" beyond the wildest expectations of the last generation in medicine. There can be little doubt that a great share of the credit is due the pharmaceutical industry. I find it a curious paradox that the drug industry is suffering its severest criticism at the very time it has produced its greatest progress. The therapeutic agents I have available to me today have made it possible for me and others like me to be far better doctors than we ever dreamed we could be. I am grateful for these new products and my patients are grateful.

Senator NELSON. May I interrupt a moment? So is the committee.

I would not want your statement to leave the impression that the committee and all of its members do not recognize many fine contributions pharmaceutical manufacturers have made. From what Mr. Stetler and some of the other critics of our hearings have said, you

would think that we did not. We have repeatedly expressed our respect for the drug industry. These hearings are not aimed at taking credit from the industry for their many accomplishments. These hearings are aimed at evaluating some problems within the drug industry which are of public concern—congressional concern. If there were no such problems, we would not be conducting hearings at all. Certainly, no one—not even the industry itself—denies that there are problems, and I might add serious problems, within the industry today.

Please go ahead.

Dr. McGILL. Ours has truly become the "Golden Age" of medicine * * * as opposed to the "Golden Age" of surgery, which occupied the first 50 years of this century.

It should not be surprising then, that those of us who are fortunate enough to practice medicine during this rather exciting period will view with increasing alarm any influence which we feel threatens our system. I cannot believe it is the intent of this committee to cripple the drug industry or hamper our continued progress in medicine. But, I would caution the committee that these hearings may produce exactly that result.

It deeply concerns me that many of our excellent drug products are becoming better known to the public, for their occasional harmful effects, than for the enormous good they accomplish. The publicity given these hearings, with the emphasis that has been placed on a small number of serious side effects, has the effect of undermining the public's confidence in our pharmaceutical industry. More than that, many patients become sufficiently alarmed that they stop taking medicines they badly need, and we have had this experience.

Senator NELSON. Would you give the committee some specific examples of the publicity given to drugs emphasizing their serious side effects?

Dr. McGILL. Well, by far the best example of it is the terrible wringing out Chloromycetin got before this committee. The birth control pill, another product that has extreme value in private practice of medicine.

Senator NELSON. Let us talk about Chloromycetin for a moment. Do you use it in your private practice?

Dr. McGILL. I certainly do.

Senator NELSON. What are the indicated uses of Chloromycetin?

Dr. McGILL. The indications of Chloromycetin are very well known and should be known to all practitioners who use the drug. This is the only effective drug for typhoid fever, the most effective drug in any of the salmonella infections, resistant staph infections. Most of the gram negative and gram positive respiratory infections will respond, although I will agree other antibiotics can do the trick here, too.

Senator NELSON. For what indication is it the drug of choice?

Dr. McGILL. It is the drug of choice in any bacterial infections that are resistant to other drugs and sensitive to Chloromycetin. Now, that can be demonstrated in the laboratory. It is the drug of choice in typhoid, the drug of choice in ricketsial fever, it is the drug of choice in hemophylis meningitis, staph pneumonia. Shall I go on?

Senator NELSON. Certainly.

Dr. McGILL. This is a valuable antibiotic. This is a lifesaving drug.

I am well familiar with the blood dyscrasia. I have seen one, not in my own practice but in one of my near associates. Chloromycetin also saved my own son's life and that has a lot of meaning to me.

Senator NELSON. I am just trying to get at the publicity as to the serious side effects of chloramphenicol that seems to concern you. What concerns you about that publicity?

Dr. MCGILL. The side effects? There has been——

Senator NELSON. No; I mean the publicity of the side effects.

Dr. MCGILL. The publicity of the side effects often carries over to the use of other effective antibiotics. Individuals in the public often are not able to differentiate between one drug and another. While taking one of these powerful antibiotics, they will say, Doctor, do you really think I should do this, because after all I read in the paper about all these harmful effects——

Senator NELSON. Are you aware of how widely chloramphenicol was misprescribed in this country?

Dr. MCGILL. I am aware of the testimony that has been heard by this committee. In fact, that is this whole copy. And I have read it from cover to cover. And I challenge much of the testimony that has been given because a great deal of this is after the fact testimony.

Senator, this is Monday morning quarterbacking. That is not quite fair.

Senator NELSON. You are welcome to peruse the committee's files on chloramphenicol, if you wish. But let me ask you a few questions. Would you prescribe it for acne?

Dr. MCGILL. This is a good question about acne. I have never prescribed it for acne but I know dermatologists that do. Let me put a hypothetical case.

Senator NELSON. To our knowledge, every single expert in the United States agrees that it is nonindicated for acne. There are doctors throughout the country with judgments against them, and more developing all the time because the doctors prescribed chloramphenicol for nonindicated cases—and acne is one.

Dr. MCGILL. Part of which has been the product of these hearings and that is the point I am getting at.

Senator NELSON. That is the good part of the hearing.

Dr. MCGILL. I disagree.

Senator NELSON. Would you prescribe it for a hangnail?

Dr. MCGILL. Certainly not. Now, understand, Senator Nelson, I am not recommending the misuse of any drug and I will not deny the fact that these drugs are being misused. But may I point out it is very well for Dr. Dameshek to sit up here and say, well, all the cases we have investigated in the past have not been proper indications for the drug. I have the world's greatest respect for Dr. Dameshek. I know him and respect him as a great hematologist. However, every one of these judgments is made after the fact. He did not have the decision to make at the time in a patient with a serious illness. That is an entirely different story.

Now, let us take the case of acne which they say is nonindicated and I would like to put that as a hypothetical question. Acne can be a serious disfiguring psychologically imparing problem to young people, particularly young women.

Now, let us take a hypothetical case. Supposing we had such a young lady with a pustular acne, that it was seriously affecting her emotional, and believe me this happens, her whole emotional development. We have cultured the bacteria and find it to be a staph infection which is Chloromycetin sensitive and not sensitive to any of the other staph preparations, and this is entirely conceivable. Now, the clinician has this choice, do I put this patient on a drug that perhaps one in 40,000 times produces a blood dyscrasia but perhaps can help her, not only her skin but her whole emotional complex, or do I deny her the advantage of a drug that I know will help her?

Senator, that is not an easy decision to make and I challenge whether this may not be a very logical decision.

Senator NELSON. You have, of course, cited a hypothetical case with special circumstance. That is not the issue here at all. Are you aware that the testimony presented to our subcommittee is that nearly 4 million people a year have had chloramphenicol prescribed—and our witnesses all agreed that at the very maximum only 10 percent of those people should have had it. Ninety precent or more were getting it for nonindicated cases.

Dr. MCGILL. That is a spurious figure. Again, this is Monday morning quarterbacking. This is by hematologists that make some sort of a wild guess without any figures to guess from at all. I have read the testimony, Senator.

Senator NELSON. Are you aware, for example, that Dr. Weston, a State medical examiner, said that in all the cases of death from aplastic anemia, from the use of Chloromycetin, he had yet to find one that was prescribed for an indicated case?

Dr. MCGILL. Yes. And I find that very regrettable but it also points out how relatively rare aplastic anemia is.

Senator NELSON. We do not have any statistics on that, you see, because——

Dr. MCGILL. They are hard statistics to get, I know that.

Senator NELSON (continuing). The case ends up with a specialist at some stage who finds out the drug has been prescribed for a nonindicated case. It does not become a part of any record any place. So, the only statistics we have are from California. Those are gross statistics of cases which are provable. Obviously the number—the percentage is much higher—but no one knows how much higher.

Dr. MCGILL. Let me put it this way, Senator. Let us take the kind of a decision I have to make as a physician. I have a patient in the hospital with a serious salmonella infection, let us say. Now, there are other drugs, Ampicillin; for example, which will work, not as well but it will work in a serious salmonella infection, but I have a critically ill patient tonight. Do I prescribe a drug I am almost certain will work, which is an excellent drug, or do I prescribe a drug I think will work as well and not have as much liability, still bearing in mind the one in 40,000 possibility of apalastic anemia? If the patient is sick enough we will chose the drug we are certain will work.

Now, Dr. Dameshek at a later date will say, Dr. McGill, you could have used another product, therefore, it was not indicated. I do not agree. The decision was the physician's at that time and that was a proper indication.

Senator NELSON. That is not at all the kind of case these doctors are talking about. For example, the kind of case they are talking about——

Dr. MCGILL. Colds, things like that, I agree.

Senator NELSON. When Dr. Dameshek was here, he used as an illustration, I believe, a case involving a lady who ended up in his care because her doctor gave her chloramphenicol for headaches. The doctor told her to take it any time she had a headache. She kept it in her medicine cabinet and that is exactly what she did. And she died.

The kind of cases we are talking about is the child who has an infected hangnail. There has been no lab testing. Or an infected tooth—or any number of such miscellaneous cases.

This, doctor, is the point we are talking about. The physicians who testified before us—the tremendous number of letters we have received—none of them are talking about the kind of case where a patient was critically ill and a decision had to be made forthwith.

So that we understand each other, the issue here is the overwhelming misprescribing of this drug all over the country for the nonindicated cases.

Dr. MCGILL. I understand that, but my cases, the case I described to you with the salmonella infection, will never come to Dr. Dameshek's attention because the patient got well and——

Senator NELSON. The kind of case that comes to his attention is the gross misuse.

Dr. MCGILL. I do not disagree the drug is overprescribed and misused and I will not defend that. We have all variations of abilities as physicians just as we do in lawyers and engineers and every other profession, but my point is chloramphenicol is a very worthwhile, life-saving drug and it has become too well known for its side effects and not well enough known for its good effects. I think you will find that this point of view is generally shared by the medical community.

Do you wish me to go on?

Senator NELSON. Anyone, of course, is entitled to disagree with the doctors whose testimony we have heard to date on this matter. But all of them agree with Dr. Paul Hoeprich of the University of California Medical School when he said "I think something should be done, the prescribing of the drug certainly far exceeds the indications of its use."

Dr. MCGILL. Every single one of those individuals—I have read this testimony. None of them suggest that it really be restricted and even Dr. Goddard before this committee said he would not suggest seriously restricting its use because it is too valuable a drug.

Senator NELSON. What do you mean by restricting its use?

Dr. MCGILL. The suggestion has been made it be restricted only to hospital use; for example, and I think in a moment you yourself said perhaps it should be taken off the market because it has done more harm than good. That is not so.

Senator NELSON. I never said that, sorry.

Dr. MCGILL. I think perhaps this may have been in a heated moment and I understand these things. But your testimony yourself: "We would be better off actually in view of what has happened if we never gave the drug at all."

Now, that is not true at all.

Senator NELSON. However, that is read out of context. The patients involved had been given it for nonindicated cases and if the testimony we have heard to date is correct, 10 percent or less of the people receiving chloramphenicol last year should have had it. In fact, Dr. Weston thought that less than 1 percent of those getting it should have it.

Dr. MCGILL. I challenge Dr. Weston's figures and I do not think he is—I recognize Dr. Weston as an authority in his area but I do not feel he has correct figures.

Senator NELSON. Do you know what happened to the use of the drug after the publicity?

Dr. MCGILL. It probably accelerated.

Senator NELSON. No. In the first 6 months of 1968, versus the first 6 months of 1967, it dropped from about 20 million grams of use for——

Dr. MCGILL. Now, when the first reports of aplastic anemia and blood dyscrasias came out and were reported in 1951 to the medical profession the use of Chloromycetin dropped almost to zero. It dropped very sharply because of this potential danger, once the facts were known.

My point is this information is not wasted. This does reach the medical profession and any doctor that has practiced in the last 15 years and does not know that Chloromycetin can produce serious blood dyscracias must be blind, dumb, and deaf because there have been all kinds of warnings.

Senator NELSON. That is exactly what the experts' testimony has been—that many doctors have been blind, dumb, and deaf. It has been a horrible tragedy in this country and it is an indictment of the medical profession. If you wish to go through our files you will find letters from parents whose children died as a result of the drug being administered for such nonindicated cases as hangnails, acne, sore throat, and the like. It is incredible—simply incredible—and it is an indictment of the medical profession.

Dr. MCGILL. Senator, I do not disagree but you are talking today to a physician whose son's life was saved by the Chloromycetin.

Senator NELSON. In your son's case perhaps it was given for an indicated condition. No one would criticize that. Certainly none of the doctors from whom we have heard. These doctors said it is an excellent drug but that because of the serious risks involved in its use, it must be restricted to the extremely limited conditions for which it is indicated.

Dr. MCGILL. But you will notice the statement is made all through the testimony that were it not for the blood dyscracies, this would doubtless be the best antibiotic ever made. That is in the record.

Senator NELSON. No one disputes that.

Dr. MCGILL. Well, my point is, I think something should be said about this valuable drug which has an unfortunate but rare complication. The fact that it is being overprescribed or prescribed for indications that are not correct, I will not defend. Not at all. And I think we within the fraternity try to do our best on this score.

Senator NELSON. Of course, that has been the testimony. All the experts say it is an excellent drug. A very valuable drug, but it should be used only in indicated cases. The testimony is that they think that in 90 percent or more of the cases, it has been used for nonindicated cases. That is the real issue here. Now——

Dr. McGILL. And all I would like to add, I do not think their figures are correct.

Mr. GORDON. Dr. McGill, May I interrupt? You said that chloramphenicol is the drug of choice for hemophilus——

Dr. McGILL. Influenzal meningitis.

Mr. GORDON. Here is a recent study [1] by the National Research Council of the National Academy of Sciences. It says that:

> It is likely that this claim (drug of choice in hemophili influenzae meningitis) is no longer justified. In meningitis of the newborn, Kanamycin is preferred as the drug of choice for empiric treatment.

Dr. McGILL. There is no question Kanamycin has come along but for many years Chloromycetin was the drug of choice, and incidentally, Kanamycin is not without its side effects.

Mr. GORDON. I might mention that the recent study by the National Academy of Sciences limits even further the uses of Chloromycetin.

Dr. McGILL. Yes; but that limitation was not based on the failure of Chloromycetin. It was based on the fact that there are newer products on the market.

Mr. GORDON. That is right.

Dr. McGILL. That is fine but this is not an indictment of Chloromycetin and that is the way it has been made to sound.

Now, we will get better drugs than these, I am sure, I sincerely hope we do, but these things all have to be interpreted in terms of the time of reference they were made. For a long time Chloromycetin was the only drug effective in this area.

Mr. GORDON. But not now, is that correct?

Dr. McGILL. Not now, although Kanamycin has its problems. I have used it.

Mr. GORDON. Incidentally, it goes into many other uses for which you said it was the drug of choice and for which it no longer is the drug of choice.

Dr. McGILL. Well, what I say at one particular moment and what may be true tomorrow may be two different things. As I mentioned, the drug industry does make progress. They put out new products and I am sure we will see the day when Chloromycetin is an obsolete drug, but for a long time it was the drug of choice of many, many physicians.

Senator NELSON. You may proceed, Doctor.

Dr. McGILL. To make matters worse, this committee has givn a public forum to certain arrogant professors of pharmacology who have openly discredited the drug-prescribing abilities of the American physician. I deeply resent this insult to our clinical integrity. The end result of this unfortunate publicity is unnecessary suffering by many individuals who are fearful of using drugs of any kind—and this is tragic. Senator, I have had this experience.

Now, a large part of the practice of internal medicine is the treatment of cardiovascular disease. I would like briefly to point to some of the improvements that have taken place during recent years. The anticoagulants have cut the death rate in half during the critical first month following a heart attack. Incidentally, those anticoagulant de-

[1] See information beginning at p. 4131, infra.

rivatives were developed in the University of Wisconsin; a great contribution to us.

In arterial occlusive disease they have allowed us to add many years of life to the individual. Thanks to our antihypertensive drugs we have managed to cut the death rate from hypertensive heart disease to about half of what it was 15 years ago. Another great breakthrough was the development of the effective oral diuretics. They not only prolong life but they have added immeasurably to the comfort of people suffering chronic cardiovascular disease. Yet, in spite of all these advances, cardiovascular disease still kills more Americans than all other causes combined. There is much more that can be done in this field and the need is urgent. This committee would be well advised to think in terms of providing greater incentives to accomplish this task rather than discrediting the system.

Senator NELSON. In what way have we been trying to discredit the system? I am curious about that.

Dr. MCGILL. We certainly have seen many areas of the drug industry criticized for their practices, and there may be some validity. I am not an expert in the drug industry and do not pretend to be, but I find it difficult to reconcile the criticism of the drug industry in these hearings with the accomplishments they have actually produced.

Senator, as a practicing physician I am concerned about new products. I want things I can treat my patients with. This is my point of view. This is my concern.

Senator NELSON. I am concerned about that, too, and your general, casual statement regarding the committee's discrediting the system.

Is it your opinion that any great industry—such as the drug industry, the automobile industry, the chemical industry—that these industries are sacrosanct? That problems which arise within an industry, whether it is price fixing, price setting, misrepresentation in advertising—and so forth—is it your view that because these companies do good things—and no one denies that they do—that as a matter of public policy we should avoid exposure of their bad practices?

Dr. MCGILL. Certainly not.

Senator NELSON. Well then, the purpose of the hearings has been to examine some of their bad practices. I don't understand the point you are trying to make when you talk about "discrediting the system."

Dr. MCGILL. There may be a difference of opinion, Senator, on what are bad practices and I will get to a couple of those later in the testimony. I think you may want to question——

Senator NELSON. Of course there always are differences of opinion. That is why we permit the industry to come in and answer whenever a point is raised regarding a particular industry. In that way we have both sides in the record.

But I do not understand what you mean by our "discrediting the system." You must have something in mind. Specifically, in what way do you feel we have been discrediting the system?

Dr. MCGILL. The criticism of the detailing, for example, and that is covered later in my testimony. A couple of areas that I think perhaps will come out as we go along, and I will be glad to enlarge on them if you would like.

Of the various issues heard by this committee, and here is one right here, none has created greater controversy than the question of generic prescribing or generic equivalency. In my view, most of the testimony has completely missed the point. It seems evident that there are both good and bad brand-name products on the market and there are both good and bad generic-name products on the market. The important point is that the product be indentified. If I prescribe a specific brand of drug products, I do so for very good reasons. And, under no circumstances do I want a pharmacist substituting an equivalent product. Any more in this direction will meet with very serious objections from the medical community.

Senator NELSON I am sure it would. You are not saying that I have suggested this?

Dr. MCGILL. No, sir. But it has been suggested before this committee.

Senator NELSON. Oh, yes. It has been suggested, and it has been opposed before the committee.

Dr. MCGILL. Do I understand your point, then? You have no objection to product identification as a matter of committee policy.

Senator NELSON. We have heard testimony, which has impressed me, to the effect that every doctor ought to be required to put the generic name on the prescription and that he may, if he wishes, designate any brand name he desires. Is that objectionable?

Dr. MCGILL. No. That is fine. That is the point we are after.

Senator NELSON. After listening to the experts, I believe that to be the correct position. But you see there is a problem. I do not want to be unfair to you, but I would like to ask you a question. There is no reason you should know the answer—but do you know what Thalinette is?

Dr. MCGILL. I am sorry.

Senator NELSON. Do you know what Thalinette is—or Profamil—or Valgis? There is no reason why you should know but I ask you——

Dr. MCGILL. I am not familiar with the products you are talking about.

Senator NELSON. Do you know what thalidomide is?

Dr. MCGILL. Certainly.

Senator NELSON. The three brand names I read are all thalidomide. There are 34 listed here in an article by Dr. Taussig who appeared before the committee some months ago. One of the reasons she gave (and almost everyone supports it) for putting the generic name on the label was that after thalidomide was on the market, it was being sold throughout the world under 34 different brand names. In many countries it was repeatedly prescribed by physicians simply because they did not recognize it by the name under which it was being sold.

Dr. MCGILL. Senator, I do not think any doctor would have the slightest objection to this. The generic name of the drug on the prescription is something I always do myself.

Now, I have read Dr. Taussig's testimony. I know her and have enormous respect for her. Her point was so that the drug could be identified by someone else, unless there is some specific reason why the doctor does not want to list it, and this could happen, but most of the time no objection. I think this would be a fine thing.

Senator NELSON. Fine.

Mr. GORDON. Dr. McGill, this is exactly what the pharmacologists advocated, putting the official or generic name on the prescription and the name of the manufacturer. I do not think we had a single pharmacologist who testified otherwise.

Dr. MCGILL. This is correct, and as far as generic versus brand name is concerned, I am sure this committee is aware that at least three-fourths of the drugs that we are using do not have generic equivalents. Therefore, you are talking about an academic point. Many times the reason we favor brand names is that they are simpler names to use. Generic names are often very complex and sometimes very hard to remember. All of us, I am sure, know the generic name when we first start using a drug but then the drug company will provide us with an easier name to use, a more popular name; so we use it and it might require a great deal of going back and restructuring our thinking to get into the generic thinking. I am sure it could be done if it needed to be, but I do not think it serves a useful purpose, as long as it is identified and I think the name should be on the label. I would have not the slightest objection to that.

Shall I go on?

Senator NELSON. Please.

Dr. MCGILL. As I mentioned, regulations that interfere with the decision, and you clarified that for me, Senator, would not be in the patient's interest and would be met with opposition.

It has been argued before this committee that some sort of a national formulary should be developed. I would like to point out an example on this business of switching products by generic names, an example in my own household. I have a diabetic son, that is the same one I refer to, saved by Chloromycetin, who takes insulin every day. Over a period of years he has always taken insulin manufactured by the Lilly Corp. On one occasion a brand of insulin made by a competitor was substituted. This was precisely the same generic type of insulin he was taking, except it was manufactured by a different company. He promptly had a rather violent allergic reaction to the new product. That is a local reaction in the skin; a large wheal.

Obviously, there is something in the competing product that is not present in the Lilly product. That does not mean the competing product is not a perfectly good one for someone else. It may be; but for this particular individual it is not the drug of choice. I would like to point out this is the type of information no pharmacist could know. Only the physician has this information available to him.

Mr. GORDON. Are you aware that insulin was not developed by the drug industry?

Dr. MCGILL. You are talking about the development of Banting & Best insulin; yes. In fact, I also know Dr. Best and I see him every time I visit there. But the development of a product in a laboratory is nothing more than a clinical curiosity until one of the drug companies is able to make it available through production.

Mr. GORDON. We know it is their business to produce it.

Dr. MCGILL. I am not criticizing this. My only point is by substituting the same generic insulin, it produced a reaction and I would never give him that brand of insulin again. Again, I am not being critical of the product. I am only pointing out this is the kind of information that

only a doctor has, you see. Another point in this area. One of the oldest drugs in common usage today is digitalis. There are many brands of digitalis on the market, all of which must meet USP standards. Yet, in my clinical practice I prescribe just one brand because I am thoroughly familiar with its effects. Among my colleagues I find this to be standard practice. In fact, we teach our students this.

Mr. GORDON. Which do you prescribe?

Dr. MCGILL. Upjohn's digitora 1.28 grains, in my own practice.

Mr. GORDON. When you write the prescription do you write "digitora," or "digitalis"?

Dr. MCGILL. I usually write "digitora" because it is easier. I would write "Upjohn" and "digitalis" but it is a little longer and more complicated.

Certainly there is variation between products bearing the same generic label. In most instances, no harm results from this variation as long as the prescribing physician is thoroughly familiar with the product he is using. The substitution of another product can easily harm the patient. This is why product identification is important. This committee would be well advised to insist on product identification. Then any kind of an abnormal reaction, any question of therapeutic value, any problem involving the quality of the product could be traced right back to the source. Certainly this would be in the public's interest. In my view, the choice of a given drug for a given problem in a given patient is a decision that only the attending physician can make.

Senator NELSON. So far as I am aware, we have not had any testimony which would argue with that.

Dr. MCGILL. Fine. I am very glad we agree on that point.

Senator NELSON. Certainly the witnesses we have had agree on that point. The problem is the propaganda which has been circulated and which is responsible for the misunderstanding.

Dr. MCGILL. I am not worried about the propaganda so much as I am sure if we agree on this point, I will feel much comforted.

Mr. GORDON. Dr. McGill, just one more point. Digitalis was also not discovered or developed by the drug industry.

Dr. MCGILL. No. It was discovered and developed about 400 years ago, as a matter of fact, by Dr. Withering who wrote an astonishing treatise on it. We have not had—we have not added much to his description, in 400 years.

The basic issue in generic prescribing revolves around the problem of drug costs. It has been argued before this committee that some sort of a national formulary should be developed and used where Federal funds are involved. The contention is that generic prescribing would result in a considerable saving of funds. I seriously question this contention and I have some firsthand knowledge in this area.

I referred earlier to my experience as the medical director of the Oregon State Public Welfare Commission. During the early 1950's, the rapidly rising drug costs became a major problem. In an attempt to solve this problem I developed, with the consultation of others, a formulary for the use of welfare recipients. To my knowledge this was the first such formularly of this type that was ever introduced in a welfare program. Frankly, I consider the development of this formulary to be the single biggest blunder that I committed as medical di-

rector. First of all, it was almost imposible to keep it current with the rapidly developing drug products. It also produced a universal storm of protest on the part of my colleagues. We, of course, made allowances for exceptional conditions, or where life-threatening situations were involved. We soon learned that the administrative costs and the alienation of the medical community far outweighed any savings we might have realized by use of the formulary. I would caution the committee to carefully weigh any such decision. The effects are indeed far reaching.

Senator NELSON. What about hospital formularies?

Dr. MCGILL. Hospital formularies are quite different, Senator Nelson. They usually represent the agreement of committees on what are the most appropriate drugs being used today and they do not restrict the physician. The reason most hospital formularies are put together is so they can buy by large quantity and therefore get certain savings which would be appropriate to quantity purchase.

Now, in my particular hospital, Good Samaritan Hospital in Portland, we have a recommended formulary but it in no way restricts the physician to the choice of those drugs. If he wishes a specific drug, he may have it.

What we are talking about is the most likely drugs to be used so they can take advantage of quantity buying. That is quite different from restricting a doctor's choice to the drugs the program can provide. This is the problem of a closed-end budget, you see.

Senator NELSON. What do you do about a situation where the public money is being spent—this is the kind of problem that I think Congress and the taxpayer, and I would presume the doctors are concerned about.

You are, of course, familiar with the Medical Letter. In June of 1967 they published their evaluation of prednisone. This is just one of any number of examples we could use.

Now, the price of Schering's Meticorten, which was far and away the predominant brand in the market, was $17.90 for 100 tablets, and Parke, Davis' Paracort was $17.88 a hundred on down the line to $10, $8, Merck's at $2 and finally down to 59 cents a hundred. There was a price gradation from 59 cents a hundred to $17.90 a hundred to the pharmacist. So the markup for Meticorten and Paracort is somewhere in the twenties or thirties.

As a result of the chemical tests and the advice of their clinicians, the Medical Letter said that in their judgment they are all equivalent. And they so advised the physicians.

Dr. MCGILL. The price differential on prednisone is really well known in the medical fraternity and I myself don't know why they don't use—have greater use of the less expensive products. On the other hand, I would not prescribe it generically without specifying the brand because where we may have five or 10 or 15 on the market today which meet certain equivalent performance, we may have 200 tomorrow, and this is why I would identify the product.

Senator NELSON. But the fact is the Meticorten at $17.90 dominated the marketplace and it was——

Dr. MCGILL. It is a good product.

Senator NELSON. Yes, but it is no better than Merck's according to the Medical Letter.

Dr. McGILL. I will agree, and I think that you have picked an extreme example but I don't disagree with you. I think this does not make sense and the less expensive Merck product should be used which I would use myself.

Senator NELSON. This isn't an exceptional example.

Dr. McGILL. That is an extreme example of price gradation.

Senator NELSON. I can give you any number of other examples right now.

Dr. McGILL. I am aware that there are price variations but I think probably the Meticorten story which has been told many times is an extreme.

Senator NELSON. The reason I used Meticorten is that otherwise the witnesses might argue that the other brands aren't as good. None of the experts before the committee felt that they would quarrel with the judgment of the Medical Letter on this.

I will give you another example. Chlorpromazine was developed by Rhone-Poulenc in France. They licensed its use to a single manufacturer in the United States and a single manufacturer in Canada. There was no research money involved on the part of either company. They were just licensed to sell it exclusively as a monopoly.

In the United States, the Defense Supply Agency paid $32.62 a thousand. I suppose this was the lowest price anyone could get in this country, since of course they purchase in large quantity. But—in Canada the Department of Veterans Affairs paid $2.60 per thousand. The same drug.

Dr. McGILL. Senator, there are several points with which I would take issue. First of all, Parke, Davis Co. has a great deal of research money in Chloromycetin.

Senator NELSON. I said chlorpromazine.

Dr. McGILL. I am sorry. Well, also there are several hundred manufacturers of these drugs in Europe and other countries where there is a very definite competition between product manufacturers. Chlorpromazine is licensed by one company and that, incidentally, will no longer be true next year, I understand, and I have no doubt the price will come down.

Senator NELSON. All I am saying is that there are vast price differences. Here we had the same drug licensed to one company in this country and one in Canada—selling at $32 a thousand in this country and around $2 a thousand in Canada. I just don't want you to think these are extreme examples, as you stated—we can give you dozens of examples.

My point, however, is what does the taxpayer say, and properly so, when all welfare patients in one particular community are getting prednisone at $17.90 plus the markup, and then 10 miles away in another community the doctors are prescribing Merck's at $2.

Dr. McGILL. I don't disagree. We are in agreement on that point.

Senator NELSON. Well, if you don't establish some kind of a formulary situation, how do you decide the issue?

Dr. McGILL. By price information, and I think that is where price information needs to be distributed more generally and it is being distributed more generally. This has become almost a standard procedure with detail men, to give price information right along with product information, and this may be one of the effects this committee has had.

One such effect is to encourage the growth of the small parasitic drug companies who cash in on the research and development of the major pharmaceutical houses. Most of these small companies make no contribution whatever to the health of the public or the growth of our science. It's only natural then, that we will favor the product of the company that developed it. The parent organization has vastly more experience in the production and quality control of the product; therefore, it is reasonable to assume greater reliability. This is what concerns us.

Senator NELSON. I don't quite follow that. Let me ask you a question. Every other company in America is in the same situation. If you discover a new drug, you patent it for 17 years and charge anything you please. At the end of the patent period anybody is free to manufacture it. That is true whether it is automobiles or anything else.

Dr. MCGILL. Fine.

Senator NELSON. Why shouldn't that apply here?

Dr. MCGILL. It does.

Senator NELSON. What, then, is the criticism?

Dr. MCGILL. This refers back to the formulary. A formulary requiring for public money the use of generic equivalents would have the effect of favoring the small company at the sacrifice of the big company who produced all the research and development. That is my concern.

Senator NELSON. That is the point I am getting at. Why does it favor the—as you say—the parasitic company. Do you call Strong, Cobb & Arner a parasite, one of the biggest generic manufacturers in America who sells to all the major companies?

Dr. MCGILL. I call any company a parasite, a parasitic company, that does not do research and development of their own. This is our concern.

Senator NELSON. All right.

You say that a formulary based on price would favor generic producing companies. I don't quite follow that. The company that discovers the product has 17 years in which to make whatever profit it sees fit. Their product is without any competition whatsoever in the marketplace—a total monopoly for 17 years. Then the patent runs out.

Is there any reason in the world why the patent should be extended—giving them further preference, so to speak?

Dr. MCGILL. No. I am not suggesting that.

Senator NELSON. What preferential treatment is there if, on the basis of price, you purchase from a generic company?

Dr. MCGILL. No, but if they were required to choose, in other words, if you put a price-oriented national formulary that we must use in public welfare or any kind of public money program, that has the effect of favoring the generic prescriber.

Senator NELSON. Why is that?

Dr. MCGILL. On a price, competition only, basis.

Senator NELSON. Why does that favor the generic prescriber?

Dr. MCGILL. Well, the assumption is that the generic prescribers, having no research and development program, can put their product out cheaper, plus they can also use the research information and patent information of the other company. Again I don't know all the economics of the drug industry. My concern is that if we—what we are going to end up doing is to eliminate two classes of drugs and end

up with drugs in the middle. The generic houses will come up to line and the few instances of very high-priced trade names will probably come down.

That might be a good thing, but what I am concerned about is if we cripple research and development, we won't get the tools we need. This is my concern as a physician.

Senator NELSON. That is why I am pursuing this. I don't understand how you cripple research and development. You have a 17-year patent. They can charge 100 or 1,000 times the production cost. In fact, it is pretty clear that in Meticorten at $17.90 a hundred versus 59 cents a hundred that they are doing this. Here is a company that can manufacture at 59 cents a hundred and make a profit. You give them the 17 years. The patent runs out. They have made all their profit.

Then I think Government, the physicians, anyone—ought to buy the cheapest equivalent drug in the marketplace. I emphasize equivalent.

Dr. MCGILL. Well, this is, of course, a different issue, whether it is equivalent or not.

Senator NELSON. There is no argument that I know of about the prednisones listed here. That is why I stressed equivalent. What happened with Meticorten? In the retail marketplace they charged $17.90. After these hearings, they reduced their price from $17.90 to $10.50 a hundred. Another company reduced from $17.88 to $3.45 a hundred.

Dr. MCGILL. Incidentally, may I say this is one of the good effects this committee has had. Everybody has gone back and taken a close scrutiny of their price structures.

Senator NELSON. Yes, but the issue here is that these companies—in this case it was Schering—was selling to the pharmacies at $17.90 a hundred while to New York City Schering was bidding and offering to sell at $1.20 a hundred. Why? Because they were taking bids in competition with these other companies. That is why they were willing to sell at $1.20 a hundred.

I don't quite understand your position with regard to a formulary. The patent runs out. You choose the lowest price equivalent drug that is reliable. Why, then, is that a disadvantage to the company which has already recovered all their research moneys and made their profit—and is now competing, like everyone else, in the free competitive economy?

Dr. MCGILL. Which they have to do right now as far as that is concerned. But my concern, and I can't help but be a little critical of the small company who does not make any contribution to me or my clients, but simply wishes to cash in on somebody else's product.

Now, call that prejudice if you like but I don't favor such a company. I also think it is up to them to establish, I repeat, it is up to *them* to establish, whether or not their product is equivalent. I don't mean USP. I mean therapeutically equivalent, and I will not use their product until that is established.

Senator NELSON. Well, I guess——

Dr. MCGILL. As a matter of fact, I think this is the area that your committee would be well advised to view, what the practices are among the small companies who do no research and development. The extent

of their research and development is the Patent Office, whose drug expires next. What contribution do they make except a pricewise contribution? They make nothing to the science. The price is important. I don't mean to be discrediting that, and I will have something to say about that a little bit later, but our concern is growth and development and we will naturally favor the ones who help us on this score.

Senator NELSON. What I am getting at is what more should you do for a company aside from giving them a 17-year monopoly? I think all of us would be very happy if, for example, in the automobile industry some one who had never designed or done anything at all would take all the patents on automobiles and come up with a car that was one-third the price of those in the marketplace and just as good. Would you attack them as a parasitic competitor? That is what a free competitive economy is all about. Otherwise you would have a monopoly forever.

Dr. MCGILL. I am glad you brought that up because I think the point should be made that the patent, the 17-year patent right is not unique to the drug industry. This is unique to the patent system of this country.

Senator NELSON. That is correct, but in every other industry, when the patent runs out, everyone is free to produce the product. Whether it be the private citizen, businessmen, or Government, everyone is going to take the best product they can get at the lowest price. They aren't going to sit back and say "I am going to pay twice as much out of gratitude to General Motors because they invented this device." Why shouldn't we do this with drugs?

Dr. MCGILL. None at all, and I think perhaps I may have overemphasized the loyalty type of argument, not that I don't think loyalty is important. I do. Yet up to a point. The drug products made up by other manufacturers that I know and where I know the reliability of their organization, if produced at a much lower price, we certainly will use the one at the lower price. Our loyalty will only go so far for a product, I don't think it serves any purpose to get into the equivalency argument in front of this committee, again, it has been heard so many times. I think that the small companies should be required to prove their product is equivalent and then I would use them if they have a better price. No objection to that at all.

Until that time we may very likely favor the original manufacturer because we have great faith in him and feel he has the experience he needs to produce the product, and there are examples of this, Senator.

Senator NELSON. Please proceed.

Dr. MCGILL. Well, I wish to go on.

In my view, if this committee wishes to critically examine any segment of the pharmaceutical industry, it should direct its attention to these noninnovators whose sole purpose in the drug field is to profit on the products other companies have developed.

Senator NELSON. I think Senator Hatfield had a question.

Dr. MCGILL. Yes, surely.

Senator HATFIELD. Dr. McGill, on this point of having no alternative but to reduce their research and development programs, don't you

think they might also have the opportunity if they are in this kind of a situation that you describe to reduce their advertising budget? As you might know——

Dr. McGILL. I have no idea, Senator Hatfield. I don't know that much about drug economics.

Senator HATFIELD. I think there are about $400 to $600 million spent by the industry each year.

Dr. McGILL. The figure $600 million has been used quite often.

Senator HATFIELD. It seems to me there might be another alternative than to cut into their research and development programs.

Dr. McGILL. In fairness, as it has been described to me, that $600 million does include their total marketing costs and not just advertising.

Senator HATFIELD. Excuse me.

Dr. McGILL. As far as marketing is concerned, I am sure it would be obvious to the committee that when we hear about a new product and read about it in our journals, it is little more than a curiosity until it is on the market where I can use it.

Well, in the advertising and promotional practices of the pharmaceutical houses, I have found it difficult to reconcile the testimony heard by this committee with the procedures actually followed in the field.

I have found the drug advertising in our professional journals to be very useful. It has also been my experience that the ethical drug houses are very careful to accurately describe their products and include all the possible side effects. We are all aware that the FDA has regulatory authority over drug advertising.

I would also like to point out that journal advertising is not the only source of information on new products. And, in fact, is probably not the most important source. In any major breakthrough of a new drug product a number of articles will have appeared in our professional journals. In all probability, it will be described in the JAMA section on new drugs. We may likely hear of it when reported in a scientific paper in one of our many professional meetings. The point is, there are many sources of information on new drug products and they are all useful to us.

I think a word should be said here about the detail men. It is my practice to see one detail man every day. In fact, the detail man is the first appointment I have every morning. In my office we keep a file of our detail men so we can contact them if we have questions about their products. The vast majority of detail men are trained professionals and they provide us with valuable information. We learn from them such important details as package size, how a given drug is supplied, whether it's liquid, tablet, injectable, suppository; whether it is in general distribution. The detail man also supplies me with price information right along with product information. This is becoming more general all the time. Contrary to what has been said in this committee, most doctors are price conscious. If they are not, they soon hear about it from their patients.

To be perfectly objective, I must admit to an unhappy experience or two with detail men, but such an individual doesn't get another appointment to see me. As a rule, he's not long on the job. Such in-

stances are rare. I have many times called upon detail men to contact their parent organization for special information. I've always found them very willing to do so. Not long ago, I ran into an unusual side effect with a drug that was not described in the package literature. The detail man called his parent company—I might point out I called him at home at 5 o'clock in the evening. I received a return call at 8 o'clock that same evening, which was 11 o'clock that night by their time, but within a matter of hours I received a call from one of the research scientists of that organization. He gave me the information I was looking for and was most helpful in all respects.

I would like to cite one further example of the services provided by detail men. I am currently treating a rather rare eye condition in a patient in consultation with one of our professors of ophthalmology at the medical school. It was his recommendation that large doses of an adrenal steroid be used in a near-heroic attempt to save her vision. These are very expensive products and we both were hesitant to subject the patient to this financial burden. I contacted the detail man of one of the large drug houses and presented my problem, hoping he could provide us with enough samples for at least a trial. More than that, he contacted his parent organization who willingly provided all the steroid the case will require.

I am happy to add that our treatment appears to be successful.

Granted, these are but small examples of special service in one doctor's practice, but they are by no means unique. Multiply these experiences by the more than 200,000 practicing physicians of this country and I think a more realistic concept of the value of the detail man emerges. I would like to point out that these are services that could not be obtained through any published journal of drug information or through the AMA's Council on Drugs. Such services can only be provided by person-to-person contact.

It has been suggested to this committee that a federally sponsored journal of drug information should be published for the use of the medical profession. A national compendium of drugs has also been recommended. These proposals have merit and deserve further study. However, if any proposal of this committee is to serve a useful purpose, it must have the confidence of the medical profession. It is imperative, then, that this committee establish and maintain its credibility with the scientific community. Anything less will not only lead to certain failure, it will provoke outright and vigorous opposition.

Senator NELSON. Let me say, Doctor, that is also my position. It has been the position of all the witnesses who have testified in favor of a formulary, from Dr. Goddard on. Everyone agreed that the formulary has to be one in which the physician has confidence. It would have to be one that——

Dr. MCGILL. Or it would not be useful.

Senator NELSON. Certainly the medical profession as well as the Government would have to be represented. You could not have a successful compendium, or anything like it, without the acceptance and broad participation of the medical profession.

Dr. MCGILL. I am happy to hear that. You are aware, of course, of the compendium being drawn up by the AMA's Council on Drugs.

Senator NELSON. Yes.