COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

67062381 L

HEARINGS

BEFORE THE

SUBCOMMITTEE ON MONOPOLY

OF THE

SELECT COMMITTEE ON SMALL BUSINESS

UNITED STATES SENATE

NINETY-FIRST CONGRESS

FIRST SESSION

ON

PRESENT STATUS OF COMPETITION IN THE PHARMACEUTICAL INDUSTRY

PART 12

MAY 6, 7, 20, AND 27, 1969

DRUG COMBINATIONS—ANTIBIOTICS



Printed for the use of the Select Committee on Small Business

U.S. GOVERNMENT PRINTING OFFICE

81-280 WASHINGTON : 1969

0489574

For sale by the Superintendent of Documents, U.S. Government Printing Office
Washington, D.C. 20402 - Price $1.25

SELECT COMMITTEE ON SMALL BUSINESS

[Created pursuant to S. Res. 58, 81st Cong.]

ALAN BIBLE, Nevada, *Chairman*

JOHN SPARKMAN, Alabama
RUSSELL B. LONG, Louisiana
JENNINGS RANDOLPH, West Virginia
HARRISON A. WILLIAMS, JR., New Jersey
GAYLORD NELSON, Wisconsin
JOSEPH M. MONTOYA, New Mexico
FRED R. HARRIS, Oklahoma
THOMAS J. McINTYRE, New Hampshire
MIKE GRAVEL, Alaska

JACOB K. JAVITS, New York
PETER H. DOMINICK, Colorado
HOWARD H. BAKER, JR., Tennessee
MARK O. HATFIELD, Oregon
ROBERT DOLE, Kansas
MARLOW W. COOK, Kentucky
THEODORE F. STEVENS, Alaska

CHESTER H. SMITH, *Staff Director and General Counsel*
JAMES P. DUFFY III, *Minority Counsel*

MONOPOLY SUBCOMMITTEE

GAYLORD NELSON, Wisconsin, *Chairman*

JOHN SPARKMAN, Alabama
RUSSELL B. LONG, Louisiana
THOMAS J. McINTYRE, New Hampshire
ALAN BIBLE,* Nevada

MARK O. HATFIELD, Oregon
ROBERT DOLE, Kansas
MARLOW W. COOK, Kentucky
JACOB K. JAVITS,* New York

BENJAMIN GORDON, *Staff Economist*
ELAINE C. DYE, *Clerical Assistant*

---

*Ex officio member.

CONTENTS

Statement of— Page

Adriani, Dr. John, Charity Hospital, New Orleans, La 5085

Bryan, Dr. Paul, Director, Bureau of Medicine Task Force, Food and Drug Administration; accompanied Dr. Herbert L. Ley, Jr., Commissioner, FDA 5134

Eichenwald, Dr. Heinz F., William Buchanan professor and chairman, Department of Pediatrics, University of Texas Southwestern Medical School, Dallas, Tex 5013

Goodrich, William W., counsel, Office of General Counsel, U.S. Department of Health, Education, and Welfare; accompanied Dr. Herbert L. Ley, Jr., Commissioner, FDA 5134

Hewitt, Dr. William L., professor of medicine, University of California School of Medicine, Los Angeles, Calif 5048

Jennings, Dr. John, Acting Director, Bureau of Medicine, Food and Drug Administration; accompanied Dr. Herbert L. Ley, Jr., Commissioner, FDA 5134

Kirby, Dr. William M. M., professor of medicine, University of Washington School of Medicine, Seattle, Wash 5002

Kunin, Dr. Calvin M., chairman, Department of Preventive Medicine, University of Virginia, Charlottesville, Va 5023

Ley, Dr. Herbert L., Jr., Commissioner of Food and Drugs, Consumer Protection and Environmental Health Service, Public Health Service, U.S. Department of Health, Education, and Welfare; accompanied by William W. Goodrich, Counsel, Office of General Counsel; Dr. John Jennings, Acting Director, Bureau of Medicine, Food and Drug Administration; and Dr. Paul Bryan, Director, Bureau of Medicine Task Force, Food and Drug Administration 5134

Wise, Robert I., M.D., Ph. D., professor of medicine and chairman, Department of Medicine, Jefferson Medical College, 1025 Walnut Street, Philadelphia, Pa 5071

EXHIBITS

Letter to physicians from J. C. Gauntlett, vice president and director, the Upjohn Co., re drug Panalba 5067

Chart: Etiologic agents of infectious diseases 5081

Chart: Therapeutic anti-infective agents 5082

Letter, dated April 17, 1969, to Charles L. Wimbley, Marketing Research Department, the Upjohn Co., from William R. Merchant, M.D., Director, Veterans' Administration Hospital, Madison, Wis., with enclosures 5138

Memorandum, dated April 29, 1969, to Dr. Paul A. Bryan, from Dr. Max B. McQueen, re Panalba review of records obtained by FDA inspector, Roy D. Sanberg, from the Upjohn Co. files on March 7, 1969 5148

Food and Drug Administration/Bureau of Medicine report on number of patients adversely affected by the use of Panalba 5165

Announcement on new labeling requirement of drug novobiocin by HEW, published in the Federal Register, May 2, 1969 5168

New labeling requirement of drug novobiocin, dated May 19, 1969 5171

Physicians' letters to Commissioner Ley on Panalba and Mysteclin-F with geographical breakdown 5188

APPENDIXES

I. Editorial: "The Clinical Use of Antibiotics in Combination," by H. F. Dowling, M.D., M. Finland, M.D., M. Hamburger, M.D., E. Jawetz, M.D., V. Knight, M.D., M. H. Lepper, M.D., G. Meiklejohn, M.D., L. A. Rantz, M.D., P. S. Rhoads, M.D., from AMA Archives of Internal Medicine, April 1957, pp. 536–538 — Page 5251

II. Article: "FDA Crackdown—Government, Industry Clash Over Bid To Curb Combinations of Drugs—Agency Calls for Withdrawal of 100 Antibiotic Products; Makers Defend Efficacy—Long Term Effect on Profits," by Jonathan Spivak, from the Wall Street Journal, May 6, 1969 — 5253

III. Advertisement: "Who Needs a Cold?" from McCall's magazine, March 1969 — 5256

IV. Letter, dated May 26, 1969, to Senator Gaylord Nelson, chairman, Monopoly Subcommittee, from C. Joseph Stetler, president, Pharmaceutical Manufacturers Association — 5257

V. Letter, dated February 28, 1969, to Senator Gaylord Nelson, chairman, Subcommittee on Monopoly, from C. Joseph Stetler, president, Pharmaceutical Manufacturers Association — 5258

VI. Special article, "Fixed Combinations of Antimicrobial Agents—National Academy of Sciences-National Research Council Division of Medical Sciences Drug Efficacy Study," from New England Journal of Medicine, May 22, 1969, vol. 280, No. 21, pp. 1149–1154, with accompanying editorial — 5258

VII. Statement of Dr. Harry F. Dowling, Department of Medicine, University of Illinois Medical Center, Chicago, Ill., with accompanying Curriculum Vitae — 5269

HEARING DATES*

May 6, 1969:
Morning session — 4999

May 7, 1969:
Morning session — 5023

May 20, 1969:
Morning session — 5085

May 27, 1969:
Morning session — 5133

*The testimony for May 15, 16, 17, June 7 and 8, 1967, appears in pt. 1 of these hearings; the testimony for June 27, 28, 29, July 24, and Aug. 8, 10, 1967, appears in pt. 2 of these hearings; the testimony for Sept. 13, 14, 29, and Oct. 13, 1967, appears in pt. 3 of these hearings; the testimony for Oct. 31, Nov. 9, 15, 16, and 28, 1967, appears in pt. 4 of these hearings; the testimony for Dec. 14, 19, 1967, Jan. 18, 19, and 25, 1968, appears in pt. 5 of these hearings; the testimony for Nov. 29, 1967, Feb. 6, 8, 27, 28, and 29, 1968, appears in pt. 6 of these hearings; the testimony for Apr. 23, 24, and May 1, 1968, appears in pt. 7 of these hearings; the testimony for May 2, 3, and Sept. 17, 1968, appears in pt. 8 of these hearings; the testimony for Sept. 18, 19, and 25, 1968, appears in pt. 9 of these hearings; the testimony for Dec. 11, 17, 18, 19, 1968, and Jan. 23, 1969, appears in pt. 10 of these hearings; the testimony for Feb. 19, 20, 26, 27, Mar. 13, 18, 25, and 26, 1969, appears in pt. 11 of these hearings.

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

TUESDAY, MAY 6, 1969

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 4221, New Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee), presiding.

Present: Senators Nelson and Dole.

Also present: Benjamin Gordon, staff economist; Elaine C. Dye, clerical assistant; and James P. Duffy III, minority counsel.

Senator NELSON. The Subcommittee on Monopoly of the Senate Small Business Committee is resuming its hearings on the pharmaceutical industry and turns its attention today to the advertising, marketing and use of fixed combination drugs.

As a result of the enactment of the Kefauver-Harris Act of 1962, the National Academy of Sciences under contract with the FDA, undertook to engage in a study of the efficacy of drugs put on the market between 1938 and 1962. One of the principal subjects of consideration was combination drugs, which, it is estimated, constitute about 40 percent of the most frequently prescribed drugs in this country.

The Commissioner of the Food and Drug Administration and the National Academy of Sciences agree that—

> . . . the use of two active ingredients in the treatment of the patient who can be cured by one . . . is irrational, illogical, unscientific, and is a disservice to the patient.

The two official compendia, the U.S. Pharmacopeia and the National Formulary do not even list these drugs because it is their judgment that there is no therapeutic basis for giving drugs in a fixed combination. The American Medical Association's Council on Drugs has for years opposed the use of combination drugs. This raises the serious question: On what basis does the Journal of the AMA or any other medical journal accept advertisements that promote bad medical practice?

An example of the kinds of problems presented by fixed combinations is Panalba, a fixed drug combination produced and marketed by the Upjohn Co. The National Academy of Sciences found—

1. That Panalba is ineffective as a fixed combination.

2. It does not seem rational to expose the patient to the potential hazards of two drugs when the beneficial effects are no greater than those resulting from the use of one.

3. A large number of papers purporting to demonstrate clincial efficacy of this combination were reviewed. No properly controlled studies were located and most consisted of reports of a few patients treated with variable results. It is the considered judgment of the panel that this combination has no place in rational therapeutics and should not be marketed.

In light of the National Academy's report that not a single properly controlled study could be found to show that Panalba was clinically effective, it is very strange that this drug is one of the 200 most frequently prescribed drugs in this country. This raises the serious question: On what basis have physicians been prescribing this drug?

The general counsel of the American Medical Association, Mr. Bernard Hirsh, testified before the House Ways and Means Committee on February 26, 1969 that (p. 1535):

> A tax-exempt organization by its very nature is dedicated and should be dedicated to performing things that are in the public interest.

Perhaps his organization can tell us how advertising drug combinations benefits the public?

Mr. Hirsh also stated (p. 1400) that—

> . . . drug advertisements often provide an important step in the process through which the physician becomes educated in the therapeutic value and risks of new drugs . . .

Do the medical journals seriously consider the considerable advertising of Panalba and other combinations as educational?

Dr. Ernest B. Howard, who is now executive vice president of the AMA, told the Kefauver committee in 1961 (p. 119, part I, Drug Industry Antitrust Act) that at the insistence of the AMA's Council on Drugs, the "board of trustees has reached a decision that the mixtures to which the Council on Drugs has referred during the last 5 years will be gradually withdrawn from the Journal, during the next 2 or 3 years."

He said this 8 years ago. This has not been done.

Could the reason be that advertising these drugs provides an important source of revenue? If so, is this a proper consideration for a professional medical society?

These are some of the questions to be explored in depth during the subcommittee's hearings this month. The issues involved are of grave importance to the health and welfare of the American people. It is our hope that the study we are making will shed some light on these perplexing problems so that we may find the means for correcting them.

Before we proceed, I would just like to mention that in an article in the Wall Street Journal [1] this morning, the writer, Mr. Spivak, commented in a rather lengthy column on the fixed combinations, and in the column he stated that:

> Democratic Senator Gaylord Nelson of Wisconsin, who has been holding months of hearings hostile to the industry, is seizing on the FDA action in an effort to embarrass the drug makers further. His Small Business Subcommittee will air criticisms of the antibiotic combinations in a new set of hearings starting today.

[1] See Appendix II, pp. 5253, infra.

I would just like to comment that I am not seizing upon FDA's action but it would seem to me a valid function of a congressional committee to conduct hearings on findings by the most distinguished panel of experts ever gathered to evaluate the efficacy of drugs in the market place.

Mr. Spivak states further:

> The manufacturers may not get an equal chance to defend their products. The Subcommittee hopes to show that the drug companies frequently foist the costly and valueless products on the public by needlessly combining already available drugs. Physicians are then persuaded to prescribe them through high pressure promotion, the critics will charge.

Another excerpt near the end of the column:

> But if the Nelson hearings follow their past pattern, the companies will have little chance to present their rebuttal. The Committee is interested in spotlighting the industry's mistakes, not in giving it a platform for self-defense, spokesmen for drug maufacturers assert.

I am sure that if Mr. Spivak had bothered to talk to the committee or read the record, that he would not have made the report in this fashion. But because he did, I would like to repeat what has been said before this committee time after time, and so that Mr. Spivak or anybody else who bothers to read the record will see that all sides and all viewpoints are invited to appear before the committee.

On January 23, 1969, at the opening of the hearings, I stated for the umpteenth time:

> 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 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 the industry. I do not know of anyone 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.

I will renew the invitation to all the representatives of the drug companies here, that if your company has any desire to appear before this committee, the invitation is open. We will arrange a date as we have stated on innumerable occasions in the past.

Secondly—I quote from the statement on January 23, 1969:

> Secondly, whenever any drug company is criticized before this Committee, we forthwith give them the opportunity to respond, with priority over everyone else. We have always done that.

I repeat that is still the policy, contrary to the implications of the Wall Street Journal piece.

Now, I might say at this point—even more specifically, so the point will not be missed, if the Upjohn representative is here today and Upjohn would like to appear to give testimony on Panalba, we will arrange a date for you at the earliest possible date. I will wait here at the conclusion of the hearings for anybody representing Upjohn or any other company that wishes to appear, because that is, and has been, and continues to be, our policy and it will be so long as I am conducting these hearings.

We are very pleased this morning to have before the committee two very distinguished doctors, Dr. William M. Kirby, professor of medicine, University of Washington School of Medicine, Seattle, and Dr. Heinz Eichenwald, William Buchanan professor and chairman of the Department of Pediatrics, University of Texas Southwestern Medical School, Dallas.

Our first witness will be Dr. Kirby. Dr. Kirby, the committee is very pleased that you have been willing to take the time from your busy schedule to come here today and present your viewpoint and the viewpoint of the Panel on Antibiotics of the National Academy of Science-National Research Council to this committee.

You may present your testimony, Doctor, however you wish. If at any time you would like to elaborate on anything you have said in your statement, just feel free to do so. Your statement will be printed in full in the record.

Dr. Kirby, the committee welcomes you here this morning.

STATEMENT OF DR. WILLIAM M. M. KIRBY, PROFESSOR OF MEDICINE, UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE, SEATTLE, WASH.

Dr. KIRBY. Thank you, sir.

As chairman of one of the five anti-infective panels for the National Academy of Science-National Research Council Drug Efficacy Review I should like to present the reasons for the recommendations made by the panels concerning fixed combinations of anti-infective drugs. Fixed combinations refer to mixtures of antibiotics, or of an antibiotic with another drug, in the same package. They were first marketed during the period 1938–62 when the FDA was charged with passing upon the safety of drugs but not on their efficacy. The Kefauver-Harris Amendments of 1962 specified that efficacy should also be evaluated, and the drug efficacy review was the mechanism chosen to implement this requirement.

The drug amendments of 1962 provide that a drug must have "the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof." For use of the drug efficacy review panels this wording was translated into a guideline specifying that for combinations of drugs "each active ingredient must contribute to the effect of the combination as claimed." The law further requires that there be "substantial evidence" in support of all claims made for therapeutic efficacy.

In reviewing claims of efficacy made for the various antibiotic combinations, the anti-infective panels found that they did not meet the above requirements and they were, therefore, given the evaluation "ineffective as a fixed combination."

Senator NELSON. Excuse me, Doctor. Would you identify the panel—did your particular panel of which you were chairman have a specific title?

Dr. KIRBY. It was called Anti-infective Panel Number 3.

Senator NELSON. I see. And that panel was assigned a certain number of drugs?

Dr. KIRBY. Yes.

Senator NELSON. And how many members were there on your panel?

Dr. KIRBY. Each of the panels had six members. There were five panels. Each had six members.

Senator NELSON. And what was the composition of your panel? In terms of their specialty, experience, background?

Dr. KIRBY. These were all clinical specialists in infectious diseases and antibiotic therapy.

Senator NELSON. Do you have with you for the record, the names and the credentials of the doctors who participated on your panel?

Dr. KIRBY. As I understand it, sir, this is not public information yet.

Senator NELSON. I see.

Dr. KIRBY. And it will not be until the final reports have been completed which I believe will be within a few weeks, and I do not have them with me.

Senator NELSON. Fine. We will put them in the record at that time, then.[1] And, was each of them a specialist in the use or some aspect of the use of the drugs that were assigned to your panel?

Dr. KIRBY. Yes. They were.

Senator NELSON. And they were in the active practice of medicine?

Dr. KIRBY. Yes. All of them are actively practicing and seeing and taking care of patients with infections treated with antibiotics.

Senator NELSON. Thank you. One more question. Do you know how the panels were selected?

Dr. KIRBY. I believe that the National Academy of Sciences appointed an executive committee of the drug efficacy review and they in consultation with many medical societies, who made suggestions, selected the panel members. In other words, it was made up of suggestions by practicing physicians and their organizations throughout the country.

Senator NELSON. Then, the National—did this executive committee that was appointed by the National—National Research Council or National Academy——

Dr. KIRBY. It was the National Research Council which as I understand it, is under the National Academy of Sciences.

Senator NELSON. And that executive board then selected the panels.

Dr. KIRBY. Yes. With consultation and advice from many medical societies.

Senator NELSON. Go ahead, Doctor.

Dr. KIRBY. In theory, fixed combinations of antimicrobial agents would appear to offer some therapeutic advantages, but in actual practice these are difficult to demonstrate. Test tube experiments about 15 years ago showed that two antibiotics sometimes acted synergistically against various bacteria, and this observation led to the marketing of a number of fixed combinations. More extensive studies subsequently showed that with most combinations the action was only occasionally synergistic, more often it was indifferent, and in some instances it was antagonistic. Tests to demonstrate these effects are available in only a few laboratories, so that the physician who gives a patient a fixed combination cannot be certain whether the action

[1] This and other supplementary information, when available, will be incorporated in a subsequent volume.

is likely to be synergistic, indifferent, or antagonistic. Furthermore, clinical studies purporting to confirm laboratory synergism were poorly conducted and controlled, and provided no real evidence that fixed combinations were more effective than when either of the antimicrobial agents was used alone.

Another reason advanced for the use of fixed combinations is that they are likely to be effective in infections caused by a mixture of bacteria, some of which are susceptible to one of the antibiotics and the rest to the other. In actual practice, however, one organism is usually chiefly responsible for clinical infections and the best results are obtained by concentrating on this major pathogen. In the instances where a second antibiotic is likely to be helpful, it is best to obtain cultures and to determine the susceptibility of the micro-organisms to a number of antibiotics. Clinical studies demonstrating the superiority of fixed combinations in infections involving mixtures of bacteria are not available.

Delaying the emergence of antibiotic-resistant bacteria is still another reason given for prescribing antibiotic combinations, but there is no substantial evidence that this objective has been accomplished by the fixed combinations now on the market. Rather, the evidence indicates that bacteria are likely to become resistant to both of the antibacterial agents present in the combination. Finally, by broadening the spectrum of bacteria affected, fixed combinations are frequently administered to increase the likelihood of providing effective therapy. However, in the infections where fixed combinations are commonly used it has not been proven by clinical comparisons that the results are better than when one of the antibiotics is given alone. In seriously ill patients where the infecting organism has not yet been determined, it is indeed proper to administer more than one antibiotic. When this is done, each antibiotic should be selected carefully on the basis of the most likely diagnosis, and they should be administered separately, with dosages being adjusted according to the patient's needs. This involves assessing many factors, including the function of vital organs such as the liver and kidneys.

Thus, aside from the fact that fixed combinations have not been proven to have therapeutic advantages, their use means that the patient is unnecessarily exposed to the toxicity and side effects of two antibiotics rather than one, there is a lack of flexibility of dosage of the individual components, and the development of resistance of bacteria to a number of antibiotics is encouraged.

It might be enlightening now to describe one of the more widely used fixed combinations in relation to the problem of efficacy. Panalba is a fixed combination of two antibiotics, tetracycline and novobiocin. Tetracycline is a first-line antibiotic with a wide spectrum of activity that has been used successfully as a single entity in a great variety of infections for over 15 years. Novobiocin has a fairly narrow range of activity, bacteria quickly become resistant to it, and it has a predilection for causing skin rashes and other side effects. Novobiocin was marketed as a single drug for a few years by Merck, who then dropped it because of its undesirable characteristics and a lack of wide acceptance. Upjohn, with access to both tetracycline and novobiocin, mixed them in the same capsule and has marketed this fixed combination under the trade name of Panalba for a number of years.

Senator NELSON. Pardon me, Doctor. Are all of the fixed combinations, save one, orally administered?

Dr. KIRBY. No, they are not oral. Some are injectable, such as combinations of penicillin and streptomycin.

Senator NELSON. Fixed combinations?

Dr. KIRBY. Yes. Some of the fixed combinations are injectable.

Senator NELSON. Do you know the number involved?

Dr. KIRBY. I do not know that number right off.

Mr. GORDON. Dr. Kirby, may I interrupt just a moment? Are you acquainted with the notice that was put into the Federal Register last week by the Food and Drug Administration on novobiocin?[1]

Dr. KIRBY. Yes, I am.

Mr. GORDON. Do you recall that there is a warning box in which it says novobiocin should be used only for those serious infections where other less toxic drugs are ineffective or contraindicated because of the following:

"1. The high frequency of adverse reactions, including hepatic dysfunction, blood dyscrasias and rashes.

"2. The rapid and frequent emergence of the resistant strains, especially staphylococci.

"3. Its spectrum of antibacterial activity is covered by several other safer and more effective drugs."

Would you comment on the hazards of novobiocin a little further?

Dr. KIRBY. Yes, sir. The hazards, I think, are considerable. I just referred to them here but did not spell them out in the detail that that statement has. And it is these hazards that persuaded Merck to stop marketing this drug after they had done so for a few years. The hazards at that time were well enough known that the drug had quite a restricted usage and was considered undesirable and that is why Merck stopped marketing it voluntarily.

Mr. GORDON. So, Upjohn then picked it up and combined it with tetracycline to——

Dr. KIRBY. Yes. I do not know whether they picked it up then or whether they had it all the time, but they had access to both it and tetracycline, and they thought that this would make a good combination which they then made and have in effect, called it a new product other than just tetracycline.

Mr. GORDON. Would it be reasonable to assume that Upjohn had access to the information on the hazards of this drug?

Dr. KIRBY. Oh, yes, they certainly did, just as much access as anybody.

In the test tube a synergistic action was demonstrated with some bacteria although studies by other investigators showed that the action was more often indifferent and sometimes was antagonistic. Novobiocin was active against staphylococci, a major problem at that time, and these organisms frequently were resistant to tetracycline. Thus, Panalba was promoted as a synergistic combination active against a wide spectrum of bacteria including staphylococci that were resistant to tetracycline and penicillin.

Senator NELSON. May I interrupt? You say thus, Panalba was promoted as a synergistic combination active against a wide spectrum of

[1] See pp. 5168–5171, infra.

bacteria. Do you mean that they simply broadened the promotion to cover a wider spectrum of diseases simply because it was effective against staphylococci?

Dr. KIRBY. No. The spectrum was broadened in that tetracycline in the mixture covered many bacteria, novobiocin covered some others, but the chief additional one that novobiocin covered, in fact probably the only one, was staphylococci, and at that time, 10 years ago, many staphylococci were resistant to tetracycline, so they were broadening the spectrum of bacteria in comparison with the tetracycline alone.

Senator NELSON. But if the combination were prescribed for staphylococci infection, and the combination includes tetracycline, tetracycline in that combination has no effect at all, then, does it?

Dr. KIRBY. No. If they are resistant to tetracycline, then the patient was being exposed to tetracycline when it was doing him no good at all.

Senator NELSON. And as a consequence of exposure to tetracycline or any antibiotic, is there a risk of developing sensitivity to that antibiotic?

Dr. KIRBY. Oh, yes. There is developing sensitivity to it, resistance to it; all of the things that one can develop. Undesirable effects are there whenever you give them, so when you give two of them, you are exposing patients to all of the undesirable effects of both of them.

Senator NELSON. So in a case in which the combination was prescribed for staphylococci infection, the tetracycline then was detrimental to the patient, I would assume.

Dr. KIRBY. Yes, I think we can say it was. It was doing no good and it was doing potential harm.

Senator NELSON. Thank you.

Dr. KIRBY. It has been widely used and in some years has had sales in excess of $20 million.

However, experts in the antibiotic field have through the years been very critical of Panalba. To many of them it meant combining a major league with a minor league drug and considering the result a new, superior product. Panalba is clearly effective in the sense that thousands of patients with infections who have received it have recovered. However, many of these are viral infections that run a benign course uninfluenced by antibiotics. Where bacteria are involved the response has been no different from that observed in thousands of similar cases treated with tetracycline alone.

Senator NELSON. There is no viral infection against which any antibiotic or any other drug is effective?

Dr. KIRBY. Not of the true viruses at the present time, no.

Mr. GORDON. Doctor, is the fact that the patients would have gotten better anyhow, the reason why many doctors say that Panalba works?

Dr. KIRBY. Well, I think so. Panalba has been used chiefly for respiratory infections and 85 or 90 percent of these are due to viruses and the antibiotics have no effect at all.

Now, this is not saying that no antibiotic should ever be used under these circumstances because the doctor often cannot tell whether it is a viral infection or a bacterial infection, and he gives an antibiotic to protect the patient. But he cannot tell which it is and the patient gets well no matter which it is and he is in no position to really conclude

whether the antibiotic cured the patient or not. That is the point we are making here.

For cases where the bacteria are resistant to tetracycline, novobiocin is present in the capsule in half the dose most experts would prescribe, and giving full doses means administering an excessive amount of tetracycline and enhancing its toxicity. No well controlled clinical studies have appeared showing that Panalba is more effective than when the individual ingredients are used alone.

In its evaluation of Panalba the drug efficacy review panel dealt specifically with the claims of the manufacturer in relation to the requirement that for a combination to be judged effective "each active ingredient must contribute to the effect of the combination as claimed." The specific claims in the package insert are as follows:

Panalba (tetracycline phosphate complex with novobiocin) is indicated in the treatment of infections due to organisms that are resistant to other antibiotics but susceptible to Albamycin (novobiocin) and Panmycin (tetracycline) or strongly susceptible to one of these antibiotics and at least moderately sensitive to the other.

The evaluation of the panel was that Panalba is "ineffective as a fixed combination." In explaining this judgment the panel added the following comments:

In infections caused by organisms "susceptible to both" antibiotics, the panel can find no evidence that the combination gives a clinical response different than when the antibiotics are used alone. Thus, it has not been shown that each active ingredient makes a contribution to the effect of the combination as claimed. It does not seem rational to expose the patient to the potential hazards of two drugs when the beneficial effects are no greater than those resulting from the use of one.

In infections caused by organisms "strongly susceptible to one of the contained antibiotics and at least moderately sensitive to the other" the panel can find no evidence of a clinical response greater than that observed when the drug to which the organisms are strongly susceptible is used alone. In this instance the correct procedure would be to omit the drug to which the organism is only moderately sensitive, and to give a larger does of the effective agent, if indicated. Again, it has not been shown that each active ingredient makes a contribution to the effect of the combination as claimed.

In vitro studies of this combination have given variable results. The effects may be antagonistic, additive, or synergistic, and are unpredictable for any particular organism. None of these in vitro data have consistent clinical correlation. There is no practical way of using in vitro tests to identify the instances in which this fixed combination may be advantageous or disadvantageous.

Another important disadvantage of this fixed combination is the inadequate amount of novobiocin present. When used singly, it is the opinion of the panel that novobiocin should be used in the same doses as tetracycline, and in relation to the claims made above there is no rational justification for giving it in half the dose in a fixed combination.

A large number of papers purporting to demonstrate clinical efficacy of this combination were reviewed. No properly controlled studies were located, and most consisted of reports of a few patients treated with variable results. It is the considered judgment of the panel that this combination has no place in rational therapeutics and should not be marketed.

Senator NELSON. May I ask a question at this point? You state that no properly controlled studies were located. I assume the company presented all the data it had to the panel, did it not?

Dr. KIRBY. It did to the Food and Drug Administration originally. All the data from the company was not made available to the panel. Part of it was and the panel made an extensive search itself of the literature to find all the articles it could.

Senator NELSON. Well, was any data of value on which the panel could make a judgment not furnished by the FDA?

Dr. KIRBY. No. Nothing was withheld.

Senator NELSON. So, all the material that the FDA had to support the efficacy of the drug was available to the panel?

Dr. KIRBY. Was available to the panel, yes, sir.

Senator NELSON. Then the panel explored the literature on the drug also.

Dr. KIRBY. Also. Yes. In addition to the FDA supplying material, the panel made its own individual search of the literature to find all the articles bearing on the subject.

Senator NELSON. Thank you.

Dr. KIRBY. Panalba is only one of more than 80 fixed antibiotic combinations reviewed by the five anti-infective panels, and they all received similar comments and evaluations.

Senator NELSON. Eighty fixed antibiotic combinations were reviewed and the judgment of lack of efficacy was found on each one of the 80?

Dr. KIRBY. Yes. I believe that is true. It is more than 80—83 or 84, I believe.

Senator NELSON. Have the five panels completed their review of antibiotics?

Dr. KIRBY. Yes, they have.

Senator NELSON. Does that number that they have reviewed cover all the antibiotic combinations in the market?

Dr. KIRBY. Yes, it does.

Senator NELSON. Did the panel find that any one of the antibiotic drug combinations met the appropriate standards of efficacy under the law?

Dr. KIRBY. I do not believe they did. I cannot answer that categorically, because I was only involved with some of them but I do not believe so.

Senator NELSON. How many antiobiotics were reviewed by panel 3? That is your panel, is it not?

Dr. KIRBY. Yes. I am sorry, I cannot give you that figure right off, either.

Senator NELSON. But every one of those reviewed by your panel was found to be——

Dr. KIRBY. Oh, yes, was judged ineffective. Every one by our panel, and I think perhaps we had the largest number, just about the largest number, at least, of the fixed combinations.

Senator NELSON. Were the findings of your panel on each antibiotic combination unanimous?

Dr. KIRBY. Yes, they were.

Senator NELSON. Go ahead.

Dr. KIRBY. A curious paradox has been the continued widespread usage of these fixed combinations despite the fact that the experts, without exception to my knowledge, have opposed them. In April of 1957 nine leading infectious disease authorities, concerned about the increasing number of fixed combinations being marketed, signed an editorial in a prominent medical journal that stated the following.[1] And this incidentally, was the Archives of Internal Medicine, the issue of April 1957, and in an editorial——

[1] See Appendix I, pp. 5251–5252, infra.

Senator NELSON. The Archives of Internal Medicine is a publication of the American Medical Association?

Dr. KIRBY. Yes, sir; it is.

Senator NELSON. And this is an editorial from the Archives.

Dr. KIRBY. Yes. An editorial from the Archive of Internal Medicine in April of 1957.

Senator NELSON. Go ahead.

Dr. KIRBY. These nine men said:

> There are no data or experience which would justify the employment of any fixed combination of two antibiotics in a single ampule or a single tablet or capsule for systemic use. It is our firm conviction that the promotion and sale of such combinations should be discouraged until and unless adequate data from controlled clinical investigation justify this practice, and then only with respect to definite combinations for specific purposes.

The opinion of the experts has not changed since that time and similar statements have appeared on numerous occasions in articles, reviews, and editorials. It should be clearly understood that these antibiotic experts are not ivory tower scientists. They are not, as a recent article in the Wall Street Journal said of the Drug Efficacy Review panelists, "for the most part academic medical experts rather than practicing physicians." On the contrary, they are physicians who practice in teaching medical centers throughout the country.

Senator NELSON. In the article this morning in the Wall Street Journal, they repeat the same statement early in the article, third paragraph. It says:

> Government and academic experts increasingly contend that many of these mixtures unnecessarily expose patients to several drugs at once, permit the physician to avoid careful diagnosis and prevents tailoring of the prescription to the patient's particular needs.

I just call attention to the fact that the Wall Street Journal is still repeating the allegation that these are academic experts. You are emphasizing here that they are practicing physicians; is that not correct?

Dr. KIRBY. Yes, sir. These are all clinicians who deal with the laboratory side and with the clinical side and are the most competent to deal with the most severe infections, and indeed, the practicing physicians out in the community refer their real treatment problems to these experts.

These are not test tube scientists. These are practicing physicians. They deal with infections ranging from mild to the most serious, and patients are referred to these centers because of the special knowledge and experience of the infectious disease specialists. Being expert at both the laboratory and clinical aspects, they are especially equipped to evaluate the true potential of antibiotics. These men have consistently opposed the use of fixed combinations for all the reasons we have mentioned, and it is not surprising that under the drug amendments of 1962 these products have been given the evaluation "ineffective as a fixed drug combination."

Why, it may be asked, if fixed combinations have these deficiencies and are opposed by the experts, have they been so widely used in the treatment of patients? The chief motive of the individual physician is to do his best for the patient, and I am not accusing him of negligence or incompetence. The answer lies, I think, in the education provided

by the drug companies, otherwise known as advertising, including elaborate displays in medical journals and at medical meetings, visits by detail men, et cetera. I would like to show an example. I have with me here a recent issue of the Journal of the American Medical Association, the entire back cover of which is an advertisement for Panalba.

Senator NELSON. What is the date of that?

Dr. KIRBY. In fact, I happen to have two of them because they show a little different format. This first one is March 31 issue of this year, and the second one is the issue of April 21.

Senator NELSON. What is the difference between the two ads?

Dr. KIRBY. Well, they contain the same information. It is just simply a matter of where the Panalba is put and the kind of picture showing the capsules themselves. A little different format. But in both instances it is the entire back cover of the JAMA that contains this advertisement for Panalba.

Senator NELSON. This ad appears at a stage in history despite the editorial in April 1957 in the——

Dr. KIRBY. In the JAMA, Archives of Internal Medicine.

Senator NELSON. Yes.

Dr. KIRBY. Yes, sir.

Senator NELSON. I might call attention at this time to an aspect of the advertising that the committee has raised with the representatives of the medical journals that have been here. The JAMA states on its title page:

Advertising principles. Advertisements in this issue have been reviewed to comply with the principles governing advertising in AMA scientific publications. A copy of these principles is available upon request from the Office of Advertising Evaluation.

Then, we have here the principles that they say guide the Journal in the acceptance of ads, the full statement of principles.[1] I would simply like to point out for the hearing record, because as I say, we have raised this issue with representatives of each of the medical journals that has appeared before the committee, that the AMA principles describe the type of data needed to support an ad.

Data should include pertinent reports published and unpublished, favorable and unfavorable, of clinical and laboratory investigations covering the efficacy and relative safety of the product under consideration—

They include the word efficacy themselves.

These data should be based upon sound studies and should be sufficiently comprehensive to permit a critical evaluation of the subject matter. While the quantity of the scientific data required will depend upon the type of product, the nature of the medical problem involved, and the claims made in the advertising copy, the quality of the evidence is regarded as highly important; in this respect the importance of suitable controls is emphasized. Compilations of subjective individual case reports and testimonials are not considered acceptable evidence.

Then in another part of the AMA principles it is stated:

Mixtures of drugs. Clinical and laboratory data should be submitted for review by the Office of Advertising Evaluation. Clearance depends primarily on showing justifications for the rationality of the combination.

I simply point out for the record that here is the most distinguished, largest professional medical organization in the country, that is con-

[1] See testimony of Dr. Edward R. Annis, Past President, AMA, pt. 11, pp. 4583–4707.

sistently violating the standards it has established for itself and is contrary to the editorial that they ran in their own publication in 1957 and contrary to the position of the Drug Council of the AMA. I raise this not for any comments by you, Doctor, but because I have raised the issue of the propriety of professional journals permitting the advertising and promotion of drugs that promote bad medical practice, and here is a case where the AMA is clearly violating its own standards as well as running contrary to the judgment of—in running the ad, to the judgment of all the scientific expertise in this country on fixed combinations.

Go ahead, Doctor.

Dr. KIRBY. This spread, which has appeared on several issues of this weekly journal during the past 4 months, is sent to almost all practicing physicians in the United States.

It is well known that the American Medical Association has an advertising department, presumably with high standards, and it can reasonably be assumed that a display of the name Panalba in such a prominent fashion is not only a reminder but is in a sense an endorsement of the product. In comparison with the occasional negative statements made by antibiotic experts, the positive message of this advertisement is brought repeatedly to the attention of the practicing physician, and with the additional incentive of an implied endorsement it is not surprising that the product is widely used. Doctors do not like to admit that they are influenced by advertising but it seems to me that the facts speak for themselves. Whenever doctors tell me that they depend on the experts, I remind them of the fixed combinations such as Panalba. Here is a product that is opposed by all the experts in the field, but it still is used widely in clinical therapy. This message is apparently very clear to the pharmaceutical houses, who spend several hundred million dollars a year in advertising their products to the medical profession. These expenditures would not be likely to continue if they did not bear results.

It should not be inferred from these remarks that I am an opponent of the drug industry. For 25 years my chief research interest has been the evaluation of new antibiotics, and this has meant close collaboration with a number of the leading firms. Their development and refinement of the many antibiotics now available has been a milestone in the relief of human suffering.

In my opinion the drug amendments of 1962 have added a valuable new dimension to the evaluation and approval of antibiotics and other drugs. Their implementation in regard to fixed combinations of antibiotics has not yet materialized, but hopefully the evaluations of the drug efficacy review panels, together with the recent directives of the FDA proposing to remove them from the market, will correct this situation.

Senator NELSON. Just for the record, Doctor, we want to put in, just on the question of prices, that the fixed combination Panalba sells to the pharmacist for $30.42 a 100, whereas the highest brand name price of tetracycline is $11.22 a 100, whereas generic tetracycline from reputable houses sells from $3 to $4.50. Panalba costs from six to 10 times the cost of tetracycline sold under the generic name.

I appreciate very much your very thoughtful statement and your very fine contribution to these hearings. We appreciate your taking the time to come.

Senator DOLE. Mr. Chairman——

Senator NELSON. Yes.

Senator DOLE. I am just wondering, as a matter of information, is this drug now being reviewed by the Food and Drug Administration as a result of the 1962 act? Do you know, Dr. Kirby?

Dr. KIRBY. Yes, sir. They set up this review mechanism under contract with the National Academy of Sciences. These panels reviewed Panalba and all of these drugs and have judged these combinations as ineffective. The FDA has studied these panel recommendations and has proposed the removal of Panalba and similar combinations from the market. They have reviewed them and they are initiating action.

Senator DOLE. When was that decision made? Was that just this year?

Dr. KIRBY. Yes.

Senator DOLE. Late last year?

Dr. KIRBY. Quite recent, within the last couple of months, "No." I guess with Panalba and some others it was about 6 months ago actually, when the initial proposal of removal from the market, and then it goes through naturally a review and appeal process, which I believe is now underway.

Senator DOLE. That is what I am wondering, what the status of the case was now, whether or not we might be prejudging or prejudicing the rights of anyone involved by this hearing.

Dr. KIRBY. I cannot comment on that, sir.

Senator DOLE. You do not know—has there been an order withdrawing Panalba from the market?

Dr. KIRBY. Yes; there has been an order and it is now in the process of the appeal and review process.

Senator DOLE. But that has not been fully completed, then, the review process.

Dr. KIRBY. Not to my knowledge.

Senator DOLE. I assume if that decision should be in accord with the FDA decision, then that is the end of the recourse as far as the drug company might have, right?

Dr. KIRBY. No, sir, It can still go to the courts, I believe.

Senator DOLE. These things sometimes drag on and on, I assume.

Dr. KIRBY. Yes, sir; I believe that is right. They could easily go through court proceeedings. I believe Commissioner Ley is going to testify and will be able to answer this very specifically.

Senator DOLE. But, I think basically, then, my only point is, as I have said in other hearings, I am not the expert that my chairman is, not having been on this committee until January this year, but there are procedures now to review these drugs, whether it be this specific drug or any other combination, and these were prescribed or at least, authorized by the 1962 act and it seems if we have the administrative procedure, then we might better follow it. I assume we will find out from the FDA witnesses, then, just what the status of it is.

Thank you.

Senator NELSON. I might say to the Senator that all of the findings and recommendations of the National Research Council of the National Academy of Sciences have been made public, have been filed in the Federal Register. We have invited Dr. Ley of the FDA and we have invited all the drug companies whose drugs are affected, to appear before the committee to present their side.

Thank you very much, Dr. Kirby.

Our next witness is Dr. Eichenwald. Doctor, the committee is very pleased to have you here this morning. As I said to Dr. Kirby, if there is any aspect of your testimony on which you would like to elaborate extemporaneously, feel free to do so. I assume you do not mind being interrupted with questions.

Go ahead, Doctor.

STATEMENT OF DR. HEINZ F. EICHENWALD, WILLIAM BUCHANAN PROFESSOR AND CHAIRMAN, DEPARTMENT OF PEDIATRICS, UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL SCHOOL, DALLAS, TEX.

Dr. EICHENWALD. Thank you, Senator, and Senator Dole.

As you gentlemen are aware, the National Academy of Sciences-National Research Council undertook a drug efficacy study in 1966 under contract with the Food and Drug Administration. Essentially, the organization agreed to review the claims for effectiveness of drugs approved between 1938 and 1962. The study was conducted by a group of 30 panels, each consisting of a chairman and five additional members. Five of the panels concerned themselves with antimicrobial agents and each had occasion to consider the claims for efficacy of several products containing fixed combinations of antimicrobial drugs. I was chairman of the Antibiotics Panel No. 1.

It is of interest that all five panels, consisting of a total of 30 recognized experts in the field of antimicrobial therapy, concluded unanimously that there was no place in the medical armamentarium for fixed antimicrobial drug combinations or for products consisting of antibiotics combined with other pharmacologically active drugs. There are few instances in medicine when so many experts have agreed unanimously and without reservation.

The panel chairmen felt it to be desirable to inform the medical profession of the facts on which the unanimous recommendations were based. Accordingly, a scientific paper entitled "Fixed Combinations of Antimicrobial Agents," was written for publication in the New England Journal of Medicine. At the time of my statement, the article has not appeared. A copy of the manuscript has been supplied to this committee. It will be generally available as soon as it has been published.

Senator NELSON. I understand that Dr. Inglefinger of the New England Journal of Medicine has accepted the article?

Dr. EICHENWALD. Yes.

Senator NELSON. And plans to publish it in an early journal.

Dr. EICHENWALD. I think within the next month, May 22.[1]

[1] See Appendix VI, pp. 5258–5269.

Senator NELSON. And this is an article which summarizes the findings of all 30 panels, is that correct?

Dr. EICHENWALD. No. This deals only with the findings on fixed combinations of antibiotics by five panels.

Senator NELSON. And this—who is the author of the article?

Dr. EICHENWALD. It is a number of people. It was basically authored by Dr. Calvin Kunin and Dr. Bill Hewitt, who were chairmen of the two of the antibiotic panels. It was also commented on and modified by the other panel chairmen.

Senator NELSON. And did all of the panel chairmen approve of the article?

Dr. EICHENWALD. Yes, sir; unanimously.

The reasons why combinations are not useful and why they are potentially dangerous are summarized in this article in the New England Journal of Medicine; in my statement, I would like to comment on some of the factors which led to these conclusions.

One might ask if expert medical opinion is so unanimously opposed to fixed combinations of antibiotics, why were these preparations ever marketed? The pharmaceutical houses have provided several justifications which, to them, provide a basis for the commercial preparation of these mixtures:

(1) They are useful in the treatment of mixed bacterial infections.

(2) There is enhancement of antibacterial activity from the use of combinations.

(3) Because combinations "widen the spectrum of activity," they provide for satisfactory treatment of infections before etiology is known or in cases when it is impossible to determine the etiology.

(4) Antibiotic combinations were used extemporaneously by physicians prior to the introduction of the fixed dosage commercially available drugs.

(5) Combinations are cheaper than the sum of the price of the individual ingredients.

(6) Combinations are easier to administer and thus more convenient.

(7) Physicians demanded combinations and the pharmaceutical houses simply followed the demand.

(8) Following their introduction, combinations were used widely, some of them in fact becoming "best sellers". Thus, the acceptance by physicians indicates that these preparations must be useful and have filled a so-called therapeutic gap.

Allow me to comment on each of these reasons.

First, the problem of mixed bacterial infections. The sort of situation, where several microbial organism work together to cause disease is relatively uncommon but may occur in such illnesses as bronchiectasis, peritonitis, urinary tract infections, chronic otitis media, and occasionally in burns. Many different species of bacteria are associated with these conditions and patterns of antimicrobial sensitivity are very variable. Thus, it is unlikely that any given fixed combination would contain either the proper drugs or the proper amounts of each drug to be effective in even a relatively modest proportion of cases. Additionally, it has been demonstrated that while under some rather prescribed circumstances a "broad spectrum" effect may be produced by the com-

bination of two antimicrobial agents, the degree of antibacterial activity is generally quite unpredictable and under other circumstances antimicrobial effectiveness may be decreased by combination therapy.

Furthermore, in the case of several of the available combinations (such as Panalba, Albamycin T, Signemycin, erthromycin-sulfa, et cetera), the dosage formulation is such that in some instances, if the manufacturer's recommendations are followed, the patient would receive too little of both drugs for maximal effectiveness, in other instances, too little of one of the two drugs in the combination, and in the case of some erythromycin-sulfa combinations, if the physician wishes to administer even moderately large doses of erythromycin, the patient will receive an excessive and potentially dangerous amount of sulfonamides.

Let me comment next on possible enhancement of antibacterial activity by two drugs. It is true that in three unusual circumstances combinations of drugs are more effective than single drugs alone. The best example is perhaps tuberculosis; bacterial and endocarditis due to group D streptococci and occasional endocarditis due to streptococcus viridans are treated more effectively by a combination than by single drugs. However, it must be emphasized that these are rare and very serious infections where dosage of each drug is usually individually adjusted on the basis of many considerations.

Senator NELSON. When you state on page 2 that it is true that in three unusual circumstances, combinations of drugs are more effective than single drugs alone, you, I take it, still are not recommending that a fixed combination be used in the treatment.

Dr. EICHENWALD. No, I am not.

In general, laboratory testing of combinations has given variable results, depending on the concentration of drug employed, the specific laboratory conditions, the nature and susceptibility of the organism, et cetera. The effects of combination may be antagonistic (which means that activity is less than the sum of the separate activities). There may be synergism (enhancement of antibacterial activities beyond the additive effects of the two drugs) and, finally, there may be addition (activity equal to the additive effect of the two drugs). None of the in vitro data, the test tube data, have consistent clinical correlations. There is no way of using in vitro tests to identify instances in which fixed combinations will be advantageous or disadvantageous.

Despite the fact that many of the drug combinations have been on the market for a decade or more, no controlled studies have appeared in the literature which would indicate that the enhancement of clinical activity claimed for these combinations exists. During the National Drug Study, each pharmaceutical firm marketing a combination was given the opportunity to provide to the panel supporting data for their claims; none were forthcoming. The data in the literature purporting to demonstrate clinical efficacy for these combinations are uncontrolled, and mostly consist of a few patients treated with variable results. In general, the results obtained were no better than those one would expect had a single agent been used.

The third theoretical argument for combinations is that they permit more ready treatment of infections before etiology is known and are useful in instances where it is impossible to determine etiology.

It is true that at times it is necessary to treat patients with severe infections before the etiology has been determined. There are indeed valid indications for the use of drug combinations in such instances. However, in all cases the drugs used should be given at least initially by the parenteral route. With one exception, penicillin-streptomycin, all fixed combinations on the market can only be given orally. Furthermore, the combinations that are useful in these limited circumstances, at least in my field of medicine, are not the drugs available in combinations. The limitation imposed upon the physician by a combination consisting of fixed amounts of drugs are again obvious, particularly in pediatrics where careful dosage control is essential. Furthermore, at the present moment there are single drug entities available which are highly effective and reasonably free of toxicity so that the so-called "broad spectrum" argument for combinations has become progressively less valid.

The fourth argument is that physicians used combinations before the pharmaceutical houses introduced them. Again, this is true but only for a very limited series of conditions. In most cases, the physicians tailored the use of two drugs to the patient's specific condition, something not possible with fixed combinations.

Senator NELSON. May I ask a question, Doctor? The fourth argument is that physicians used combinations before the pharmaceutical houses introduced them. Did physicians actually make up their own fixed combinations?

Dr. EICHENWALD. No. What they did was prescribe two antibiotics simultaneously to the patient.

Senator NELSON. So the argument of the drug companies, when they said doctors used combinations, still does not apply to fixed combinations?

Dr. EICHENWALD. That is right. As I indicated, the physicians tailored the use of the drugs to the patient's specific condition.

Furthermore, some of the more popularly used oral combinations such as penicillin and sulfa and erythromycin and sulfa, which have been employed in the past in the treatment of middle ear infections in children have subsequently been shown to be no more effective than either penicillin or erythromycin alone. However, the important point is that a physician, in those limited instances when he did use combinations in the past, adjusted the dosages of the different components to the specific needs of the patient.

The claims of greater convenience and lower expense should be considered. Since combinations are clinically only very rarely indicated and then only in adjustable dosage, this argument for the existence of combinations is silly. This whole business involves a type of circular reasoning which totally avoids the issue of effectiveness and safety.

The last two reasons given by the pharmaceutical industry for the existence of drug combinations can be considered together. It is claimed that the physicians demanded them and their usefulness is shown by the fact that they are widely used. This, again, involves some circuitous reasoning because the pharmaceutical houses point to the admittedly widespread use of combinations to state that physicians must, therefore, demand them. In fact, the opposite is true,

the demand was created by misleading advertising and by the inability of many physicians to evaluate the claims made for these agents.

Mr. GORDON. Dr. Eichenwald, may I interrupt at this point? I would like to read a statement to you. This is from a very prominent doctor.

I do not pay much heed to all this scientific testing, this measurement of blood levels, this testing in animals. I am accustomed to certain brands and I have good luck with them. The final test is the patient himself. If I want to know if a drug is any good or not, I ask my patients.

What do you think of that?

Dr. EICHENWALD. Well, I think this attitude is a rather strange one in this era of science. I think if one asked a patient whether a powdered unicorn horn helped him he would also say yes, because we are all aware of the fact that most illnesses are self-limiting and the administration of any material does have a so-called placebo effect. This is why patients always feel better when they get a medicine, whether the medication really helps them or not.

Certainly, the patient is perhaps the last individual who can evaluate therapeutic usefulness of a drug.

Mr. GORDON. You might be interested to know that that statement was made by Dr. Robert S. Long, head of the American Society of Internal Medicine as quoted by U.S. Medicine and he testified before our committee not too long ago.

Dr. EICHENWALD. All I can say is I do not agree with the statement.

No one can argue that these drugs are not widely employed. In the case of some of them, such as Signemycin and Panalba, this amounts, in my mind, to a strong indictment of the ability of many physicians to judge what is effective and what is not. All of us are aware that the great majority of conditions for which these drugs are employed are, in fact, self-limiting; many represent viral infections of the respiratory tract which run their course totally unaffected by any type of therapy.

I cannot overemphasize the fact that the demand for these agents was created by advertising which made claims which are still, a decade or so later, unsubstantiated on the basis of controlled observations. Thus, the guillible physician was lulled into a sense of security which substituted a "miracle combination" for his own diagnostic judgment or laboratory work. The pressures went something like this:

You can treat nearly everything you encounter with one of these combinations, then why bother to make exact diagnoses or perform laboratory work required for the identification of a specific bacterial agent causing the disease in question.

What are the disadvantages of the fixed combinations and why do I feel that they have no place in medicine?

In the first place, there is no antimicrobial agent which is not potentially dangerous. I know you are aware of the disastrous consequences that follow the use of penicillin in certain individuals allergic to it. The toxicity of chloramphenicol has been discussed before this committee many times. Even the minimally toxic antibiotics, such as erythromycin, can produce liver disease in some individuals. There are no harmless antibiotics. Reactions to all antimicrobia agents are common and reactions can be severe and fatal. The use of two drugs simultaneously increases the risk to the patient at least twofold; it is

possible that certain combinations are synergistically toxic. Furthermore, if a patient on a drug combination does develop an untoward reaction, it is difficult and usually impossible to determine which one of the agents is responsible.

I have already spoken of the disadvantages of fixed drug combinations in terms of efficacy and potential toxicity. When the physician is dealing with fixed combinations, he will never find it possible to increase or lower the dose of one component of the mixture without at the same time affecting the dose of the other. In this circumstance, the tendency is either to raise the dose of one drug to a desired level and thus inadvertently to give an overdose of the other or to lower the dose of one compound and, consequently, give an insufficient dose of the other. All humans differ from each other, not only in such readily observable measurements as size, weights, and age, but also in terms of their ability to metabolize and excrete certain agents, their tendency toward the development of allergy, et cetera. The fixed combinations assume that everyone is the same, that an 80-year-old man differs little from a 20-year-old.

Furthermore, a number of the available combinations consist of agents which have either no usefulness, or limited usefulness combined with high toxicity, at least in the child population. A good example are the tetracycline-novobiocin combinations, Panalba and the tetracycline-oleandomycin combination, Signemycin. I might quote the overall evaluation of novobiocin prepared by my antibiotic panel of the National Research Council-National Academy of Sciences.

In summary, novobiocin is limited by (1) a narrow spectrum which duplicates that of many other agents, (2) rapid emergence of resistant strains, and (3) high frequency of adverse reactions, especially skin rashes and hepatic dysfunction. The development of safer and more effective drugs has virtually eliminated the need for novobiocin. The majority of the panel believes that orally administered novobiocin should be taken off the market.

Similarly, the panel's evaluation of triacetyl-oleandomycin and oleandomycin is as follows:

For each of the infections specifically mentioned in the package insert under "Indications" for which there are data to support chemotherapeutic activity, there are several antimicrobial drugs that the panel would recommend preferentially to triacetyl-oleandomycin (or oleandomycin).

It is dangerously misleading to list triacetyl-oleandomycin (or oleandomycin) without qualification as the drug to be used for any infection.

Furthermore, in a recent summary of the value of tetracyclines in pediatric practice, prepared at the request of the editors of The Journal of Pediatrics, my associates and I make the following statements:

The tetracyclines possess an unusually high index of toxicity, and a low order of activity against most of the organisms responsible for common infections in pediatrics. Thus, this group should be relegated to the position of limited purpose drugs, prescribed only if other more effective and less toxic antimicrobials cannot be administered, as well as in a few, relatively specialized situations. Even in hospitalized patients, the tetracyclines find limited usefulness.

I would like to emphasize I am dealing here again, with children.

Senator NELSON. When you say even in hospitalized patients, you are referring to——

Dr. EICHENWALD. Children.

Senator NELSON. Pediatrics.

Dr. EICHENWALD. Yes, sir.

Senator NELSON. What are the commonest cases for the use of tetracycline?

Dr. EICHENWALD. In children?

Senator NELSON. Children—there are some uses in children, is that right?

Dr. EICHENWALD. Yes, sir. They are very limited.

Senator NELSON. What are they?

Dr. EICHENWALD. We use tetracyclines for certain urinary tract infections. We use tetracycline for certain types of shigellosis, if the organisms are resistant to other agents. We use it in the Rocky Mountain spotted fever and other rickettsial diseases. Sometimes in the treatment of peritonitis.

Senator NELSON. And what are its commonest indications for use in nonpediatric practice?

Dr. EICHENWALD. I would prefer Dr. Kirby answer that question. I am a pediatrician. He is an internist.

Dr. KIRBY. Well, tetracyclines are still valuable in a number of instances. For example, for one kind of anaerobic bacteria called bacteroides, they are very specifically active. In certain of the less common types of venereal infections, such as lymphogranuloma venereum, they are specifically useful. And in a number of other less common diseases such as rickettsial infections, they have value. In treatment of peritonitis and generalized intestinal infections they are often, because of their coverage, useful. I would say there is no question that tetracyclines still play a very valuable role in therapy.

Senator NELSON. Thank you.

Dr. EICHENWALD. Thus, both components, tetracyclines and oleandomycin, of the most widely advertised and used combinations have been judged to be relatively highly toxic, and of very limited usefulness, at least in children.

I would not wish to end this statement without commenting on combinations which include an antimicrobial agent, as well as a variety of other drugs. One example of this type that might be cited is Tain, which consists of triacetyl-oleandomycin plus an aspirin-like compound, an oral nasal decongestant, and an antihistaminic drug. One might wonder why the manufacturer did not include vitamins, sex hormones, a contraceptive, and corticosteroids to cover all other eventualities.

Mr. GORDON. Dr. Eichenwald, was this one of the drugs reviewed by the drug efficacy panel?

Dr. EICHENWALD. Yes, this was reviewed by my panel.

There is no bacterial condition which I know of which requires the use of these various agents even when given singly. Secondly, I have already commented on the high toxicity of triacetyl-oleandomycin, and this fact, combined with its relative ineffectiveness, has led the panel to recommend its withdrawal from the market. Furthermore, combining four drugs, each with rather distinct pharmacologic properties to which there are considerable individual sensitivities in patients, greatly increases the overall risk of side effects. If the dosage of triacetyl-oleandomycin is increased for therapeutic reasons. There is a great risk of side effects from the other drugs. On the other hand,

the patient will be undertreated with triacetyl-oleandomycin if the dosage is reduced to avoid the side effects of the other compounds. Tain, along with other similar combinations represents an ineffectual, toxic, and totally illogical preparation.

I am citing Tain to bring to your attention the fact that antibiotics are not only combined with each other but also with other pharmacologically active ingredients. Occasionally, these situations are reduced to the point of utter absurdity when an antimicrobial agent, ineffective against the organisms producing the syndrome for which its use is recommended, is combined with a substance that is a placebo, devoid of any useful pharmacologic activity. An example of this situation is the combination of streptomycin with a kaolin-pectin material, resulting in a mixture recommended, and used, for the treatment of diarrhea. Streptomycin administered orally is not useful in the treatment of any bacterial diarrhea and the value of the kaolin-pectin material, while no doubt harmless, has, in my judgment, never been adequately established.

Senator NELSON. Is this combination administered orally?

Dr. EICHENWALD. Yes, sir; it is an oral combination.

Senator NELSON. Is streptomycin effective as a bacterial agent in diarrhea used parenterially?

Dr. EICHENWALD. No, sir. There is no type of bacterial diarrhea that is effectively dealt with by streptomycin.

Senator NELSON. So, neither the combination or ingredients combination is effective for this purpose?

Dr. EICHENWALD. That is right. However, this material enjoys relatively widespread use. The only thing one can say in its favor is that it is probably relatively innocuous, unless used for very prolonged periods of time, since the streptomycin is only poorly absorbed.

In this statement, I have interwoven my own opinions with those of panels of the National Research Council-National Academy of Sciences. This would appear to make little difference since our recommendations concerning the combinations were unanimous and thus, my own personal observations would correspond closely to those of the 29 other individuals knowledgeable in the field of infectious diseases and their treatment.

I would like to add to my statement that it has been stated in recent weeks by various individuals and various organizations that physicians who work in academic institutions are not qualified to assess the value of drugs because they "do not treat patients," but sit in an ivory tower.

This, of course, is nonsense. I, like other members of the academic community, am responsible for the treatment of more patients directly or indirectly than any practicing physician. Furthermore, the practicing physician obviously thinks that I know what I am doing since he asks me to take care of his own children whenever they get sick. I have also taken care of children of executives as well as line employees for the pharmaceutical houses. So, I do not think they believe their own statement.

I am sure the situation is true also for that of other academic physicians.

Finally, if a physician in an academic institution is unqualified to evaluate therapy, then he should not be teaching in medical schools.

Senator NELSON. Thank you, doctor.

These panels were directing their attention to that aspect of the 1962 law that required adequate proof of efficacy——

Dr. EICHENWALD. Yes, sir.

Senator NELSON (continuing). In order to stay in the marketplace. You have commented, as did Dr. Kirby, on other problems of combinations including safety. As I understand it, prior to 1938, there was no necessity for proving either safety or efficacy. Would it be your judgment as to this question: Do the combinations pose a sufficient safety consideration to justify their removal on that basis?

Dr. EICHENWALD. I believe some of them do while others do not. Certainly, in my judgment, the combinations of tetracycline and novobiocin and tetracycline and oleandomycin, possess sufficient hazard that on the basis of toxicity alone they should not be on the market. Some of the other combinations are more innocuous. Erythromycin and sulfa and this would not be——

Senator NELSON. What about the question of any antibiotic sensitizing a patient so that a subsequent administration may be serious?

Dr. EICHENWALD. This is true for all antibiotics, of course. This has an inference by use of combinations.

Mr. GORDON. Dr. Ernest Howard, who is now executive vice president of the American Medical Association, stated before the Kefauver committee—

Inevitably a useless drug will not be used because of the training and experience of physicians, because of their experience with this useless drug, if it is permitted to be marketed. * * * We feel that a profession fully knowledgeable in a free market economy will soon bring about the withdrawal from the market of a useless drug.

What do you think about that?

Dr. EICHENWALD. Well, I would not agree with that statement for a number of reasons. As I mentioned earlier, drugs have a certain placebo value. Giving the patient anything, particularly if it is injectable and if it hurts, will make the patient feel better whether the patient is in fact, improved or not.

Secondly, also I think the whole history of medicine has indicated that this statement is not correct. I might refer to a drug that was removed prior to the Kefauver hearings from the market, a drug called Altafur, which was marketed by a pharmaceutical house under the advertising slogan: "A new star on the antibiotic horizon."

Mr. GORDON. What did you say? New star?

Dr. EICHENWALD. Yes. New star on the antibiotic horizon. I remember that very well. The drug was totally ineffective. A variety of therapeutic trials indicated it to be totally ineffective. In fact, it produced no blood levels that were measurable. However, because the Kefauver amendments had not been passed, the only recourse FDA had to remove this drug from the market was because of its toxicity. It was a highly toxic agent. It had, unfortunately, been allowed on the market and a series of hearings was held. I testified as to the toxicity of the drug. But here is a good example that an agent that was totally devoid of any therapeutic activity was widely used and could only be removed from the market because of its high toxicity. I think this would go against the statement made that the drug would not have sold. It sold quite well.

Mr. GORDON. Concerning novobiocin, is it correct that the panels of the NAS–NRC recommended that it be taken off the market?

Dr. EICHENWALD. In the case of novobiocin, if I remember correctly, there was a split vote. A majority of the panel felt it should be removed. A minority felt that it should be permitted to remain on the market with a very stringent warning note. This is information that was transmitted to the FDA.

Senator NELSON. I want to thank both of you for your very valuable contribution to these hearings, and again repeat, we appreciate your taking the time from your very busy schedules to come here today.

Thank you very much.

We will resume hearings at 9 o'clock tomorrow morning.

(Whereupon, at 11:35 a.m., the hearing was recessed, to reconvene at 9 a.m., Wednesday, May 7, 1969.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

WEDNESDAY, MAY 7, 1969

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

The subcommittee met, pursuant to recess, at 9:25 a.m., in room 4221, New Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senators Nelson and Dole.

Also present: Benjamin Gordon, staff economist; Elaine C. Dye, clerical assistant; and James P. Duffy III, minority counsel.

Senator NELSON. We will now open the hearings this morning.

We have three witnesses. Dr. Calvin Kunin, chairman of the department of preventive medicine, University of Virginia at Charlottesville; Dr. Robert Wise, who is chairman of the department of medicine at the Jefferson Medical College at Philadelphia; and Dr. William Hewitt, the University of California School of Medicine at Los Angeles, and professor of internal medicine.

Our first witness this morning will be Dr. Kunin.

Dr. Kunin, the committee is very pleased to welcome you back again. You may present your testimony in any fashion you desire. The complete statement will be printed in the record. You are free to extemporize from it at any point that you may desire to elaborate on anything you have said.

I assume that you have no objections to questions being raised during the course of the testimony.

Your biography will be printed at the end of your testimony and will be printed in full in the hearing record.

You may proceed, Doctor.

STATEMENT OF DR. CALVIN M. KUNIN, CHAIRMAN, DEPARTMENT OF PREVENTIVE MEDICINE, UNIVERSITY OF VIRGINIA, CHARLOTTESVILLE, VA.

Dr. KUNIN. Senator Nelson, I believe I will begin by reading the testimony, and then if there are portions of it on which you would like to interrupt me, I would be delighted to answer questions.

Senator NELSON. I think it would be helpful if you would identify your panel of the National Research Council.

Dr. KUNIN. I am chairman of Panel 4 of the National Academy of Science. Dr. Hewitt is chairman of Panel No. 2 of the National Academy of Science-National Research Council.

Senator NELSON. And your responsibility as chairman of Panel 4 was in what area of drugs?

Dr. KUNIN. The drugs under our purview were penicillin G, streptomycin, sulfonamide, all of the various new penicillins, a number of antifungal drugs, and a number of minor drugs of lesser importance.

Senator NELSON. All the drugs were antibiotics?

Dr. KUNIN. Yes.

Senator NELSON. Were they all fixed combinations?

Dr. KUNIN. Fixed combinations were one small part of the entire package. Since Dr. Hewitt had the streptomycin and I had the penicillin, we decided that we had better collaborate concerning the combination of penicillin and streptomycin. After we had completed our considerations of penicillin and streptomycin combinations we submitted our draft to Dr. Hewitt, and he submitted his draft to us in turn. We found remarkable agreement between the two panels, and were able to synthesize our thoughts in a more or less composite paper which describes both combinations.

In addition, with the sulfonamides, we also collaborated with other panels.

All the panel chairmen know each other very well, and had met prior to the initiation of the proceedings of the panels, and they sort of staked out their areas and the areas of collaboration.

Senator NELSON. How many members were there on your panel?

Dr. KUNIN. Five members of each panel.

Senator NELSON. And has there been an announcement yet of the membership of the panel?

Dr. KUNIN. There has been no announcement except, I believe, to congressional committees. There will be a full disclosure of the names of the members of my panel and Dr. Hewitt's panel when the paper that I have here will be published in the New England Journal on May 22. I will be delighted to submit this paper to you. It gives you the findings of the panel which have been transmitted to the Food and Drug Administration.

The only question about the actual text of the paper, which is actually cited in my testimony in large part, is that it is obviously a responsibility of the editors of the New England Journal to have the first priority if some materials are published with them.

Senator NELSON. The committee would not ask you for the text. I think that the Journal and Dr. Inglefinger are entitled to publish the papers first. So we do not ask you for a copy of that text.

Dr. KUNIN. Thank you.

Senator NELSON. Go ahead, Doctor.

Dr. KUNIN. I will just read a little bit. I will start at the back instead of at the front.

You have heard excellent testimony from Dr. Eichenwald and Dr. Kirby who were chairmen of other panels, both of whom are good friends of all three of us. And I suspect that we concur very closely with their points of view.

I would like to mention to you that there are some examples of combinations which might be rational. The reason I say this is that I had the opportunity to be in Uganda for the past month, and observed two combinations that might be of value.

The point I am trying to get across is that one doesn't necessarily have to make a blanket statement that all fixed combinations are bad. It just so happens that many are. But on occasion one can find a combination that might be valuable. I think we ought to have an open mind and judge each on its merits.

There are two examples that I want to cite which are used particularly by the British in the underdeveloped areas of the world. Here there is a tremendous amount of tuberculosis. Instead of using just isonazid alone, which is the usual drug for tuberculosis, they also combine it with another material called thiacetazone.

These can be put in the same capsule, and the African or the Asian patient can take one capsule a day, rather than as we do in the United States, give them isoniazid and another drug, para-aminosalicylic acid, which has to be taken in huge quantities which are not acceptable in that part of the world.

Senator NELSON. I didn't understand what is not acceptable in that part of the world.

Dr. KUNIN. It requires about 12 grams a day of para-aminosalicylic acid. That means that if you are going to send a fellow off into the bush after he has been diagnosed as having tuberculosis, he would have to carry a bucket with it, and he probably won't take it. So in this part of the world a fixed combination of isoniazid and thiacetazone, as used by the British, seems to be reasonable for certain practical purposes.

This is currently of no great importance to the United States, I am just citing it as an example.

Senator NELSON. So it is not that it is the best way to administer a drug under the best circumstances, but that under the circumstances over there it is about the only way?

Dr. KUNIN. That is right.

All I am trying to say is that, as we review all of the combinations of antimicrobial agents used in the United States today, one cannot make a good case for their continued use. However, one should keep an open mind and say, if one can demonstrate the efficacy of a combination which is greater than any one of the ingredients, and which has some economic or sociological advantage, we should be prepared to accept that combination provided that the evidence for efficacy is presented. Our charge is efficacy. Here we find all of these compounds not to be effective as fixed combinations. But there may be some exceptions.

I want to keep the door open just a little bit.

Senator NELSON. If I understand what you are saying thus far, the panel has not reviewed any fixed combination that they felt met the statutory standard of efficacy.

Dr. KUNIN. That is right. We want to be prepared, however, for any new evidence that the companies may have, any new development that may occur, so that we don't become so fixed and inflexible that we cannot be prepared to accept new advances that might be of advantage.

Actually when the combinations first came out, there was some rationale, at least one could present points of view that seemed to be reasonable. I think one of the questions that may trouble you, Senator Nelson, is why do physicians continue to use these combinations even after so many years of condemnation by, you might say, the academic men of the community. The reason, I believe, is that in the very be-

ginning combinations were thought to be rational because they might delay the emergence of resistant mutant strains, the synergistic effect, the amelioration of certain symptoms, and so forth.

It seemed reasonable to put these together. Unfortunately, there is no current support for these reasons. That whole area of development is simply now an anachronism. What we are dealing with now is a holdover. Actually, in the 1950's, very well known authorities, Dr. Finland, Dr. Weinstein, Dr. Jawetz, Dr. Hewitt, and other people, pointed out very clearly that these combinations were bad medicine.

Senator NELSON. This is over 10 years ago?

Dr. KUNIN. Oh, yes. I would just like to read you a very brief paragraph that was prepared by Dr. Finland in 1957. That is 12 years ago. This statement was signed by the leading experts in antimicrobial therapy at that time, and most of them are still around ticking, yet they really had no action on this point. This is a very brief paragraph showing you the state of affairs in 1957. The remarkable thing is that our opinion is exactly the same as pronounced by these individuals.

Senator NELSON. You mean the conclusions of your present panel are the same as the conclusions reached in 1957?

Dr. KUNIN. That is right. In other words, there is very little that we actually have added that was not fully known and fully published more than 12 years ago. In a sense one of the real pleasures, I believe, for myself and my colleagues is to be able to bring to the public through journals, such as the New England Journal, a reiteration and a rejustification of the position held by the experts in 1957.

This is Dr. Finland's statement. He says:

> Considerable caution is warranted in accepting the trend to fixed antibiotic combinations as inevitable or in lending support to a trend that may not be desirable. We would be remiss in our duties as physicians, teachers, and investigators were we to encourage, adopt, and recommend the use of new agents that we cannot consider to be as good as, or no better than, those previously shown to be good, even if they are legally certified. It is particularly incumbent on us to be very circumspect about the use of drugs of any sort in fixed combinations that do not offer the physician discretion as to the choice of components, or of the ratios in which they are used. The presence in any combination of a new or unproved components, or of a substance that may be inferior to others that might well be used instead, should make us even more cautious. They should be recommended and adopted, if at all, only after adequate, carefully controlled, and critically evaluated, study shows them definitely to be useful and superior.

And that position was taken prior to the enactment of the Food and Drug Act amendments. It is a position that is as good today as it was before, and it still keeps the door open for any drug that can be shown to be efficacious.

Senator NELSON. Please go on.

Dr. KUNIN. I won't read this in detail.

Senator NELSON. If you wish to summarize it in some places, feel free to do so. We will have a few questions as you go along. We have the time.

Dr. KUNIN. The first area of consideration is the combination of penicillin and sulfonamide. This is where our joint panels pick up first. Our charge was to examine the efficacy of a compound according to the claims made for it, so that the analysis by each of the panel was in relation to claims that appeared on the package insert. One of the indications given for the use of oral sulfonamide-penicillin combina-

tions is mixed baterial infection. Then we mentioned that various mixed bacterial infections, including bronchectasis, a condition of the lung; peritonitis, inflammation of the abdomen; urinary tract infection and chronic infection of the ears. These are the common diseases that can be caused with the infection of more than one kind of bacterium. Because many bacteria cause these infections, and because the bacteria are commonly very resistant to antibacterial therapy, treatment should not be started until appropriate cultures and sensitivity tests have been initiated.

I would like to digress on this point of appropriate cultures and sensitivity. This does not mean that a physician has to withhold therapy until he has very last bit of information from the laboratory.

All we ask is that he obtain the material so that it can be in process during the period of time that he has to make the initial clinical judgment. He doesn't have to withhold therapy or restrain his treatment. And he can treat his patient right away. But prior to that point he should prepare himself for having to change his mind on the basis of laboratory evidence.

In many instances, however, therapy need not be started until these data are determined. In other words, the patients aren't that sick, thus allowing the use of specific and effective agents. It is highly doubtful that oral penicillin-sulfonamide mixtures would ever be the drug of choice in the conditions that I have just listed above.

I cite Dr. Weinstein here in terms of his own studies of so-called broad spectrum effect of the penicillin sulfonamide combinations.

He has done some studies, and he just feels that there is really no evidence for that.

Another claim made by the manufacturers is that the penicillin and sulfonamide produce an enhancement of antibacterial activity. There are many circumstances where we use drugs in combination, that is, individual drugs in combination. We have no objection to the use of individual drugs in combination. We cite certain conditions in which it is valuable to use individual drugs in combination. One is tuberculosis, and another is endocarditis, which is an infection of the heart valves, and in certain types of urinary infections.

But in these particular examples the combinations are never penicillin and sulfonamide. They are usually penicillin and streptomycin for one of these and other variations, but never penicillin and sulfonamide.

There is never any justification for this particular fixed combination.

We also note that when you mix two drugs you can have an additive effect, you can have what we call a synergistic effect, where the action is greater than the sum of the two, or you can have an antagonistic effect. One problem that disturbs us is that there is also a potential for antagonism, and you may get less for your money than you might anticipate.

Another argument used by the manufacturers is that it is good to have drugs to use when you don't know what is wrong with the patient, and you sort of have to give blind therapy. We acknowledge this, this is true.

There are indeed valid indications for the use of drug combinations, particularly in infection of the newborn. Dr. Eichenwald is an expert in this area. He wanted to be sure to mention the newborn here.

In all such circumstances, however, the drugs should be given by the parenteral route. These drugs, oral sulfonamide and penicillin in question are not injectible, and, therefore, would not be very helpful in the very serious infections.

Senator NELSON. Are any of the combinations injectible?

Dr. KUNIN. Yes. The combination pencillin and streptomycin is injectible. But we will get to that and tell you all the reasons why we don't think this combination is rational either.

Senator NELSON. But most of them are administered orally.

Dr. KUNIN. Most of them are administered orally.

The market of course is always greater for oral preparations than for injectible preparations.

In addition to the use of the other fixed mixtures which have been shown to be much more effective than single drugs—let me put it this way.

If you have to treat with multiple agents, one would rarely use sulfonamide and penicillin, there are so many other mixtures given individually that would be much more effective.

Now, the only area that there is some discussion concerning the use of penicillin-sulfonamide seems to be a common occurrence in pediatrics, that is the running ear or earache. Here there are three organisms that are important. Some of these ears are infected with pneumococcus, and some with streptococcus, and some with an organism called *Hemophilus influenzae*. Pneumococci and streptococci are quite sensitive to penicillin. *Hemophilus influenzae* is not sensitive and requires a different kind of drug. We have two alternative drugs. We have Ampicillin and tetracycline for this particular organism.

One of the major claims is that the sulfonamide component of the penicillin-sulfonamide mixture might have some advantage for this particular organism. We point out, however, that this particular organism is almost only seen in children less than 3 or 4 years of age, and actually in the literature it has been very difficult to demonstrate any superiority of the combination of penicillin and sulfonamide over penicillin alone in this particular condition. This is probably because most of these infections are not due to bacteria, but to virus infections of the ear where no antibiotic would be of any value.

Then we discuss the question of exposure to multiple drugs. This is probably one of the key objections in this area. The sulfonamide and penicillins are potentially dangerous drugs. Reactions are common. They can be severe and even fatal. The use of both drugs simultaneously therefore increases the risk to the patient, and is to be avoided for this reason. Other troublesome aspects of this problem is the difficulty in detecting the drug causing the reaction when multiple drugs are used.

Senator NELSON. Under the law now, in order to get an NDA approved, there has to be proof of safety. That became the law in 1938, and safety and efficacy became the law in 1962. Your panels have been reviewing this problem from the standpoint of efficacy. If I understand you correctly, what you are saying is that in combinations there is also a serious safety problem.

Dr. KUNIN. Yes; because you are adding on another drug. The problem of safety is that no drug is safe. All drugs are dangerous.

The less you can use the better off you are. Here we are being forced to use two drugs when one will probably do just as well.

Senator NELSON. So in many of these cases, if I understand you correctly, you are saying that the fixed combination unnecessarily exposes the patient to a safety problem that he should not be exposed to?

Dr. KUNIN. That is right.

The question of the control of drug usage, dosage, is another point that probably upsets us as much as anything else. As you know, if you want to up the dose of one component, you must up the dose of the other. You might up the dose of the other to a toxic level, or if you want to reduce the dose of one, you are forced to reduce the dose of the other. So you have no control over the appropriate dosage.

The manufacturers claim that they make the formulations to fit the requirements of individuals in the general population. This may or may not be true. But it really binds the physician into—forces him into a position of using the specific dose in a sense against his will. This is one of the major problems, I think, in combinations.

This is particularly important with the penicillin-streptomycin combinations, because penicillin is a drug which we tend to use in very large doses for very serious infections. If we were to raise the dose of penicillin appropriately we would have severe toxicity from the streptomycin component. There is no question about that. If we were to treat a disease such as an infection of the heart valve with the combination, the fixed combination of penicillin and streptomycin, using the proper doses of penicillin, we would easily exceed the threshold of toxicity to the streptomycin.

This is a specific example where it would be very unwise to use the combination.

Our recommendations in terms of penicillin and sulfonamide are as follows: "The above discussion indicates that the contraindications for the use of any sulfonamide-penicillin combination by the oral route far outweigh any indications for such use. These data from the more recent literature are amply supported by editorial comments from the literature of the early 1950's. With all this in hand, it is strongly recommended that the use of these fixed combinations should no longer be recommended."

That ends our section on penicillin and sulfonamides.

With penicillin and streptomycin I have already alluded to the problem of the manipulation of combinations. We considered each of the claims. In this particular testimony I listed the 15 claims that are found on just about all of the package inserts.

We examined each of these claims in the case of lung abscess, aspiration pneumonia, and so forth. And in every instance we could not find sufficient evidence that this particular combination was effective, that is, more effective than the penicillin component alone or the streptomycin component alone in some instances. This particular combination really is blind therapy.

Perhaps the greatest argument of all against penicillin and streptomycin combinations, even greater than the potential toxicity of the streptomycin, has been the widespread use of this combination. And it is widespread. Indiscriminate use throughout the country and the world has almost led to disaster. The disaster primarily is the

emergence of resistant strains to penicillin and particularly resistant strains to streptomycin, making streptomycin almost worthless today for many gram negative infections. This has led to the emergence of resistant organisms to penicillin, one of our most valuable and least toxic drugs.

Senator NELSON. And this has come about in your opinion because of its indiscriminate use in combinations?

Dr. KUNIN. Yes, the streptomycin-penicillin combination I think is more to blame for the irrational use of antibiotics and the evolution of the resistance problem than any other mode. I would be most interested to hear my colleagues on my right support this contention. But I think this is the thing that really upsets us more than anything else, the blind use of these drugs in large doses indiscriminately for a wide variety of problems.

This is the major reason for doing away with this particular combination.

A physician can always prescribe these two drugs singly, if he wishes. There are instances in which they are valuable drugs when used individually or together in a nonfixed fashion. But as a fixed combination the temptation has always been too easily to use both.

Senator NELSON. Do I understand you to be saying that this fixed combination has been widely used for nonindicated cases; in other words, whatever the affecting agent was, neither of them would be indicated for it anyway?

Dr. KUNIN. Yes. The best example of this would be what we call the prophylactic use of penicillin and streptomycin in either the unconscious patient or the patient undergoing clean surgery. This is an area where I really believe that the surgeons have clearly demonstrated to their own colleagues very, very nicely—most of these studies have been done by surgeons—indicating that the prophylactic use, that is, the arbitrary use of this drug in an individual that is undergoing surgery which is not necessarily complicated by infection—this was a widespread practice at one time—has no effect, and not only does it have no effect, but it always runs the danger of superinfection now with a resistant organism. Because of its change or its impact on the flora, of the ecology of the entire body, it probably is one of our important factors in the resistant variety of staphylococcus infections. This is well demonstrated by the surgeons and should not be part of the practice.

There are many, many papers that clearly indicate this to be true. This probably would be the area of greatest misuse of this agent.

On page 9 we provide general comments and a review of the indications for penicillin and streptomycin. These fixed combinations would usually not provide optimum therapy for the complex clinical problems encountered with these 15 conditions. In each case, the characteristics of the invading organisms and the results of in vitro bacterial sensitivities must be known. Many of these infections could be treated with penicillin alone, with penicillin and streptomycin in a different ratio, or with other antimicrobial agents.

In the judgment of Antiinfective Panels II and IV, the availability of fixed combinations of streptomycin and penicillin has:

1. Led to inappropriate use of these drugs for treatment of disease states in which the combination is no more effective than one of the

components or in which the fixed combination is not the treatment of choice;

2. Exposed the patient to the increased toxicity inherent in a combination without increasing the benefit;

3. Denied flexibility of the dosage of the components;

4. Ignored the marked changes in the pattern of bacterial susceptibility in recent years and the development of new and better antimicrobial agents; and

5. Ignored the availability of penicillin and streptomycin individually for combined use at the discretion of the physician.

These considerations and the limited indications for these combinations have rendered fixed-dosage forms of penicillin and streptomycin of little value in therapeutics. Accordingly, the Panels seriously question whether they still belong in the therapeutic armamentarium. It is the judgment of these two Panels that the use of these fixed combinations should no longer be recommended and that the physician should continue to use the individual components according to his best clinical laboratory information.

You can summarize all of that by saying in one word that they are "obsolete."

Finally this last paragraph—I would like to leave a little disclaimer here—there may be special instances where fixed combinations are of value—and this is what I alluded to before. They include the combined use of isoniazid and thiacetazone in the treatment of tuberculosis because of great convenience.

Senator NELSON. In this country?

Dr. KUNIN. No. I don't believe that these drugs are used in this country at this time—but if evidence were to be provided that would be satisfactory to an expert panel, or to the Food and Drug Administration, that there was an advantage to this particular combination, then I think the Food and Drug Administration, for the benefit of the American public, should accept evidence of that kind. That is why I am leaving this door open. I mentioned that such combinations are particularly useful in underdeveloped nations where it is much more preferable to give a single dose each day. In addition, evidence is accumulating—and here is the second example—that antimicrobial synergy—that is the effectiveness of the combination is greater than the sum of the individual activities of the ingredients exists when a drug called trimethoprin is combined with a sulfonamide.

This particular combination is undergoing extensive evaluation in the United Kingdom and other parts of the world. Actually it is licensed in the United Kingdom, and it is being used fairly widely.

Senator NELSON. What is the drug?

Dr. KUNIN. It is a combination of trimethoprim, which blocks the synthesis of a particular metabolite at one site, and sulfonamide blocks the same pathway at another site, so that the two together appear to have synergy or an effect greater than the sum of the two. It looks very promising.

Now, "promising" doesn't mean necessarily that it should be approved or accepted by our Food and Drug Administration. Nevertheless, there has been a fair amount of work with this, and it has been released in the United Kingdom. We will just have to look at the data and the evidence for this particular combination.

Senator NELSON. Is it marketed in this country?

Dr. KUNIN. It is not marketed in this country.

Senator NELSON. Is there any difference—if there is a synergistic effect—by combining two drugs, is this any difference from the synergistic effect that is achieved in a fixed combination versus individual administration of the drug at——

Dr. KUNIN. Theoretically you can give the two drugs separately. But the whole advantage of the combination is that they really do work together. It is nice to get the two drugs in at the same time, the one capsule. If the manufacturers can show evidence that this particular combination has great efficacy, then I believe we should accept it. But we should examine the data. Yes, it would be much more convenient to have them together.

Senator NELSON. But would you get a better effect.

Dr. KUNIN. Yes; you can get a better effect, you can be more sure that the patient took the two drugs at the same time in the appropriate way. One of the major problems that a physician always has in prescribing drugs is: Will the patient have the prescription filled and will he take his medicine properly? These are just small areas. I am just leaving a crack of the door open so that we can have an open mind, and so that we don't, you might say, unnecessarily punish the pharmaceutical industry for past sins.

They may be able to offer us some fixed combinations that are good.

Senator NELSON. What you are really saying is what the law states—if the FDA is presented adequate clinical and testing proof that the drug is safe and efficacious, then it ought to be approved like any other drug?

Dr. KUNIN. Of course. And also I would say that if the manufacturers of the combinations that we condemn can provide new information that is properly conducted by good clinical investigators and good clinical pharmacologists that indicates that any of the combinations that we condemn currently are actually effective in the sense we are talking about, then I believe we should review the material and be judicious about this. I doubt, however, whether they will be able to do this. They have had plenty of time to do this, these combinations have been around a long time, and there has been ample opportunity to investigate these possibilities. But I believe the door always should be open for a hearing of well-conducted scientific study of efficacy.

Senator NELSON. The law was passed in 1962, so we are going on 6 or 7 years in which there has been opportunity for any company to prove efficacy of a drug that was in the marketplace at the time the law was passed.

Dr. KUNIN. Theoretically, in 1957, when Dr. Finland prepared his editorial the pharmaceutical industry could easily have responded at that time—that is 12 years ago—in relation to his condemnation of this combination. He didn't invent this in 1957, this was known in early 1950. There has been ample opportunity to do clinical studies and to support these claims.

They have not been forthcoming. I doubt that, in many instances, will evidence be brought to bear that they are effective as a fixed combination.

Not all fixed combinations are necessarily bad medicine, is what I want to say here. I want to leave that door open. But the claims must

be justified so that the consumer and the prescribing physician are not forced to use an expensive and irrational combination when a single, inexpensive drug may do equally well or better.

That is essentially my testimony.

(The complete prepared statement and curriculum vitae of Dr. Kunin follows:)

STATEMENT OF DR. CALVIN M. KUNIN, CHAIRMAN, DEPARTMENT OF PREVENTIVE MEDICINE, UNIVERSITY OF VIRGINIA

Senator Nelson and Members of the Committee, I am pleased to have the opportunity to present my opinions before this Committee once again. You may recall that I testified before you on August 8, 1967, concerning problems related to promotion of drugs. My curriculum vitae is attached to this statement.

My current task is to discuss the problem of use of fixed dosage combinations of antibiotics. As you may know, I served as chairman of Anti-Infective Panel IV of the National Academy of Science-National Research Council during its review of over 3,000 drugs licensed between 1938 and 1962. The other Panel chairmen are also testifying before this Committee. I would expect that some of my comments will overlap theirs. I believe, however, that you will find a great deal of unanimity among us.

It is important to emphasize that the task of our various Panels was to review various drugs for efficacy based on the literature, information supplied by the manufacturer, consultation with respected colleagues, and personal observation. Our review was focused on the claims made for the product as stated in the package insert. We did not attempt to assess relative efficacy of drugs nor were we concerned with relative cost to the patient.

Guidelines for our work were set down by the Policy Advisory Committee of the NAS–NRC study. Initially, four categories were selected: effective, probably effective, possibly effective, and ineffective. These judgments were made for each individual claim and were supported by extensive comments and citation of the pertinent literature. Judgments were then transmitted to the Food and Drug Administration for appropriate action.

During the course of our deliberations, it became evident that a fifth category was required to handle the question of fixed combinations of antimicrobial agents. This category, e.g., ineffective as a fixed combination, was defined as the combination is no more effective than any one of its active ingredients. Some liberty was taken with the original guidelines since one could have also judged the combinations as "effective but. . ." with a long comment noting why the particular claim was not warranted. In any even, "ineffective as a fixed combination" or "effective but. . ." really say the same thing, but the former emphasizes the point we wished to make.

Fixed dose combinations have been on the market for some ttime. The logic used by the manufacturers is based on one or more of the following arguments:

(1) Combinations could provide broader antimicrobial spectrum or coverage. This would presumably serve to catch organisms before definitive bacteriologic information and sensitivity tests were available,

(2) Combinations might act in a synergistic fashion, that is, the efficacy of the combination is greater than the sum of its parts,

(3) Combinations could provide greater convenience, that is, only one dosage form or injection would be needed,

(4) Combinations would delay the appearance of resistant mutant strains,

(5) Certain combinations might prevent side reactions induced by the active ingredients,

(6) Certain combinations might aid symptoms at the same time they were destroying bacteria.

Each of these points seem reasonable on face value, but our task was to examine the evidence that this was indeed the case for specific combinations. I believe that it is important to emphasize here that each claim must be examined on its individual merits.

My own Panel, together with Anti-infective Panel II, chaired by Dr. William Hewitt, Professor of Medicine at UCLA medical school, jointly considered fixed combinations of penicillin and streptomycin and penicillin and sulfonamides. We presented our judgments to the FDA based on claims made for them that these were ineffective as fixed combinations. We felt that the issues involved were so

important that white papers were prepared to present our thoughts in some detail. We also felt that it would be most important for practicing physicans to be aware of our arguments since the judgment recently taken by the FDA to remove them from the market would affect their practice. To this end, a paper was prepared for publication in The New England Journal of Medicine which will appear in the May 22, 1969, issue. A copy of the paper is now submitted to you, but we respectfully request that its contents not be released until published. This is asked as a courtesy to the Journal. I am, however, at complete liberty to discuss our opinions and some of this testimony will contain direct quotes from the paper.

Other Panel Chairmen testifying before you will provide information on their judgments concerning fixed combinations of tetracycline and novobiocin and tetracycline and antifungal agents.

The issue of fixed combinations is not new. It has been commented upon extensively in the literature as long as 10–15 years ago. Excellent reviews of the situation have been prepared by Dr. Ernest Jawetz, professor of Microbiology at the University of California, Dr. Maxwell Finland of Harvard Medical School, Dr. Louis Weinstein of Tufts Medical School, and Dr. Harry Dowling of the University of Illinois. Each of these men have repeatedly condemned the use of fixed dosage forms and given most cogent arguments. The task before our own Panels was to once again review the evidence and bring the matter to a head.

I shall now provide you with the following excerpts from our white paper on penicillin-streptomycin and penicillin-sulfonamide to permit you to see how we devoloped our arguments.

PENICILLIN-SULFONAMIDES

One of the most common indications given for the use of oral sulfonamide-penicillin combinations is mixed bacterial infection. Bronchiectasis, peritonitis, urinary tract infections, and chronic otitis media are the most common entities that can be caused by simultaneous infection with more than one kind of bacterium. Because many bacteria cause these infections and because the bacteria are commonly very resistant to antibacterial therapy, treatment should not be started until appropriate cultures and sensitivity tests have been initiated. In most instances, therapy need not be started until these data are determined, thus allowing the use of specific and effective agents. It is highly doubtful that oral penicillin-sulfonamide mixtures would ever be the drugs of choice in such cases.

Weinstein has shown that, under some circumstances, a "broad-spectrum" effect is produced when sulfonamide-penicillin mixtures are given. It is pointed out, however, that the degree of antibacterial activity is generally unpredictable, and antimicrobial effectiveness is often decreased by this type of therapy. In another publication, Weinstein refers to this same subject as follows:

"Such therapy is given not to produce an increase in antibacterial effectiveness but for the purpose of a 'broad-spectrum' effect in the hope that any infecting agent may be eradicated. This combination of drugs is used most extensively for the treatment of upper respiratory infections, the bulk of which are known to be due to viruses. There are no data in support of the concept that antibiotic-sulfonamide mixtures are more active in any way than the single constituent compounds. There is therefore no basis on which such combinations can be recommended, and their use must be considered to be entirely empiric."

For the above reasons, recommendations cannot be made from available data for the use of penicillin-sulfonamide combinations for the treatment of most "mixed" bacterial infections.

Enhancement of antibacterial activity

Another reason commonly given for the use of drug combinations is that some types of infections are more effectively treated by two or more drugs given in concert. Tuberculosis, subacute bacterial endocarditis due to group D streptococci, and possibly some strains of *Steptococcus viridans* are cited as examples of such infections. Some data suggest that this may be true also for some forms of brucellosis and some infections due to *Proteus mirabilis*. Penicillin and sulfonamide combinations, however, are never the mixtures of choice in any of these infections.

Careful laboratory studies have shown that the use of the combination of penicillin and a sulfonamide can have three possible results: enhancement of antibacterial activity beyond the additive effects of the two drugs (synergism), activity equal to the additive effects of the two drugs (additive), and activity less

than the sum of the separate activities (antagonism). It has been pointed out, however, that it is not possible generally to predict which of these results will ensue. For this reason, sulfonamide-penicillin mixtures should usually not be chosen because of the ever-present possibility of drug antagonism.

Treatment of infections before etiology is known or where it is impossible to determine etiology

It is necessary at times to treat patients with severe infections before the etiology has been determined. There are indeed valid indications for the use of drug combinations in such instances, particularly in infections of the newborn. In all such circumstances, the drugs used should be given by the parenteral route which in itself precludes the use of oral sulfonamide-penicillin mixtures. In addition, the use of other drug mixtures has been shown to be much more effective than sulfonamide-penicillin combinations.

Many of the same points can be made regarding the use of sulfonamide-penicillin combinations in patients in whom it is difficult or impossible to determine an etiologic agent. A possible exception to this is the use of penicillin-sulfonamide combinations in the treatment of acute otitis media. The common causes of acute otitis media are group A streptococci, pneumococci, and *Hemophilus influenzae*. However, *Hemophilus influenzae* causes otitis media very rarely after the age of 3–4 years, so multiple antibacterial agents are not indicated for the treatment of this entity in older children or in adults. Because *Hemophilus influenzae*, group A streptococci and pneumococci cause otitis media during the first few years of life, it has been the common practice to use sulfonamide-penicillin combinations in this age group. Data to support this regimen are lacking. Indeed, recent evidence indicates that sulfonamides have limited action against *Hemophilus influenzae* and that results with penicillin alone are as good as results with penicillin in combination with the sulfonamides. Furthermore, other drugs, such as the tetracyclines and ampicillin, have been shown to be effective in *Hemophilus influenzae* infections when given alone.

Exposure of patients to multiple drugs

The sulfonamides and penicillin are potentially dangerous drugs; reactions are common and can be severe and even fatal. The use of both drugs simultaneously therefore increases the risk to the patient and is to be avoided for this reason. Another troublesome aspect of this problem is the difficulty in detecting the drug causing a reaction when multiple drugs are used.

Use of "fixed" drug mixtures

The question of control of drug dosage should always be considered when using "fixed" drug combinations. In this situation, it is never possible for the physician to raise or lower the dose of either component without affecting the dose of the other. The tendency, then, is to raise the dose of one drug to a desired level and inadvertently give an overdose of the other, or to lower the dose of one to a desired level and consequently give an insufficient amount of the other. This subject is well covered by Weinstein as follows:

"The most important problem in the field of combined chemotherapy is the use of 'fixed-dose' mixtures. On the basis of the presently available knowledge, it appears patently clear that these mixtures have no place in the treatment of infection. The attitude that physicians should adopt toward such preparations has been outlined in an editorial by Finland (1957), written as a joint expression of the views of investigators and teachers in the field of infectious diseases, as follows:

" 'Considerable caution is warranted in accepting the trend to fixed antibiotic combinations as inevitable or in lending support to a trend that may not be desirable. We would be remiss in our duties as physicians, teachers, and investigators were we to encourage, adopt, and recommend the use of new agents that we cannot consider to be as good as, or no better than, those previously shown to be good, even if they are legally certified. It is particularly incumbent on us to be very circumspect about the use of drugs of any sort in fixed combinations that do not offer the physician discretion as to the choice of components, or of the ratios in which they are used. The presence in any combination of a new or unproved component, or of a substance that may be inferior to others that might well be used instead, should make us even more cautious. They should be recommended and adopted, if at all, only after adequate, carefully controlled, and critically evaluated, study shows them definitey to be useful and superior.'

"Encouragement of the use of such 'fixed-dose' antibiotic mixtures and the manner in which they are being exploited represent a major backward step in the management of infections."

Recommendations

The above discussion indicates that the contraindications for the use of any sulfonamide-penicillin combination by the oral route far outweigh any indications for such use. These data from the more recent literature are amply supported by editorial comments from the literature of the early 1950's. With all these at hand, it is strongly recommended that use of these fixed combinations should no longer be recommended.

PENICILLIN-STREPTOMYCIN

This combination was considered to be ineffective or ineffective as a fixed combination for the following claims:

I. Bacterial Endocarditis in patients with:
   A. Penicillin-susceptible streptococcal endocarditis (0.1 mcg/ml or 0.1 unit/ml or less).
   B. Endocarditis due to enterococci or other streptococci not sensitive to 0.1 mcg/ml or less.
II. Lung abscess
III. Aspiration pneumonia
IV. Mediastinitis
V. Peritonitis
VI. Mixed wound infections and abscesses
VII. Abdominal surgery in a contaminated area
VIII. Gonorrhea
IX. Urinary tract infections
X. Middle ear infections and mastoid infections
XI. Bronchiectasis, bronchitis, and other respiratory infections
XII. Brain abscess
XIII. Osteomyelitis
XIV. Secondary infections in patients being treated for tuberculosis
XV. Other infections in which the causative agent cannot be identified without operative procedures

GENERAL COMMENTS ON REVIEW OF INDICATIONS

These fixed combinations will usually not provide optimal therapy for the complex clinical problems encountered with these conditions. In each case, the characteristics of the invading organism and the results of *in vitro* bacterial sensitivity tests must be known. Many of these infections could be treated with penicillin alone, with penicillin and streptomycin in a different ratio, or with other antimicrobial agents.

Judgment of the Panels (Anti-Infective II and IV)

The availability of fixed combinations of streptomycin and penicillin has—

1. Led to inappropriate use of these drugs for treatment of disease states in which the combination is no more effective than one of the components or in which the fixed combination is not the treatment of choice;
2. Exposing the patient to the increased toxicity inherent in a combination without increasing the benefit;
3. Denied flexibility of the dosage of the components;
4. Ignored the marked changes in the pattern of bacterial susceptibility in recent years and the development of new and better antimicrobial agents; and
5. Ignored the availability of penicillin and streptomycin individually for combined use at the discretion of the physician.

These considerations and the limited indications for these combinations have rendered fixed-dosage forms of penicillin and streptomycin of little value in therapeutics. Accordingly, the Panels seriously question whether they still belong in the therapeutic armamentarium. It is the judgment of these two Panels that the use of these fixed combinations should no longer be recommended and that the physician should continue to use the individual components according to his best clinical and laboratory information.

I would like to add several points to the above comments. There may be special instances where fixed combinations are of value. These include the com-

bined use of isoniazid and thiacetazone in the treatment of tuberculosis because of great convenience. Such combinations are particularly useful in underdeveloped nations whether it is much more preferable to give a single dose each day. In addition, evidence is accumulating that antimicrobial synergy (that is, the effectiveness of the combination is greater than the sum of individual activities of the ingredients) exists when trimethoprin is combined with a sulfonamide. Thus not all fixed combinations are necessarily bad medicine. But, the claims must be justified so that the consumer and prescribing physician are not forced to use an expensive and irrational combination when a single, inexpensive drug may do equally well—or better.

I very much appreciate this opportunity to testify before you. I am most willing to answer any questions directed to me.

CURRICULUM VITAE—CALVIN MURRAY KUNIN

Birth: May 3, 1929, Burlington, Vermont.

Degrees: A.B. Columbia College with honors and special distinction in zoology, 1949; M.D. Cornell University Medical College, 1953.

Scholarships: New York State Regents Scholarship; Dr. John A. Hein Scholarship, Cornell University Medical College.

Fellowships: Student Fellow of the National Foundation for Infantile Paralysis; Post-Doctoral Research Fellow, National Institutes of Health, 1958–59; Career Development Award, U.S.P.H.S., 1966–71.

Summary of Career, Date, Appointment, and Institution:

1953–54, Intern in Medicine, New York Hospital, N.Y.C.

1954–56, S.A. Surgeon (R) USPHS, Dept. of Health, Education and Welfare, Communicable Disease Center, Atlanta, Georgia.

1956–57, Assistant Resident in Medicine, Peter Brent Brigham Hospital, Boston, Massachusetts.

1957–59, Research Fellow, Thorndike Memorial Lab., Boston City Hospital and Harvard Medical School.

1959– Attending Physician, University of Virginia Hosp., Charlottesville, Virginia.

1959–63, Assistant Professor of Preventive Medicine & Internal Medicine, University of Virginia School of Medicine.

1963–67, Associate Professor of Preventive Medicine & Internal Medicine, University of Virginia School of Medicine.

1967– , Professor of Preventive Medicine & Chairman; Professor of Internal Medicine, University of Virginia School of Medicine.

Licensure: No. 24977 Massachusetts, June 13, 1957; No. 14161 Virginia, December 1, 1959.

Board Certification: 1963 Diplomate American Board of Internal Medicine; 1963 Diplomate American Board of Microbiology.

Honors: Phi Beta Kappa, Alpha Omega Alpha, Sigma Xi, John & Mary Markle Scholar in Medical Sciences (1961–66), Fellow American Academy of Microbiology, Fellow American College of Physicians 1966, President and Visitors Research Prize (Sigma Xi) 1966.

Societies: Virginia Society of Internal Medicine, American Academy of Microbiology, American Association for Advancement of Science, American Association of Immunologists, American Society of Nephrology, American Epidemiological Society, American Federation for Clinical Research, American Society for Clinical Investigation, Southern Society for Clinical Research, Society for Epidemiologic Research.

Military Status: U.S. Public Health Service (Reserve), Active duty 2½ years, Inactive commission at present; Surgeon (R) Promotion as of April 1965 in Inactive Reserve.

Consultant: Food and Drug Administration—Committee on Protocols for Safety Evaluation 1966– ; U.S.P.H.S.—National Health Survey 1966– ; National Academy of Science—National Research Council, Chairman of Panel on Drug Effectiveness 1966; Kidney Disease Control Program—National Center for Chronic Disease Control—1968; Food and Drug Administration—Consultant,

Committee on Protocols for Safety Evaluations, Bureau of Science, 1968– ; Food and Drug Administration—Chairman, Anti-Infective Agents Advisory Committee, Bureau of Medicine, 1969– .
Editorial Boards: The Journal of Infectious Disease, Hospital Practice.

Senator NELSON. You made reference in the beginning, and you specifically state on page 3, that—

> We felt that the issues involved were so important that white papers were prepared to present our thoughts in some detail. We also felt that it would be most important for practicing physicians to be aware of our arguments, since the judgment recently taken by the FDA to remove them from the market would affect their practice. To this end the paper was prepared for publication in the New England Journal of Medicine which will appear in the May 22, 1969, issue.

I take it that the objective is to advise the medical community. Why wasn't the paper published by the American Medical Association?

Dr. KUNIN. It was submitted by the National Academy of Science, not by myself personally, but by the executive officer of the National Academy of Science to the Journal of the American Medical Association. It was not accepted by that journal. I informed Dr. Inglefinger, the editor of the New England Journal of Medicine, of this rejection, and he accepted it for publication. In his letter he said:

> As much as I regret taking a paper that has been rejected by the JAMA, I am delighted to take this one for the New England Journal.

Senator NELSON. Was any reason given for rejecting it at that time?

Dr. KUNIN. No reason was given for the rejection.

Senator NELSON. I don't expect you to speculate on the reasons for their rejection of the paper. But I think we should call attention in the record to the fact that the Council on Drugs of the AMA has taken the position for years in opposition to fixed combinations, that in the principles of advertising of the American Medical Journal—and I put that in the record yesterday, so I will just paraphrase it at the moment—in their principles of advertising they emphasize that those who wish to advertise must establish standards and they emphasize how important good standards are. And among them they say that there must be proof of efficacy of the drug.

Then we note—which is a serious question I have raised with all the representatives of the various journals here—that they accept advertising which makes claims in the ads that they would find unacceptable in any scientific paper that they print in the text of the magazine, and that in two recent issues the full back page of JAMA was a paneled ad for Panalba. The paper that was submitted to JAMA was a paper by a distinguished scientific panel that rejects Panalba on the ground that it does not meet the statutory requirement of efficacy. And it seems to me, to be perfectly honest and blunt about it, that it throws some kind of cloud over the question of the objectivity of JAMA itself.

I noticed that as far back as 1961 before the Kefauver committee in the hearings on S. 1552, part one, on page 69, that Dr. Hussey, who was then chairman of the board of trustees of the AMA, in answer to a question by Senator Kefauver, said:

> I am proposing essentially that this is mainly a job of education, and that this resolves itself into a problem of communication. The physician who has available to him on the market a drug which in extended usage turns out to be inefficacious, although originally thought to be effective, or which turns out to be dangerous, although originally thought to be safe, the physician must learn

the facts about that drug. It is a matter of delivering to him information quickly and in a form that he will interpret accurately. To my mind, this is something that the profession, especially the American Medical Association, has an obligation to do.

And it strikes me that they are not living up to their own standards when they reject a paper, prepared by panels of distinguished authorities, stating that drugs that they are advertising are not efficacious.

And it strikes me as strange that the most distinguished and widely known medical journal in this country would decline to accept a scientific paper done by a group of scientists that convened to review the efficacy of drugs in the market place, among the most important at least, if not the most important, scientific papers on drugs in the market place ever presented in this country. Their scientific judgments should be made known so as to educate the profession, yet the Journal of the American Medical Association declined to accept a paper by that panel.

Senator DOLE. I have a few questions, Mr. Chairman. I have two other committee meetings to attend. I wonder if I might ask them?

Senator NELSON. Go ahead.

Senator DOLE. I am a new member of this subcommittee, and I am curious to know more about the panel. You are on what panel and how many members are on this panel that you serve on?

Dr. KUNIN. Panel No. IV. I hate to have a number like that. But it is a roman number. There are five members of the panel in addition to the chairman. That is true of all the panels, to my knowledge.

Senator DOLE. As I understand, it is like this committee, you understand, not many appear. There are several on this committee, but it is generally a one-man operation. What I am really trying to determine is whether or not the members of the panel themselves have the time to look into all the things you say have been done—or is it done by some staff person or persons, and then submitted to you as a panel, or do you approve these segments in absentia—just how does the panel operate?

I recognize that you are a very busy man. I don't know how you do it all.

Dr. KUNIN. I must say that one of the feelings of guilt that I have is that the work presented in this white paper was really prepared by the members of our panel themselves. And this is why it is so important to indicate in the publication and identify their names.

Senator NELSON. You say that because your name appears as the author?

Dr. KUNIN. No——

Senator NELSON. You mentioned a feeling of guilt.

Dr. KUNIN. That is right. Actually my name does not appear as the author, my name and Dr. Hewitt's name are simply in a footnote indicating that we were chairmen. We were very fortunate in obtaining a release from the National Academy of Science to identify the members of both panels. The panels worked very hard as individuals. My particular panel met, and all the panels actually met, on many, many occasions. The men did their homework in great detail. And some of them worked many, many hours on their individual assignments.

The way this was done was that—let's assume that we had about 10 preparations to consider for our panel, of which there might be 20 or 30 different brand names. Each panel member was assigned the job of reviewing, say, two of these, with all the variety of preparations by many manufacturers. They went over every claim. They brought this out in long hand and prepared it and presented it to us as a group. Then we met together and went over individually every consideration that each individual brought up. We did have staff assistance in the sense of the assistance to find out where we were going to meet and to take care of our travel, and to perhaps help us with a reference or two. But basically this was work done by the members and prepared by the members.

These white papers were prepared by the members of the committee, not by the staff—we were the staff.

Senator DOLE. I think that is interesting for me to know, and I am certain the chairman is aware of it.

Then based on your statements, and the statements of the other experts in this field, what do you recommend now as far as what this committee might do? I understand now everything is being reviewed by the FDA. Is there anything you feel that the committee should be doing, or should we wait and see what happens at the FDA level?

Dr. KUNIN. Well, I personally believe that the members of the panel and the medical community should be made aware of the valuable work of the Food and Drug Administration, and particularly the pressures and strains that Dr. Ley is undergoing at this time. I believe personally that Dr. Ley has taken these recommendations extremely seriously, and that he is a very responsible official. I believe that the process that he is going through is very appropriate. It is more important that the sentiment among physicians and the population should be in support of Dr. Ley's activities.

From time to time he may judge that he would permit a company to provide more evidence, and give them a little time to bring forth some evidence. This is based perhaps upon some new evidence that a company may come up with. Dr. Ley should be entitled to have some flexibility. But I am thoroughly convinced, after discussing this with him, and watching his performance, that he will see to it that the judgments of the panels are carried through. I am sure he is dedicated to that position. I think what your committee can do and what the physician can do is support the Food and Drug Administration and give it the backbone it needs.

Senator. DOLE. But I understand you are not critical of the FDA?

Dr. KUNIN. No, sir.

Senator DOLE. The only thought I have, I wonder if we are sitting in judgment or whether the FDA is sitting in judgment, because there appears to be rather complete unanimity with reference to the subject matter. And I would guess in accordance with the 1962 act, the FDA is acting efficiently and properly, in making a determination. You are not critical of the speed or what they are doing?

Dr. KUNIN. Absolutely not. The FDA is perfectly aware of the fact that there are certain procedural problems that they have to go through. It is true that if Dr. Ley felt that the drugs were extremely

injurious that he could through his administration have them removed immediately from the market. I believe, however, that he is taking a different course because of the complexities of these issues. He prepared for the Federal Register his judgments. If the companies would like to have hearings and other judicial procedures, I think this is quite appropriate. He is doing what he feels is best in relation to the importance of these issues.

I think he is doing it properly. He needs every bit of support to follow through with appropriate action.

Senator DOLE. And it may be that these hearings provide that support.

Dr. KUNIN. Yes.

Senator DOLE. It may be that we are, in effect, prejudging what should be done. I am not certain. But as a member of the committee I am interested in finding out.

Dr. KUNIN. That is the reason why we prepared the article for the New England Journal, because we wanted to demonstrate—to make the medical community aware of the fact that Dr. Ley was not working in a vacuum, that he was working in conjunction with a good opinion, so to speak. The reasons for these judgments should be explained to the physicians in detail.

I believe that this paper will be of great help to Dr. Ley in providing the climate of opinion that is so necessary for implementation of his actions.

Senator DOLE. I share your opinion, if there is such great unanimity, then I believe something should be done. I also agree that perhaps it is being done properly, and if there is any danger of great injury it can be, as I understand, speeded up by the FDA.

Dr. KUNIN. Oh, sure.

Senator DOLE. What I was really trying to determine was whether you feel that we should be prodding the FDA in this committee. If they are not moving quickly enough, and not responding to the findings made by your panel and other panels, then perhaps we should have had the FDA up here yesterday or last week or last year.

Dr. KUNIN. No, I think what you should do, if I may suggest, is to increase the budget for the Food and Drug Administration, increase the salary for the officers that have to take tremendous responsibility, and give them the staff that is necessary. If you compare the budget and the responsibility of the Food and Drug Administration to that of the National Aviation and Space Administration, there is a tremendous discrepancy. The Food and Drug Administration has been suffering for a long time under inadequate funding and inadequate status. I think this committee or the Congress should hasten to improve the status of the Food and Drug Administration, permit it to do some research, be able to attract first-rate individuals, and fill the vacant positions. There are plenty of vacancies there. There is no thanks for a man who is regulating an industry. There is no academic praise for a man who is regulating an industry. These people need a tremendous amount of support. They also have a great deal of discouragement. They need psychologic support. I think the committee would be very helpful in this area.

Senator DOLE. I share that view. I served on a House committee that delved into this to some extent, and found the very thing that you

mentioned; discouragement, disparity, low salaries, and vacancies. I guess the Congress has taken care of raises in some areas this year. Maybe there will be others.

That is all I have, Mr. Chairman.

I have to go to the hunger hearings now.

Senator NELSON. Just to complete the thought I had—in the same year 1961 on page 119 Dr. Howard, who was at that time the assistant executive vice president of the AMA, and who, as I understand it, is now the executive director, was asked a question by Senator Hruska:

Did the council ever exercise life or death censorship on specific advertising, that is, the drug council?

And Dr. Howard answered:

The Council on Drugs through staff had a greater control over the acceptance and rejection of the advertising copy prior to 1955 than it does today. However, I repeat that the only difference of opinion there even today is with respect to the acceptance of certain mixtures, that is being considered and discussed by the board of trustees and the council. The board of trustees has reached a decision that the mixtures to which the Council on Drugs has referred during the past five years will be gradually withdrawn from the Journal during the next two or three years.

That was 1961. And, of course, the Journal continues to carry a substantial number of ads promoting the mixtures that their executive vice president and Council on Drugs were critical of in 1961. So it raises again the question of how serious the AMA was at the time they were testifying before the Kefauver committee 7 years ago.

Mr. GORDON. Dr. Kunin, when was the white paper completed?

Dr. KUNIN. You are giving me a hard time when you ask me about dates. I would expect about 6 months ago—would you say, Dr. Hewitt?

Actually we had drafts a year and a half ago when we first began, we had drafts prepared by members of our committee. And we reviewed them, and the final material, about 6 months ago, it was completed about 6 months ago.

Mr. GORDON. And approximately when was it submitted to the Journal of the American Medical Association?

Dr. KUNIN. I would estimate about 3 or 4 months ago.

Dr. HEWITT. That is correct.

Mr. GORDON. What was the holdup in submitting it? There were apparently quite a few months that elapsed between the time of completion and submission. And there was apparently additional information, and as you say, the medical profession should be getting this information.

Dr. KUNIN. I must state that there was no undue delay as far as I know. Ordinarily when you submit a paper to a journal you should expect at least 1 month's delay for review. This gives adequate time for the reviewers and the people they may qualify to review this.

Mr. GORDON. I mean the time between the completion and the submission for the first time.

Dr. KUNIN. Well, we finished our work. We submitted it. We had to wait a while, because after all we had to transmit the information to the Food and Drug Administration prior to submitting it to a journal. We had to have their permission. You see, the National Academy of Sciences was under contract to the Food and Drug Administration. So

that actually the Food and Drug Administration had to receive the material, review it and decide that it wanted to release the material.

This is the property of the Food and Drug Administration. After it had reviewed this material, along with a mass of other material, it was released to us to publish. It was submitted by the National Academy of Sciences. I did not personally submit this. And it was rejected within an appropriate period of time. It was not held back or delayed.

Senator NELSON. But it was a submission by the National Academy of Sciences to the JAMA?

Dr. KUNIN. That is right, it was officially done by them rather than by myself.

Senator NELSON. So it was a rejection of a paper by the National Academy of Sciences rather than some single individual?

Dr. KUNIN. That is right. Now, I have submitted a number of papers to the Journal of the American Medical Association personally, and I have had a number published, maybe one rejection, and about three or four acceptances.

Senator NELSON. Your standing is better than the National Academy of Sciences, apparently.

Dr. KUNIN. I might add that one of my papers dealt with the criticism of an item, a manufactured device that we felt was inferior. The Journal published this as a lead article not too long ago under my name, which was grossly critical of a particular device. So that if you try to build up a tissue of evidence in a sense, a framework in relation to the Journal, in many instances they have been quite outstanding in their publication of material. And in this particular instance it was for everyone to judge. In other instances they have been extremely good about publishing material that has been helpful to physicians.

Senator NELSON. I wasn't trying to build up anything. I think the facts have to speak for themselves.

Dr. KUNIN. That is right.

Senator NELSON. This is quite a dramatic case, it seems to me, particularly in view of their strong position against combinations themselves for a good many years, and their acceptance of advertising on the very combinations which they don't believe constitutes rational prescribing. Yet, they decline to put in their editorial columns an article by an organization as distinguished as the National Academy of Sciences.

Dr. KUNIN. All I am trying to say is that never have they ever shown any specific prejudice against me as an individual.

Mr. GORDON. I just wanted to highlight the point, Dr. Kunin. You say these drugs we are dealing with are extremely injurious, and at the same time this white paper was prepared at least 6 months ago, and maybe before that time, still this information has not reached the doctors, it hasn't been published yet.

Dr. KUNIN. This information has been available to physicians for 15 or more years. It has been available in good medical journals, including the New England Journal, and little bits and pieces of the JAMA itself. This is not new. This is old hat. This is what every medical student today learns in textbooks. What we are doing is, we are highlighting, reemphasizing in relation to the Kefauver-Harris amendment our position on this. This is not new. Every physician could find this.

Senator NELSON. That is not news. What is news is that they are still so widely prescribing the combination drugs.

Dr. KUNIN. Exactly. The news is that despite a tremendous amount of education and information—and the three of us have been really involved in many, many talks and lectures—is that these drugs are still widely used, that is the news, that is correct.

Mr. GORDON. How do you account for that?

Dr. KUNIN. I think this is a combination of the advertising of the agents, and practice, and the fact that they have advantages in terms of convenience, and habit. There was a rationale that seemed appropriate earlier. There are patterns of practice that simply haven't changed.

We have undergone a revolution in medical practice in the last 20 years, a fantastic revolution in medical practice. I expect that the physicians that have graduated in the last 10 or 15 years or since the war are using a very sophisticated form of medical practice. But there is a lot of residual, as in any group. We hope that that residual will disappear rapidly.

Mr. DUFFY. Doctor, I would just like to pursue one line of thought for a moment, if I may. You indicated just a moment ago at the commencement of your testimony that you had not really done anything to significantly advance the state of knowledge about the drugs that we are discussing this morning.

Dr. KUNIN. That is right.

Mr. DUFFY. You say that most of this literature was available in 1950, or perhaps even prior to that time. Now, if I understand the procedures that are followed in medical research correctly, data will be published and made available to the practicing medical community, and they are then to test that data, is that correct, and to examine the report and determine whether it is valid, and support it, or deny it, and so on?

And your conclusion has been that nothing has come forth to date to challenge the validity of these assumptions, or these basic reports, is that correct?

Dr. KUNIN. Yes. As far as we know, the judgments that we have made are appropriate and correct. We are prepared always to hear new evidence. Our minds are always open to new evidence that can be presented.

Mr. DUFFY. Did you assume in your study that the documents that you were basing your report on were valid?

Dr. KUNIN. Yes, sir. Well, valid in the sense that they said what they said. There are articles of high quality and articles of poor quality. One of the most important things is not to take all the articles in favor of a particular combination and put them on one side of the scale and then all the ones that are opposed and put them on the other side of the scale and weigh them. That is not the way to weigh evidence. You weigh evidence in terms of the quality of the two bits of information. We weighed the quality as opposed to the mass of material.

Mr. DUFFY. You would have "weighed the quality" by just reading other articles, you yourself did not conduct any further clinical studies?

Dr. KUNIN. No. We were not ready to perform clinical studies. If we were, then we wouldn't have any answer for 5 years from now in terms of the results. What we did was weigh the evidence as presented by competent individuals, and some less competent individuals, and made our judgments based upon good information.

Mr. DUFFY. In other words, you determined to your satisfaction that the basis for your conclusions were circumstantially valid?

Dr. KUNIN. Sure.

Mr. DUFFY. The testimony of other doctors before this committee has indicated that the effect of the disclosure that these combinations were harmful was blunted by the advertising the drug companies had done and the contacts made by the drug company salesmen, and so on. I am just wondering whether you might be able to draw another inference from the fact that much of this material has remained unchallenged. Could it be either that people did not consider it worthy of comment, or could it be that people disagreed with the viewpoints taken and did not feel that it was necessary to go out and clinically demonstrate that they were correct.

Dr. KUNIN. What do you mean by people?

Mr. DUFFY. The medical profession that may have been reading these articles and apparently ignoring them. I am greatly troubled by the fact that for 15 years this knowledge could be available, and it has apparently been ignored. You have suggested, and others have suggested, that this is largely because of the advertising that drug companies have done.

I am just trying to see if there is not another possible inference that we might draw from this set of circumstances.

Dr. KUNIN. There is no question that physicians are swayed intensively by advertising, and that they are intensively swayed by the very effective representatives of the pharmaceutical industry that call upon them. The problem here is to discern the wheat from the chaff.

Very often an advertisement does have some value, it does inform physicians of the development, and so does the representative. Unfortunately it is extremely difficult to dissect out what part of the advertisement and what part of the material that is presented by the representative is valid. In many ways the material is colored.

Most of the postgraduate education today is done by the pharmaceutical industry. I believe personally that the medical schools and medical institutions should have a greater opportunity to indulge in postgraduate medical education.

There was meeting at the National Academy of Science, with discussion of the problem of what I call counter detail men, or medical center representatives, in whom we would be able to have a group of individuals whose opinion, based upon the judgments of our drug and formulary committees, should be presented individually to physicians as friends in court, so to speak, visiting physicians, in the same way that a pharmaceutical representative visits a physician.

Now, this has to be finalized.

We did a study last summer in which we had one of our medical students visit over 200 physicians in the central area of Virginia. He was extremely well received by these physicians. He presented information on two new drugs that had been evaluated by our drug

and formulary committee. They were willing to have him come back. They wanted to see him at least once every 5 weeks at least 15 to 20 minutes to provide them with up-to-date information.

This is the sort of individual response that we should have. I think we should learn the techniques of the presentation of information to the physician from the manufacturers. I think they have developed this to a fine art.

What we need is the financial support to do this. There is no mechanism for this financial support for us to really engage in a counterpropaganda operation. After all, we have many, many medical meetings. But sometimes when we present information in a medical meeting it may not be appropriate to the direct problem a physician has in practice. We may be speaking over their heads about material that isn't very practical.

I think the pharmaceutical industry has learned that the best way to do this is a face-to-face confrontation in a physician's office by someone who is nonthreatening, and can provide information that they need, and present it in a good way.

This is what we would like to do, and this is what we have demonstrated can be effective. There can be a tremendous amount of good will between the medical centers and the physicians if we demonstrate our good will to the physicians. Certainly in central Virginia there is no problem at all on this matter.

So in a sense I am applying for a grant to do this.

There are many groups of clinical pharmacologists in this country which are fully qualified to do this very thing.

This isn't the same thing as having a man stand in the drugstore and tell the patient all about what drug he has. This is a direct representative of a responsible medical center going to physicians and telling them the latest findings and giving them information. This man does not have to be an expert. He is simply a means of communication from a responsible committee to the physicians in the area that that medical center serves.

I think we can go a long way here in advancing the kind of information and postgraduate medical education which is needed. It is not an expensive enterprise, because you don't need a very highly trained individual. There are other things that he can do as well. He can determine some special need of the physician, and bring this back to the medical centers and modify the program from time to time.

I think we have done a poor job in postgraduate medical education, because all we have done is send a man out to see physicians and give them a little talk, and then he goes away. We have to have someone who maintains a continuous contact with physicians, so he has an area that he serves, and a group of physicians that relies upon him for information.

This is our proposal.

In other words, we are fully aware of all these points that you raised, Senator, and we feel very responsible in this area.

Senator NELSON. The minority counsel raises a question that we have been examining, and on which we have comments and testimony from a variety of distinguished medical witnesses. It is this:

If you went to a doctor, or to a medical student, and said, "Now here is the infecting agent, go ahead and do the research and come back

and report what drug, if any, you would use." If he looked in the U.S. Pharmacopeia or the National Formulary, he would not find any fixed combination listed, because they don't list them, for the very reason that your panel rejects them. If they looked in the literature that distinguished people have written he would find a negative response to fixed combinations. He would come back with that answer.

Dr. KUNIN. That is right.

Senator NELSON. So, therefore, the interesting question is, Why is it that the fixed combination is so widely used? Or, for example, why has it been that, contrary to all the experts who have written on the matter, chloramphenicol is still widely prescribed for nonindicated cases? We have raised the questions—from what source do doctors get their information on combination drugs? It has to come from some place. In other words, the doctor didn't look in USP because he couldn't find the fixed combination there, he didn't look to the experts who authored the best papers written and the best articles, but he got the information some place. I think it is quite obvious that he began to use it and does use it based upon advertising and promotion.

This brings us to the question which we have raised here, that most of the journals rely for 50 percent of their income upon drug company advertising, and the medical press 100 percent, those that don't have subscriptions, just 100 percent. And then they carry in their own journals ads that are very cleverly done that promote the use of the drug which the magazine—the journals in their text, will say is not a proper use. And this is one aspect of the hearings that we are pursuing and will continue to pursue, because it seems to me that the journals ought to be responsible in respect to what they are willing to accept. My own conclusion is, from what I have seen, that they aren't very responsible in that particular respect. However, they are very responsible, the journals, in terms of what they will accept as a scientific paper in the text of the very journal in which they accept an ad that they would reject in the text.

Thank you very much, Doctor, for your very valuable testimony. The committee appreciates your taking the time to come here.

I should have said at the beginning that any one of the panel here is free at any time to add comments, observations, or information. What we are trying to do is get a record that represents all of the best viewpoints on all of these issues.

So don't hesitate to make any suggestions or comments you wish at any time during anybody else's testimony.

We will now call upon Dr. William Hewitt, professor of Medicine at the University of California School of Medicine, Los Angeles.

Dr. Hewitt, you may present your testimony however you wish.

Did you submit a biographical sketch? Yes; I see that you did.

Dr. HEWITT. I did submit one, three copies.

Senator NELSON. That will be printed in the record at the end of your testimony.

If you wish to comment on anything Dr. Kunin said, just go ahead.

Dr. HEWITT. I think I will do that in the course of this.

I think I will be more organized if I read this testimony. And I hope you will feel free to interrupt me any time you wish.

STATEMENT OF DR. WILLIAM L. HEWITT, PROFESSOR OF MEDICINE, UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE, LOS ANGELES, CALIF.

Dr. HEWITT. The purpose of my report is to describe the scientific basis for the judgments reflected in the evaluation of individual products by the drug efficacy study panels of the National Academy of Sciences-National Research Council and my view of the place of combinations of antibiotics in the rational therapy of infectious diseases. The discussion will consist of the organization of my panel and the characteristics of its membership, the categorical areas which provided evidence as a basis for the evaluations of drug efficacy, and an historical perspective upon the introduction, development, and present usefulness of antibiotic combinations. Some conclusions will be stated which appear justified in the present state of our knowledge as to the present position which the combinations should occupy.

ORGANIZATION OF THE PANEL

I am a professor of medicine at the University of California Medical School, Los Angeles, in charge of the division of infectious diseases. I have the responsibility for teaching medical students and young house staff physicians who for the most part will leave the University Medical Center environment well trained for private practice. The major portion of this teaching is performed at the bedside of sick patients. I also manage a clinical research and training program oriented toward infectious diseases. Lest there be any misunderstanding I would like to emphasize that I am not an ivory tower basic scientist. By training and experience as well as in my research I have been concerned with the study of disease and the methods for its treatment. I have had a practice of my own for 20 years and even to the present rely upon this type of activity for one-third of the income I derive from professional activities. The majority of patients I see result from the requests of medical colleagues who apparently regard me as sufficiently practical and competent to help them with both common as well as unusual or difficult problems of sick people and do not classify me as an isolated scientist pronouncing without benefit of experience. All of these qualifications were the basis for my selection as chairman, as well as the others, of drug efficacy panels dealing with antibacterial agents used for the treatment of infections.

The five members of my panel consisted both of internists concerned with adult medicine and a pediatrician, particularly appropriate since a large volume of antibiotic combinations is prescribed for children. These gentlemen, likewise, were not sitting in libraries writing textbooks and giving lectures to medical students but rather were daily seeing sick patients and caring for their medical and emotional needs. All of us participate liberally in local and national societies, the membership of which consists largely of "general physicians" concerned with both general and specialized medical problems.

We were concerned primarily with the evaluation of the efficacy; as Dr. Kunin has described of drugs such as streptomycin and sulfonamides. And it was these agents which occasioned the cooperation with Dr. Kunin's panel which was concerned with the evaluation of

the penicillins. In addition to these agents, my panel was also responsible for a number of other groups of drugs.

The evaluation of the efficacy to my knowledge was not rigidly defined in the drug amendments of 1962 and to the Federal Food, Drug, and Cosmetic Act of 1938. This should not, however, present formidable problems if one takes a simplistic view with the welfare of the patient as the central focus. In order for a drug to be effective there should be "substantial evidence" that it has a beneficial effect in the treatment of human disease and that these are the effects it is purported to have. It is obvious that some drugs will be better than others for an identical purpose but this rightfully was not a concern of the panels and should properly be relegated to avenues for physician education where it may receive adequate discussion and dissemination and be periodically updated on the basis of new scientific evidence. None of these drugs can be administered without some risk of ill effects and this must obviously have some bearing on efficacy. A drug should clearly have more benefit than harm. Thus, although penicillin would, strictly speaking, be effective for the treatment of streptococcal sore throat in a patient with a previous history of anaphylactic shock from penicillin, it could not logically be considered an effective drug for this particular patient.

Senator NELSON. How do you define anaphylactic shock.

Dr. HEWITT. Anaphylactic shock is a condition which follows quickly the administration of the drug, and is characterized by shortness of breath, difficulty in breathing, spasm of the bronchial muscles, swelling up of the tongue, and the air passage, often times resulting in sudden death.

Senator NELSON. Please continue.

Dr. HEWITT. Similarly, although chloramphenicol is highly effective in the treatment of urinary tract infections, its well-known toxicity precludes its use and it is not regarded as effective for this purpose when other less toxic agents are available. Finally, some antibiotics, although active and effective, have a much more limited role than when they were initially discovered, and, indeed, may have no distinctive role at all, because of subsequent discovery of other agents which are more active and less commonly attended with side effects. In such cases effectiveness obviously cannot be denied in the strict sense of the word. It would seem perfectly clear from the standpoint of practical therapeutics, however, that these once useful agents are no longer effective as drugs of choice and should be reserved for special limited indications for which they may still be useful and which in all but a few cases will be extremely uncommon. Thus, streptomycin, formerly widely used for the treatment of gram-negative bacillary infections is now reserved almost entirely for the treatment of tuberculosis because of the advent of more effective antibiotics (kanamycin and gentamicin). Novobiocin, once useful as an antistaphylococcal agent and, rarely, for the treatment of urinary infections due to Proteus, has been superseded by other more active and less troublesome agents to the point that it is seldom, if ever, an antibiotic of choice.

Now the basis for evaluations consisted of—

1. General principles of chemotherapy.
2. Published data relating to efficacy.
3. Opinions of consultants with special competence in specific areas.

Senator NELSON. May I ask a question at this point?

Dr. HEWITT. Yes.

Senator NELSON. You mean that the panel consulted specialists on some specific aspects of the drugs you were considering?

Dr. HEWITT. That is correct. A good example of this, for example, was the question of the usefulness of the penicillin-streptomycin combinations in the treatment of surgical infections. This is alluded to later on in the testimony. None of the members of my panel were surgeons. And consequently we solicited the opinions of three outstanding surgeons who had really devoted their careers to the study of surgical infections—obtaining from them their studied opinion as to how these combinations or how streptomycin indeed might apply to the management of infections in their particular area of competence.

4. Personal experience and judgment of the panel members.

5. Needs of practicing physicians.

I think the first three of these have been dealt with satisfactorily.

I might say that we relied more on published data as a basis for evaluations than any other source, and that the degree to which we relied upon the personal experience of the panel members was relatively limited. And we tried to keep this within judicial bounds.

It may be of some interest, with particular reference to the combination that we recognized, that the areas and types of medical practice in which physicians are active is subject to wide variation, and that the plurality of their need is equalled by the diversity of the diseases they encountered, and the demands of their patients.

Senator NELSON. May I ask a question. You are on page 5, is that correct?

Dr. HEWITT. Yes.

Senator NELSON. At the top of page 5 you say that at a final meeting concerned with the evaluation of antibiotic combinations, in addition to many of the people already mentioned, a general practitioner who was also a prominent member of the Academy of General Practice was consulted as to his views with specific reference to the role of combinations in general practice. What view did you get from the member of the Academy of General Practice?

Dr. HEWITT. His view was in concurrence with the view of the panel as to the evaluation of the antibiotic combinations on the basis of evidence that was available, and he did not seem to feel that the general practitioners would be discommoded by the evaluations which the panels were proposing.

This occurred at a final meeting after the evaluation of all the drugs. And at this time all the panel chairmen were gathered together, along with representatives of the policy advisory committee of the Drug Review Board, and representatives of the FDA for a discussion of exactly how this evaluation might best be implemented. And I would like to state that at that meeting I was very concerned as to whether or not our panel evaluations even could be implemented, because of the uncertainty that the Food and Drug Administration would receive the necessary support from organized medicine, the pharmaceutical industry, and even the Congress itself, where important pressure groups may have influence. The forthright stand taken by the FDA representatives at that time was a very refreshing one, particularly anticipating the adversity that they were very likely to get.

Mr. GORDON. Dr. Hewitt, why did you have doubts about organized medicine?

Dr. HEWITT. Well, I think that one can safely say that at least some areas of organized medicine have not been known for their ability to select the side of issues which will eventually prove to be either the best ones or even correct. And it was that general misgiving that I had at the time. To some extent I think this has been confirmed by some of the remarks which Dr. Kunin has alluded to in terms of the attitude of the JAMA toward this white paper.

I hope I am not disappointed in terms of what the Congress will do.

Now, I think we may then go on to the combinations of antibiotics and rational treatment——

Senator NELSON. On what page is that?

Dr. HEWITT. That is on page 6.

The combinations of the antibiotics in the rational treatment of infectious diseases. At least some of this can be eliminated. Dr. Kunin has already stated these indications that have been advanced for prescribing these drugs. And the evidence for and against these indications may be discussed in brief.

I might answer one of Mr. Gordon's questions which had to do with the question of delay in publication of the white paper. I think this really has a simple answer. The white paper was prepared by Dr. Kunin and myself and reviewed by the other panel chairman as well as the other members of the panel. This I think completed our portion of the work.

It was then necessary that this be submitted to our board group consisting of the policy advisory committee of the Drug Review Board.

This took a certain amount of time. It was then submitted to JAMA and rejected, which took an additional amount of time. Actually once submitted to Dr. Inglefinger at the New England Journal of Medicine I think this paper was accepted within a week.

And the remainder of the delay is related to the fact that journal space is limited and necessarily must be planned. I don't know how long it takes to get something published in the Federal Register, but I would assume that there is no limitation as to the length to which this may go, and it is primarily determined by the amount of material which is required to be printed, which is certainly not true with the journal.

So this I think in terms of general consideration is achieving prompt publication.

Dr. KUNIN. May I add a point there.

Ordinarily this paper should be published in June, according to the schedule of the New England Journal. But they moved it up to May, so that they really advanced it a month rather than later.

Dr. HEWITT. Dr. Kunin has further discussed the fact that these specific combinations of drugs would be poor choices for the purposes suggested, the fact that they are not available in acceptable and effective dosage in the combinations which exist. And I think that——

Senator NELSON. I meant to ask a question a moment ago. As I said to Dr. Kunin, Dr. Inglefinger and the New England Journal were entitled to publish the paper first. I don't think there is any question about that. But may I ask, is this quite a comprehensive review of all the drugs, the antibiotics that were covered by the panel?

Dr. HEWITT. No; it really is meant to present first of all the composition of the panels and the principles upon which they came to their decision, and to present two types of format in which these evaluations appeared, namely, there is a somewhat different format for the penicillin-sulfonamide combinations and in the case of the penicillin-streptomycin combinations.

It was thought that the format in which these evaluations were normally organized might be of interest and importance to the profession.

And finally, they present general conclusions with regard to the use of antibiotic combinations without detailed reference to anyone.

Dr. Kunin made reference to one point having to do with the rational use of antibiotics as it is applied to laboratory diagnosis. And I have a few remarks I would like to make on that at the top of page 8.

The claims for most of the commercially available antibiotic combinations are exaggerated usually by implications related to the above poorly supported indications. Emphasis is placed on the concept that rational treatment based upon sophisticated laboratory methods is fine for urban practice and a medical center but more than a clinical diagnosis may be difficult in a less luxurious setting. Faced with this problem "broad-spectrum" coverage is desirable and the antibiotic combinations provide this. In actual fact, a reasonably accurate clinical diagnosis sufficient to decide the antibiotic of choice is usually possible and most of these combinations are employed for purposes which do not require combinations at all.

And by this I mean that there certainly are many instances of serious infections which require specific laboratory methods for diagnoses. But in the majority of the cases that the general practitioner, the community physician as well as the person who practices in a medical center, in the infections these people see generally speaking encounter, most of the time one can make an educated clinical guess. And it may not be necessary to do a lot of complicated laboratory tests. So that one cannot retire behind this requirement of laboratory testing to justify the necessity of antibiotic combinations.

The statements then appear at the bottom of page 8 which Dr. Kunin has already read really from the white paper. And states:

It was for these reasons——

Mr. DUFFY. If I may interrupt you, was there any substantial doubt in your mind, or in the minds of any of the members of the panel, at the commencement of your investigation of these drug combinations, that your conclusion would be otherwise than these statements?

Dr. HEWITT. Would you restate your question.

Mr. DUFFY. I would be happy to. Did you have any serious doubts at the commencement of your investigation, that your conclusions would be other than the conclusions that you state here?

Dr. HEWITT. No. I think they are up to date and current, there has been no additional evidence presented since the panel studied this problem. And I think they are quite current. And I have no reason——

Mr. DUFFY. I think I was addressing the question to the time of the commencement of your studies of this problem. Before you were empaneled, let's say, did you have any serious doubts that after you

had gone through your review procedure that your conclusions would be other than——

Dr. HEWITT. Your question relates to one of bias.

Mr. DUFFY. It really doesn't relate to one of bias. I am not very familiar with this area. But in reviewing the testimony yesterday and the testimony this morning, it seems to me that you could have stated these conclusions prior to actually sitting down and going through the studies that your panel conducted, is that not correct?

Dr. HEWITT. I think that that is a valid statement. And I think the basis for that statement is the fact that all of us are generally familiar with the medical literature, and consequently much of the data which we had occasion to review in a formal fashion all of us had been informally aware of for a number of years. And again this reflects the remarks which Dr. Kunin made, that all this information essentially has been available for the last 10 years.

Senator NELSON. Dr. Wise.

Dr. WISE. I would like to make the statement a bit stronger. One who works in the field of infectious diseases, in teaching, as a consultant in the field, and as a scientist, remains aware of every development in the field.

As soon as he becomes involved in it, therefore one has an opinion at all times. And the beginning of a scientific investigation with penicillin began back in 1937, and it was available to investigators in this country. I worked with penicillin in 1937. Of course I was acquainted with this up until the time the panel began, and had my own very definite opinion and conclusions at the beginning of the study, yes.

Mr. DUFFY. Let me pursue this just a little further, if I may. Do you think that these conclusions are any more valid now that your panel has acted to reinforce these conclusions than they were prior to the action that your panel took?

Dr. HEWITT. I think we might all answer that. Let me say that I think they are no more valid now than they were when the panels first convened.

I think the only difference is that they now have the stamp of approval. And exactly what that means remains to be seen.

Dr. KUNIN. Remember the climate of regulation of drugs. Efficacy was not a criterion, as you may remember, for a long, long time. This was very, very new. It was purely a matter of safety. So that our opinions at that time were based not on anythng that was legal, it was a matter of judgment. The beauty of this particular opportunity is that we are charged with the efficacy question. And here we have the opportunity to present these opinions fully.

Dr. WISE. May I comment on that. In a scientific community one does not have to wait on a charge of efficacy. And therefore those who were maintaining a sense of inquiry were certainly charged with efficacy by the scientific opinon long before such a legal responsibility was placed upon us.

Mr. GORDON. Doctor, isn't it true, though, that some new facts have been uncovered about the dangers of some of the drugs? For example, novobiocin, and the components of, say, Signemycin, oleandomycin, so it is now a question of safety in addition to efficacy, isn't that right?

Dr. HEWITT. Mr. Gordon, I chose to check on this point before I

came here. And actually essentially all the important information on the toxicity of novobiocin was published in a monograph by Dr. Finland in 1956. And to my knowledge, although there may have been some refinement of statistics, there really is no significant new information which was not adequately described by that time in, I should say, about a 350- or 400-page monograph on the subject.

Mr. GORDON. Why did the FDA wait until last week to change its label?

Dr. HEWITT. That is a question——

Dr. KUNIN. I would like to comment on that, to be fair to the Food and Drug Administration. Remember that every drug has toxicity, and it is a matter of relative toxicity in terms of the advantages or disadvantages of the drug. Novobiocin at that particular point in time was one of the potentially good drugs for staphylococcus infection. We did not have the new semisynthetic penicillins. So it was not unreasonable to use novobiocin fairly liberally at that time. Therefore the FDA really had no reason to act prior to that time. The development of the new semisynthetic penicillins is quite recent, actually.

Mr. GORDON. How long ago?

Dr. KUNIN. I would say the really good oral semisynthetics have been in the market about 2 years now.

Dr. HEWITT. Longer than that, about 4 years.

Dr. KUNIN. Four years.

And with that the utilization of novobiocin alone is—I think there is hardly any market for it. I don't think anybody uses it, or very rarely.

Dr. HEWITT. I have some figures on that. Maybe I should allude to those figures, however, which will clearly, I think, establish the fact that novobiocin is not used actually alone to any extent at all, in fact it probably alone is one of the least used of the antibiotics at the present time.

Senator NELSON. But it is used in a fixed combination?

Dr. HEWITT. Yes; to a very considerable extent.

Now, because I guess I may be the oldest gentleman here, and because I was involved with the early penicillin streptomycin program under Dr. Kiefer at the time when Cal Kunin was a house officer in the Boston City Hospital——

Dr. KUNIN. I wasn't even a medical student then.

Dr. HEWITT. I would like to sketch briefly in historical perspective the introduction, development, and current position of antibiotic combinations which may assist in making clear a scientific, sound, and reasonable approach to this problem. By curious coincidence the first two antibiotic agents of great medical importance were penicillin and streptomycin, the former coming into wide use in the middle 1940's and the latter in the early 1950's. Penicillin was primarily active against one of two large groups of bacteria known as gram-positive organisms and streptomycin was primarily active against the other large group of bacteria known as gram-negative organisms. Both classes of these bacteria may be present in a variety of infections, especially those in areas communicating with our environment and, therefore, particularly those in the respiratory, genitourinary, and gastrointenstinal tracts. The logic of "broad-spectrum activity" and the use of multiple drugs in the treatment of such infections appeared

relatively early. Many laboratories investigations and clinical reports of series of infections treated with the penicillin/streptomycin combination appeared to document the favorable response of patients to the combination.

Subsequent carefully controlled studies, increased insight into the importance of mixed bacterial flora and the significance in these infections of individual components of that flora, as well as the advances in chemotherapy with the discovery of new antibiotics have all operated to alter appreciably the logic behind this particular antibiotic combination.

The next portent of things to come and the initial departure from sound principles of chemotherapy appeared under the advocacy of Dr. Henry Welch, then Director of the Division of Antibiotics of the Food and Drug Administration. This was first documented in his opening remarks at the Fourth Symposium on Antibiotics and later published in Antibiotics Annual. By this time over 20 antibiotic agents had been described indicating this would be a fertile field for the discovery of agents beneficial in the treatment of disease. Already the ingenuity of the clinical investigators as well as the pharmaceutical industry was stimulated by speculation concerning the effect of various antibiotic combinations, particularly in connection with the agents in which they were individually involved. Dr. Welch specifically mentioned twelve combinations of antibiotics, a number of which fortunately have never found their way to the market place. No allusion was made to fixed combinations of antibiotics but these had already appeared and received the tacit approval of the Food and Drug Administration.

Mr. GORDON. Dr. Hewitt, is it true that Dr. Welch was the FDA official responsible for the approval of the marketing of these fixed combinations?

Dr. HEWITT. I think that at this time Dr. Welch's title was director of the division of antibiotics of the FDA. I don't think he was the administrator, but I think he was the one that was responsible for the approval of such—or at least let's say certifying—I would presume as to their safety.

Mr. GORDON. His activities had something to do with popularizing them too.

Dr. HEWITT. Oh, yes. His opening statements at this particular meeting were very dramatic ones. And it was immediately recognized by all the clinical investigators and medical people present at this meeting that this was a distinct policy which was now being promulgated. And at this time it was recognized by him, if not the majority of the people, that it was a very had policy.

Senator NELSON. When was this?

Dr. HEWITT. The reference is given here, 1956.

This concept was further supported by the statement that there was "a distinct trend toward combined therapy, not an old fashioned 'shotgun' approach, but a calculated rational method of attacking the problem of resistant organisms." Despite this statement it was clear to many that the commonest purpose for the fixed combinations which were appearing was precisely that it was claimed not to be; namely, a shotgun approach to the treatment of undiagnosed disease. This was defined as a third era of antibiotic therapy, one in which combined

therapy with combinations of chemotherapeutic agents, particularly synergistic ones, would be customarily used.

In response to this and at the same meeting a number of outstanding competent physicians and clinical investigators in the field of infectious diseases spoke out politely but firmly both publicly and in private conversation with regard to the folly of this view. Notable among these were Drs. Maxwell Finland, Harry Dowling, and William Altemier.

These quotations were published in the written testimony. Dr. Kunin has read one of Dr. Finland's statements which really essentially summarizes these. It might possibly be well to read Dr. Dowling's comments, because they are particularly lucid, I think, in this connection.

> Therefore, one takes the chance in every case that (the bacteria causing an infection) is resistant to a certain antibiotic when he uses it. If he tests against two antibiotics and finds that the organism is sensitive to both, then he can get just as good a result with one. Why use two? If he finds it is resistant to one and not to the other, then he is not going to get any effect by using the antibiotic to which it is resistant. Then we return to the fact that it may be sensitive to both. Is the patient any better off if we use two antibiotics? We may delay—and our work certainly does not show that we delay to any great extent—the appearance of resistant strains in these cases. Would the patient not be better off if we used good doses of one antibiotic and concentrated on that? If this fails, then we can use another antibiotic. We know exactly what we are doing. We know exactly where we are going and I doubt whether we do when we use more than one antibiotic.

These principles, along with entreaties to the industry, were repeatedly stated from then to now, but achieved comparatively low pitch in the next phase of development because of the economic rewards of pharmaceutical gimmickery and the tremendous impact of promotional activities by the industry. Two major broad-spectrum antibiotics, tetracycline and chloramphenicol, had become available by this time.

Chloramphenicol was discovered, patented, and marketed solely by Parke, Davis and Co. to whom these rights belonged. Tetracycline, on the other hand, was available and was marketed by at least four major ethical pharmaceutical houses. The urge for survival in such a climate would be sufficient to stimulate the utmost ingenuity among these competitors in the drug industry. It is, therefore, a curious coincidence that chloramphenicol with a spectrum of activity quite similar to that of tetracycline was never considered to benefit by fixed combinations with other antibiotics.

Senator NELSON. Why was that?

Dr. HEWITT. I think the reason for that may be apparent in the next sentence.

Contrariwise, tetracycline appeared in combination with a variety of antibiotic and nonantibiotic substances, depending upon the pharmaceutical company responsible for its marketing and design, to provide promotional material which would convince physicians to use one tetracycline rather than another.

You understand, of course, that all these tetracyclines are identical.

Mr. DUFFY. Is chloramphenicol as susceptible to being combined with other drugs as is tetracycline?

Dr. HEWITT. I see no reason why, in terms of its chemistry and compatibility, I see no reason why it shouldn't be susceptible.

The enormous success of this maneuver is best typified by the combination of tetracycline and novobiocin. This combination with its fixed proportions was based upon the most fragmentary theoretical or objective scientific evidence, yet it was responsible for an estimated $20 to $25 million in sales at its peak and in 1968, at a time when the panels of the National Academy of Sciences-National Research Council evaluated it as "ineffective as a combination" it was still responsible for generating $16,860,000 in revenue.

At this point it might be well to at least give the medical profession credit for recognizing that novobiocin itself is a very poor drug, because in 1968 both in hospitals and in outpatient practice they prescribed only $200,000 worth of novobiocin in contrast to the $18 million retail value of tetracycline-novobiocin. And I would conclude from these figures on the basis of the cost and the village prescription pharmacy in Westwood that the net theft from the public is approximately $12 million, since the cost of tetracycline is one third that of tetracycline-novobiocin.

At this point we emerge into a phase of deterioration, disenchantment, and dismay which I would entitle the evaluation of drugs by the method of popular vote. This method, although courted several times previously, has been most recently and glaringly espoused by the vice president and director of a major ethical pharmaceutical house.

The copy of this is attached to my statement.

From the outset I must emphasize this is not to be misconstrued as a vicious attack on either the pharmaceutical industry in general or an individual in particular. The specific company in question is in excellent standing in its own peer group as well as with the physicians of this country. Its clinical and scientific organization includes men of the highest integrity and motivation as well as highly competent scientists, many of whom (at least up to the present) I count as close friends and valuable colleagues with whom I have had occasion to cooperate in scientific endeavors on a number of occasions. On the other hand, high and powerful position carries with it a requirement for responsible action. The introduction of ill-founded, confusing, threatening, and dangerous methods of deciding scientific issues of medical practice requires close public scrutiny. Those who oppose such methods are entitled to be satisfied that they are, indeed, poorly conceived; and, if they are, such methods should be held up for all to see in order that the mistake need not be repeated.

The appeal of the Dear Doctor letter in question represents, in my opinion, a bold, unscrupulous and selfish attempt to raise the spectre of Government regulation against the inalienable right and, indeed, duty of every physician to manage his patient's problems to the best of his ability. I can understand the responsibility a corporate executive must feel for the financial welfare of his company. I am saddened by the prospect that he deems it necessary to resort to an appeal which I consider insulting to the intellectual and scientific training of physicians and detrimental both to the practice of medicine as well as to the necessary efforts of regulatory agencies to protect the public from truly unscrupulous promoters. This in no sense is to imply a blanket endorsement of the Food and Drug Administration with whose

policies and methods I am by no means always in complete agreement. In this case, however, it is difficult to categorize their action as punitive when the demand is simply to provide evidence, thus far unavailable, that these drugs are effective for the claims they are purported to have. I am confident some pharmaceutical groups involved in this controversy will attempt to provide such evidence. These data should be evaluated critically, objectively, open mindedly, and reevaluations of efficacy considered and accepted, regardless of whether they agree or differ from the ones which now stand. I emphasize why with Dr. Kunin.

The implication that a large number of practicing physicians have gathered evidence which is valuable with respect to evaluation of drug efficacy and which has not been adequately considered by the panels deserves brief examination. It might be appropriate to consider the type of contribution which the practicing physician can best make which is valuable in the advancement of scientific and medical knowledge. It is a practical impossibility to project reliably all the results, good and bad, from extensive drug usage with the necessarily somewhat limited scientific investigations of each agent prior to its public release. To accomplish this might not always but often would work to the public detirment and unnecessarily delay the availability of many valuable drugs for the treatment of human ills. What may happen, however, is exemplified by the bone marrow toxicity of chloramphenicol producing usually fatal loss of white blood cells. This became clear only several years of general use and it was actually only a few years ago that the toxicity of chloramphenicol for premature infants was recognized.

Dr. Bryan Williams, now a practicing physician in Dallas, Tex., and myself published one of the first extensive clinical investigations of chloramphenicol and noted that the white blood count in several patients fell to low normal or low levels following cure of their infection. Although the implications may be clear in retrospect we were not sufficiently insightful to recognize them at the time.

It remained for the use of the drug by practicing physicians to make clear the importance of this phenomenon. Another example is provided by an agent which prevents manufacture of cholesterol, MER–29, from which the serious side effects requiring its removal from commercial distribution were appreciated only after its introduction into medical practice.

Mr. GORDON. May I correct you there. As I understand it, Richardson-Merrill knew about the side effects of MER–29 before it went on the market, but withheld the information from the FDA and from the medical profession. They were subsequently convicted in a criminal case for violating the Food and Drug Act.

Dr. HEWITT. I stand corrected.

Senator NELSON. As to the question of chloramphenicol, as I recall it, the first time evidence of serious damage to blood occurred was in 1954, and I think it came on the market in 1949.

Dr. HEWITT. Yes. The reference to this article of Dr. Williams and myself is 1950.

Senator NELSON. The point I wanted to raise is this: It is correct, is it not, that the scientific community has been aware, since the mid-

1950's at least, that chloramphenicol, then being marketed only as Chloromycetin, did have these serious side effects in a certain number of cases?

Dr. HEWITT. Oh, yes. The point I wished to make was that there was oftentimes a delay, the wide usage oftentimes was necessary to bring out rare instances of infection. And it was in this area particularly that the practicing physician who is alert, observant, but communicating his observations to the profession, can really contribute a valuable piece of scientific information.

With that in mind, then, on the other hand, critical, closely controlled, often double-blind studies are required to evaluate the effects of drugs upon common, sometimes self-limited diseases of brief duration where the effect of treatment must be compared to the natural course of the untreated or differently treated disease. The practicing physician has neither the training, time, or facilities to accomplish this. Furthermore, many physicians are truly experts in the administration and provision of community and individual medical care. Their methods and opinions in this important area and their experience should be listened to and carefully evaluated. Invidious comparisons should not be made between physician-scientists responsible for research and patient care in a medical center and physician-doctors responsible for the care of patients in a community setting. The special talents and competence of both must be recognized and their shortcomings in the alternative area accepted. Granted, this philosophy may be an ideal, and to an extent naive, but it appears to me it is the one which will promote the greatest development and exchange of knowledge for the advancement of medical practice and, consequently, human benefit.

The present state of affairs was well summarized by one of my former mentors and one of the greatest men in American medicine today in the following fashion:

> It is only fair to say that they who have sown the wind must now reap the whirlwind. By they, I mean the FDA as well as the responsible drug manufacturers. All of them followed a bad leader and must suffer the consequence.

Senator NELSON. And who was that?

Dr. HEWITT. I asked permission from this man to quote him, and he said he would give me permission to quote him without indicating his name. But I might say that if you will read some of the editorials and articles on this subject it wouldn't be hard to conclude who might have said this.

I might add, and plagiarize one more literary than I, that men, and the medical organizations they represent, who stray from the paths defined by the principles of scientific inquiry, are not keeping pace with their more responsible companions. Although their words may be music to some, with good fortune their drumbeats may become sufficiently far away to fade to the point of bare audibility.

That is the end of my statement.

(The complete prepared statement and supplemental information submitted by Dr. Hewitt follow:)

STATEMENT OF DR. WILLIAM L. HEWITT, PROFESSOR OF MEDICINE, UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE

NATIONAL ACADEMY OF SCIENCES—NATIONAL RESEARCH COUNCIL DRUG EFFICACY EVALUATIONS AND ANTIBIOTIC COMBINATIONS

The purpose of this report is to describe the scientific basis of the judgments reflected in the evaluation of individual products by the Drug Efficacy Study Panels of the National Academy of Sciences—National Research Council and my view of the place of combinations of antibiotics in the rational therapy of infectious diseases. The discussion will consist of the organization of my panel and the characteristics of its membership, the categorical areas which provided evidence as a basis for the evaluations of drug efficacy, and an historical perspective upon the introduction, development, and present usefulness of antiobiotic combinations. Some conclusions will be stated which appear justified in the present state of our knowledge as to the present position which the combinations should occupy.

Organization of the panel. I am a Professor of Medicine at the University of California Medical School, Los Angeles, in charge of the Division of Infectious Diseases. I have the responsibility for teaching medical students and young House Staff physicians who for the most part will leave the University Medical Center environment well trained for private practice. The major portion of this teaching is performed at the bedside of sick patients. I also manage a clinical research and training program oriented toward infectious diseases. Lest there be any misunderstanding I would like to emphasize that I am not an ivory tower basic scientist. By training and experience as well as in my research I have been concerned with the study of disease and the methods for its treatment. I have had a practice of my own for twenty years and even to the present rely upon this type of activity for one-third of the income I derive from professional activities. The majority of patients I see results from the requests of medical colleagues who apparently regard me as sufficiently practical and competent to help them with both common as well as unusual or difficult problems of sick people and do not classify me as an isolated scientist pronouncing without benefit of experience. All of these qualifications were the basis for my selection as chairman, as well as the others, of Drug Efficacy Panels dealing with antibacterial agents used for the treatment of infections.

The five members of my panel consisted both of internists concerned with adult medicine and a pediatrician, particularly appropriate since a large volume of antibiotic combinations is prescribed for children. These gentlemen, likewise, were not sitting in libraries writing textbooks and giving lectures to medical students but rather were daily seeing sick patients and caring for their medical and emotional needs. All of us participate liberally in local and national societies, the membership of which consists largely of "general physicians" concerned with both general and specialized medical problems.

The panels were concerned primarily with evaluation of efficacy which to my knowledge was not rigidly defined in the Drug Amendments of 1962 to the Federal Food, Drug, and Cosmetic Act of 1938. This should not, however, present formidable problems if one takes a simplistic view with the welfare of the patient as the central focus. In order for a drug to be effective there should be "substantial evidence"* that it has a beneficial effect in the treatment of human disease and that these are the effects it is purported to have. It is obvious that some drugs will be better than others for an identical purpose but this rightfully was not a concern of the panels and should properly be relegated to avenues for physician education where it may receive adequate discussion and dissemination and be periodically updated on the basis of new scientific evidence. None of these drugs can be administered without some risk of ill effects and this must obviously have some bearing on efficacy. A drug should clearly have more benefit than harm. Thus, although penicillin would, strictly speaking, be effective for the treatment of streptococcal sore throat in a patient with a previous history of anaphylactic

*As defined in the 1962 Drug Amendments, "the term 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

shock from penicillin, it could not logically be considered an effective drug for this particular patient. Similarly, although chloramphenicol his highly effective in the treatment of urinary tract infections, its well known toxicity precludes its use and it is not regarded as effective for this purpose when other less toxic agents are available. Finally, some antibiotics, although active and effective, have a much more limited role than when they were initially discovered, and, indeed, may have no distinctive role at all, because of subsequent discovery of other agents which are more active and less commonly attended with side effects.

In such cases effectiveness obviously cannot be denied in the strict sense of the word. It would seem perfectly clear from the standpoint of practical therapeutics, however, that these once useful agents are no longer effective as drugs of choice and should be reserved for special limited indications for which they may still be useful and which in all but a few cases will be extremely uncommon. Thus, streptomycin, formerly widely used for the treatment of gram-negative bacillary infections is now reserved almost entirely for the treatment of tuberculosis because of the advent of more effective antibiotics (kanamycin and gentamicin). Novobiocin, once useful as an antistaphylococcal agent and, rarely, for the treatment of urinary infections due to Proteus, has been superseded by other more active and less troublesome agents to the point that it is seldom, if ever, an antibiotic of choice.

Basis for evaluations. The categorical areas which provided the basis for evaluation of efficacy of antibiotics, singly and in combinations, were as follows:

(1) General principles of chemotherapy
(2) Published data relating to efficacy
(3) Opinions of consultants with special competence in specific areas
(4) Personal experience and judgment of the panel members
(5) Needs of practicing physicians.

It would be inappropriate to enter into an extended discussion of the general principles of chemotherapy in the present setting. They are readily and lucidly available in a variety of standard textbooks. It is obvious that the successful treatment of infections must be rational which requires that a film diagnosis or a considered assumption as to the nature of the disease must be made, even though it may later be proved wrong. Although occasional exceptions exist, the use of powerful, potentially toxic antibiotics for most trivial infections is improper. Disregard for this principle unfortunately accounts for much unnecessary antibiotic usage.

My panel relied more upon published data in the literature as a basis for its evaluations than on any other source. I am confident this would be approved by all thoughtful practicing physicians as well as an overwhelming majority of others engaged in scientifically based activities. Such data constitute the storehouse of information upon which further scientific progress must be based. It is the primary source in which evidence, and the methods by which it was derived, can be held up for critical review to ascertain the quality and, therefore, the validity of the data and the conclusions which are drawn therefrom. Although testimonial observations have value, they cannot be accorded the same credence as carefully controlled studies characterized by meticulous collection and recording of data. The literature survey with respect to each agent covered the references the manufacturer was invited to present to document the claims for his product and additional bibliographic search by the panel members to make certain that all pertinent data were reviewed.

The opinions of consultants were sought in areas where they had special competence. Since none of my panel members were surgeons, specific questions concerning the effectiveness in surgical infections of some of the compounds and antibiotic combinations were addressed to three competent, widely recognized surgeons whose careers have been concerned with the nature and treatment of those infections. Other outstanding authorities of long experience in general internal medicine, infectious diseases, and pharmacology were frequently available to assist in our deliberations. At a final meeting concerned with evaluation of antibiotic combinations and in addition to many of the people already mentioned, a general practitioner and prominent member of the Academy of General Practice was consulted as to his views and with specific reference to the role of combinations in general practice. Consultations with representatives of the Food and Drug Administration were obtained to determine the administrative action and practical impact these evaluations might have on medical practice. Speaking entirely personally, I expressed major concern as to whether the panel

evaluations of the antibiotic combinations could be implemented because of my uncertainty that the Food and Drug Administration would receive the necessary support from organized medicine, the pharmaceutical industry, and even the Congress itself where important pressure groups may have influence. The forthright stand taken by the Food and Drug Administration representatives at this meeting was a refreshing one, especially in the face of considerable predictable adversity. The other four panel chairmen and their twenty panel members were also available for opinions. The final classification of efficacy was reviewed by all the three panel chairmen concerned with antibacterial agents other than those used only for tuberculosis.

The background and current activities of the panel members and the confidence placed in them by the Policy Advisory Committee of the Drug Review Board, National Academy of Sciences, justified conservative and limited use of their personal experiences and judgment. All the panel members have contributed liberally to the published literature concerning the specific agents under review. All of them are currently active in the study and treatment of infections so their familiarity with the problems are current in scope.

The geographic areas and types of medical practice in which physicians are active is subject to wide variation. The plurality of their needs is more than equaled by the diversity of the diseases they encounter and the demands of their patients. It is essential that the value of their judgment, the validity of their experience, and the integrity of their beliefs be respected. Keeping the welfare of the patient as the focal point of medical practice, an ideal which in my belief the vast majority of physicians continue to accept, the needs of these practicing physicians was carefully considered. The consequences of the panel decisions on the effectiveness and efficiency of the delivery of health care by those physicians in their communities was also thoroughly discussed. It should be observed, however, that the prescribing habits of physicians are not necessarily valid criteria for efficacy or, indeed, even for proper usage and may poorly reflect the true state of knowledge. An extreme example of this is the indiscriminate use of chloramphenicol. Countless other less striking instances when antibiotics do more harm than good emphasize the great need for continuing physician education by the most effective possible methods. The types of contributions which practicing physicians are best able to make will be discussed subsequently.

Combinations of antibiotics in rational treatment of infectious diseases. The following indications have been advanced for prescribing two antibacterial drugs together:

(1) Mixed infections.

(2) As an attempt to control fever while investigating an obscure and/or serious illness.

(3) To permit reduction in dose of a potentially toxic agent by the additive effect of another.

(4) To prevent or delay the development of bacterial resistance.

(5) To achieve antibacterial synergism, that is, an effect with two drugs which is signficantly greater than might be expected from the purely additive effects of each drug alone.

The evidence for and against antibiotic combinations should be considered separately in two categories:

(1) The validity of their use for the above indications.

(2) The propriety of the existing formulations both in terms of the individual antibiotics in the combination and the proportions in which they exist in a fixed ratio entirely insusceptible to manipulation by the physician.

A further question which is not applicable in the present context but should be recognized concerns whether *all* fixed combinations are inherently bad; this is, I believe, a complicated issue. A review in the form of a "white paper" of the claims for the use of antibiotic combinations and the judgments of their validity will appear in the New England Journal of Medicine, 22 May, 1969. Suffice it to say that none of the first three indications are valid for the fixed combinations of antibiotics currently available. Either the specific combinations of drugs would be poor choices for the purposes suggested or when a certain combination of drugs is indicated they are not present in the commercially available combination in an acceptable and effective dosage. Several of the combinations with less than compelling theoretical basis for their usefulness, especially to prevent the development of bacterial resistance, can be discarded competely because of the advent of more active agents to which resistance occurs rarely, if ever. Tuberculosis provides the major example for the use of combination

drugs for this purpose but none of the fixed antibiotic combinations are applicable. The use of more than one drug to enhance antibacterial action is the most valid of the five indications. Clinical situations when this principle is applicable, however, are not frequently encountered, are usually serious diseases for which facilities for specific diagnoses are hopefully available, and for which antibiotic dosage requires specific tailoring. The administration of the appropriate combinations in the dosage indicated for these situations would be impossible with any of the fixed combinations commercially available.

The claims for most of the commercially available antibiotic combinations are exaggerated usually by implications related to the above poorly supported indications. Emphasis is placed on the concept that rational treatment based upon sophisticated laboratory methods is fine for urban practice *and* a medical center but more than a clinical diagnosis may be difficult in a less luxurious setting. Faced with this problem "broad-spectrum" coverage is desirable and the antibiotic combinations provide this. In actual fact, a reasonably accurate clinical diagnosis sufficient to decide the antibiotic of choice is usually possible and most of these combinations are employed for purposes which do not require combinations at all. Such examples are antibiotic coverage in surgical operations to prevent infection when this may be entirely unnecessary or an attempt at "shotgun treatment" of diseases of unknown nature which may or may not be infectious in origin. In several of the combinations, such as those containing one antibiotic combined with streptomycin or novobiocin, patients are subjected to unnecessary adverse effects from these agents because they add nothing to the therapeutic effect of the primary agent with which they are combined.

It was for these reasons that the panels unanimously stated that:

(1) Fixed combinations of antibiotics now available lead to the inappropriate use of these drugs for the treatment of disease states in which the combination is no more effective than one of the components or when the fixed combination does not even contain the individual antibiotics of choice.

(2) Patients have been exposed to increased toxicity inherent in the combination without increasing therapeutic efficiency.

(3) Fixed combinations deny flexibility with respect to the dosage of the individual components of the combination.

(4) Fixed combinations now available ignore developments which have occurred in the pattern of bacterial susceptibility and the appearance of new and better antibacterial agents.

(5) The agents in fixed combinations are readily available individually for combined use at the physician's discretion as to the choice of agents and their proper dosage.

Finally, I would like to sketch briefly in historical perspective the introduction, development, and current position of antibiotic combinations which may assist in making clear a scientific, sound, and reasonable approach to this problem. By curious coincidence the first two antibiotic agents of great medical importance were penicillin and streptomycin, the former coming into wide use in the middle 1940's and the latter in the early 1950's. Penicillin was primarily active against one of the two large groups of bacteria known as gram-positive organisms and streptomycin was primarily active against the other large group of bacteria known as gram-negative organisms. Both classes of these bacteria may be present in a variety of infections, especially those in areas communicating with our environment and, therefore, particularly those in the respiratory, genitourinary, and gastrointestinal tracts. The logic of "broad-spectrum activity" and the use of multiple drugs in the treatment of such infections appeared relatively early. Many laboratory investigations and clinical reports of series of infections treated with the penicillin/streptomycin combination appeared to document the favorable response of patients to the combination. Subsequent carefully controlled studies, increased insight into the importance of mixed bacterial flora and the significance in these infections of individual components of that flora, as well as the advances in chemotherapy with the discovery of new antibiotics have all operated to alter appreciably the logic behind this particular antibiotic combination.

The next portent of things to come and the initial departure from sound principles of chemotherapy appeared under the advocacy of Dr. Henry Welch, then Director of the Division of Antibiotics of the Food and Drug Administration. This was first documented in his opening remarks at the Fourth Symposium on Antibiotics and later published in *Antibiotics Annual*.[1] By this time over

[1] Welch, Henry, opening remarks, *Antibiotics Annual*, 1956–7, 1–2, Medical Encyclopedia, Inc., New York, 1957.

twenty antibiotic agents had been described indicating this would be a fertile field for the discovery of agents beneficial in the treatment of disease. Already the ingenuity of the clinical investigators as well as the pharmaceutical industry was stimulated by speculation concerning the effect of various antibiotic combinations, particularly in connection with the agents in which they were individually involved. Dr. Welch specifically mentioned twelve combinations of antibiotics, a number of which fortunately have never found their way to the market place. No allusion was made to fixed combinations of antibiotics but these had already appeared and received the tacit approval of the Food and Drug Administration. This concept was further supported by the statement that there was "a distinct trend toward combined therapy, not an old fashioned 'shotgun' approach, but a calculated rational method of attacking the problem of resistant organisms". Despite this statement it was clear to many that the commonest purpose for the fixed combinations which were appearing was precisely that it was claimed not to be, namely, a shotgun approach to the treatment of undiagnosed disease. This was defined as a third era of antibiotic therapy, one in which combined therapy with combinations of chemotherapeutic agents, particularly synergistic ones, would be customarily used.

In response to this and at the same meeting a number of outstandingly competent physicians and clinical investigators in the field of infectious diseases spoke out politely but firmly both publicly and in private conversation with regard to the folly of this view. Notable among these were Drs. Maxwell Finland, Harry Dowling, and William Altemier. We are only today echoing the remarks of Dr. Harry Dowling recorded in the same publication as those of Dr. Henry Welch which were as follows:

"Therefore, one takes the chance in every case that (the bacteria causing an infection) is resistant to a certain antibiotic when he uses it. If he tests against two antibiotics and finds that the organism is sentitive to both, then he can get just as good a result wth one. Why use two? If he finds it is resistant to one and not to the other, then he is not going to get any effect by using the antibiotic to which it is resistant. Then we return to the fact that it may be sensitive to both. Is the patient any better off if we use two antibiotics? We may delay—and our work certainly does not show that we delay to any great extent—the appearance of resistant strains in these cases. Would the patient not be better off if we used good doses of one antibiotic and concentrated on that? If this fails, then we can use another antibiotic. We know exactly what we are doing. We know exactly where we are going and I doubt whether we do when we use more than one antibiotic." [2]

Further echoes are apparent in the remarks of Dr. William Altemier again at the same meeting:

"I feel it is very difficult and almost dangerous to practice medicine by generalities or by rules of thumb; that in infections of moderate severity produced by single species of bacteria, such as staphyloccocci, that one antibiotic should be used, and, wherever possible, it should be selected on the basis of the sensitivity results. Two should not be used in surgical infections under those circumstances, because if the surgical procedure necessary for the treatment of that case is timed in relation to the antibiotic therapy, the duration of that antibiotic therapy should be not longer than ten days and preferably usually five days, a period during which resistant strains are not apt to emerge and a period during which the infection is brought under control. I think the tendency to use two or more antibiotic agents in infections leads to procrastination in surgical infections, to delaying necessary operative procedures, and to an increased emergence of resistant strains." [3]

These principles, along with entreaties to the industry, were repeatedly stated for then to now,[4 5] but achieved comparatively low pitch in the next phase of development because of the economic rewards of pharmaceutical gimmickery and the tremendous impact of promotional activities by the industry. Two major broad-spectrum antibiotics, tetracycline and chloramphenicol, had become available by this time. Chloramphenicol was discovered, patented, and marketed solely

---

[2] Dowling, H., Susceptibility of Microorganisms to Antibiotics isolated from Hospitalized and Non-Hospitalized Persons (Panel Discussion), *Antibiotics Annual,* 1956–7, p. 1103, Medical Encyclopedia, New York, 1957.

[3] Alteimer, William, *Ibid.,* p. 1105.

[4] Dowling, H. F., Finland, M., Hamburger, M., Jawetz, E., Knight, V., Lepper, M. H., Mieklejohn, G., Rantz, L. A., and Rhoads, P. S., Clinical Use of Antibiotics in Combination. *Archives of Internal Medicine, 99:* 536, 1957.

[5] Edit., Antibiotic Combinations. *New England Journal of Medicine, 255:* 1057–9, 1956.

by Parke, Davis and Company to whom these rights belonged. Tetracycline, on the other hand, was available and was marketed by at least four major ethical pharmaceutical houses. The urge for survival in such a climate should be sufficient to stimulate the utmost ingenuity among these competitors in the drug industry. It is, therefore, a curious coincidence that chloramphenicol with a spectrum of activity quite similar to that of tetracycline was never considered to benefit by fixed combinations with other antibiotics. Contrariwise, tetracycline appeared in combination with a variety of antibiotic and non-antibiotic substances, depending upon the pharmaceutical company responsible for its marketing and design, to provide promotional material which would convince physicians to use one tetracycline rather than another. The enormous success of this maneuver is best typified by the combination of tetracycline and novobiocin.

This combination with its fixed proportions was based upon the most fragmentary theoretical or objective scientific evidence yet, it was responsible for an estimated 20–25 million dollars in sales at its peak and in 1968, at a time when the panels of the National Academy of Sciences—National Research Council evaluated it as "ineffective as a combination" it was still responsible for generating $16,860,000 in revenue.[6]

At this point we emerge into a phase of deterioration, disenchantment, and dismay which I would entitle the evaluation of drugs by the method of popular vote. This method, although courted several times previously, has been most recently and glaringly espoused by the Vice President and Director of a major ethical pharmaceutical house.[7] From the outset, I must emphasize this is not to be misconstrued as a vicious attack on either the pharmaceutical industry in general or an individual in particular. The specific company in question is in excellent standing in its own peer group as well as with the physicians of this country. Its clinical and scientific organization includes men of the highest integrity and motivation as well as highly competent scientists, many of whom (at least up to the present) I count as close friends and valuable colleagues with whom I have had occasion to cooperate in scientific endeavors on a number of occasions. On the other hand, high and powerful position carries with it a requirement for responsible action.

The introduction of ill-founded, confusing, threatening, and dangerous methods for deciding scientific issues of medical practice requires close public scrutiny. Those who oppose such methods are entitled to be satisfied that they are, indeed, poorly conceived; and, if they are, such methods should be held up for all to see in order that the mistake need not be repeated. The appeal of the Dear Doctor letter in question represents, in my opinion, a bold, unscrupulous and selfish attempt to raise the spectre of government regulation against the inalienable right and, indeed, duty of every physician to manage his patient's problems to the best of his ability. I can understand the responsibility a corporate executive must feel for the financial welfare of his company. I am saddened by the prospect that he deems it necessary to resort to an appeal which I consider insulting to the intellectual and scientific training of physicians and detrimental both to the practice of medicine as well as to the necessary efforts of regulatory agencies to protect the public from truly unscrupulous promoters. This in no sense is to imply a blanket endorsement of the Food and Drug Administration with whose policies and methods I am by no means always in complete agreement. In this case, however, it is difficult to categorize their action as punitive when the demand is simply to provide evidence, thus far unavailable, that these drugs are effective for the claims they are purported to have. I am confident some pharmaceutical groups involved in this controversy will attempt to provide such evidence. These data should be evaluated critically, objectively, open-mindedly, and re-evaluations of efficacy considered and accepted, regardless of whether they agree or differ from the ones which now stand.

The implication that a large number of practicing physicians have gathered evidence which is valuable with respect to evaluation of drug efficacy and which has not been adequately considered by the panels deserves brief examination. It might be appropriate to consider the type of contribution which the practicing physician can best make which is valuable in the advancement of scientific and medical knowledge. It is a practical impossibility to project reliably all the results, good and bad, from extensive drug usage with the necessarily somewhat limited scientific investigations of each agent prior to its public release. To

[6] Davee, K. M., *Pharmaceutic Market, Drug Stores, Hospitals*. Davee, Koehlein, and Keating Company, 111 West Jackson, Chicago, Illinois, 1968.
[7] Gauntlett, J. C., Dear Doctor Letter, 28 January, 1969.

accomplish this might not always but often would work to the public detriment and unnecessarily delay the availability of many valuable drugs for the treatment of human ills. What may happen, however, is exemplified by the bone marrow toxicity of chloramphenicol producing usually fatal loss of white blood cells. This became clear only after several years of general usage and it was actually only a few years ago that the toxicity of chloramphenicol for premature infants was recognized.

Dr. Bryan Williams, now a practicing physician in Dallas, Texas, and myself published one of the first extensive clinical investigations of chloramphenicol and noted that the white blood count in several patients fell to low normal or low levels following cure of their infection.[8] Although the implications may be clear in retrospect we were not sufficiently insightful to recognize them at the time. It remained for the use of the drug by practicing physicians to make clear the importance of this phenomenon. Another example is provided by an agent which prevents manufacture of cholesterol, MER 29, from which the serious side effects requiring its removal from commercial distribution were appreciated only after its introduction into medical practice. The efficacy of various agents in the treatment of serious and unusual diseases just because of their infrequency cannot be sufficiently accomplished during the early phase of clinical investigation. Reports on such individual cases by the practicing physician provide additional valuable evidence.

On the other hand, critical, closely controlled, often double-blind studies are required to evaluate the effects of drugs upon common, sometimes self-limited diseases of brief duration where the effect of treatment must be compared to the natural course of the untreated or differently treated disease. The practicing physician has neither the training, time, or facilities to accomplish this. Furthermore, many physicians are truly experts in the administration and provision of community and individual medical care. Their methods and opinions in this important area and their experience should be listened to and carefully evaluated. Invidious comparisons should not be made between physician-scientists responsible for research and patient care in a medical center and physician-doctors responsible for the care of patients in a community setting. The special talents and competence of both must be recognized and their shortcomings in the alternative area accepted. Granted this philosophy may be an ideal, and to an extent naive, but it appears to me it is the one which will promote the greatest development and exchange of knowledge for the advancement of medical practice and, consequently, human benefit.

The present state of affairs was well summarized by one of my former mentors and one of the greatest men in American medicine today in the following fashion:

"It is only fair to say that 'they who have sown the wind must now reap the whirlwind.' By they, I mean the FDA as well as the responsible drug manufacturers. All of them followed a bad leader and must suffer the consequence."

I might add, and plagiarize one more literary than I, that men, and the medical organizations they represent, who stray from the paths defined by the principles of scientific inquiry, are not keeping pace with their more responsible companions. Although their words may be music to some, with good fortune their drumbeats may become sufficiently far away to fade to the point of bare audibility.

BIBLIOGRAPHY

Altemier, William, Susceptibility of Microorganisms to Antibiotics Isolated from Hospitalized and Non-Hospitalized Persons (Panel Discussion), *Antibiotics Annual*, 1956–7, p. 1105, Medical Encyclopedia, New York, 1957.

Davee, K. M., *Pharmaceutic Market, Drug Stores, Hospitals.* Davee, Koehlein, and Keating Company, 111 West Jackson, Chicago, Illinois, 1968.

Dowling, H., Susceptibility of Microorganisms to Antibiotics Isolated from Hospitalized and Non-Hospitalized Persons (Panel Discussion), *Antibiotics Annual*, 1956–7, p. 1103, Medical Encyclopedia, New York, 1957.

Dowling, H. F., Finland, M., Hamburger, M., Jawetz, E. Knight, V., Lepper, M. H. Mieklejohn, G., Rantz, L. A., and Rhoads, P. S., Clinical Use of Antibiotics in Combinations. *Archives of Internal Medicine, 99*: 536, 1957.

Edit., Antibiotic Combinations. *New England Journal of Medicine, 255*: 1057–9, 1956.

[8] Hewitt, W. L. and Williams, B., Clinical and Pharmacologic Studies with Chloromycetin. *New England Journal of Medicine, 242:* 119–27, 1950.

Gauntlett, J. C., Dear Doctor Letter, 28 January, 1969.
Hewitt, W. L. and Williams, B., Clinical and Pharmacologic Studies with Chloromycetin, *New England Journal of Medicine, 242*: 119–27, 1950.
Welch, Henry, opening remarks, *Antibiotics Annual*, 1956–7, 1–2, Medical Encyclopedia, Inc., New York, 1957.

CURRICULUM VITAE

Name: William Lane Hewitt, A.B., M.D.
Address: University of California Medical Center, Department of Medicine, Los Angeles 24, Calif.
Birthplace and date: November 25, 1916; Hebron, Nebr.
Education: A.B., University of California, 1938; M.D., University of California, 1942.
Certified: California License, 1942; American Board of Internal Medicine, 1950.
Medical training and appointments: Internship—San Francisco Hospital (City and County), San Francisco, 1941–42; Chief of Medical Officer: U.S. Albireo, (AKA 90), 1943. Staff Member—National Institutes of Health, Bethesda, Md., 1944–45. Assistant Resident and Resident in Medicine, Evans Memorial Hospital, Massachusetts Memorial Hospital, Boston, 1946–48. Visiting Physician—Evans Memorial Hospital, Massachusetts Memorial Hospital, 1948–49. Assistant Professor (in residence), University of California, Los Angeles, 1949–51. Associate Professor of Medicine, University of California, Los Angeles, 1952–58. Professor of Medicine, University of California, Los Angeles, 1958. Chief of Medicine (Acting), Harbor Hospital, Torrance, 1965–66.
Societies: Alpha Omega Alpha; American Board of Internal Medicine; American College of Physicians; American Medical Association; Los Angeles County Medical Association; Los Angeles Society of Internal Medicine; Massachusetts Medical Society; Sigma Xi; Western Association of Physicians; Western Society for Clinical Research; and Infectious Disease Society of America.
Present positions: Professor of Medicine, University of California Medical School, Los Angeles; Attending Specialist, Internal Medicine, Medical Service, Wadsworth General Hospital, Veterans Administration Center, Los Angeles; Associate Consultant in Internal Medicine, Student Health Service, University of California, Los Angeles; Senior Attending Physician, Harbor General Hospital, Torrance; Courtesy Staff, St. John's Hospital, Santa Monica; Consultant Staff, Santa Monica Hospital, Santa Monica; Consultant, Internal Medicine, Veterans Hospital, San Fernando; Anti-Infective Panel Chairman, Drug Efficacy Study, National Academy of Sciences; and Training Program Director, U.S. P.H.S. Graduate Training Grant in Infectious Diseases, UCLA Medical Center and Veterans' Administration Center, Los Angeles.

THE UPJOHN CO.
Kalamazo, Mich., January 28, 1969.

DEAR DOCTOR: Because of misleading and possibly misunderstood statements which have appeared in the lay press, we would like to take this opportunity to clarify our position and to assure you that Panalba remains available.

In the Federal Register of December 24, 1968, the Food and Drug Administration published a notice about Panalba and certain other combination antibiotics. The question is whether certain combinations of drugs should be allowed to remain on the market.

Approximately 40% of the drugs prescribed today are combinations of one form or another. In principle, if the physician's right to prescribe is denied for one category of useful drugs, it is conceivable this same right may be denied for others. We believe the decision as to whether these drugs are used should rest in the hands of the praciticing physician.

In accordance with the Federal Register, all interested persons who may be adversely affected by removal of these drugs from the market are invited to comment. Correspondence should be directed to Dr. Paul Bryan, Special Assistant for Drug Efficacy Study Implementation, Bureau of Medicine, Food and Drug Admiistration, 200 "C" Street, S.W., Washington, D.C. 20204. If you elect to write to Dr. Paul Bryan we, too, would appreciate a copy of your correspondence.

Sincerely,

J. C. GAUNTLETT,
Vice President and Director.

Mr. GORDON. Dr. Hewitt—and this will be for Dr. Wise and Dr. Kunin too—would it be fair to say that many people have been injured through the use of these fixed combination drugs?

Dr. HEWITT. Yes, I think that is a fair statement.

Dr. KUNIN. Yes.

Dr. HEWITT. I think many of the injuries may not be of the obvious sort, such as with chloramphenicol. But I think the evidence is clear that in the case of streptomycin damage—well, let's say, in some instances it is as clear as the case of chloramphenicol. For example, occasionally instances of dramatic streptomycin toxicity after a few doses of the penicillin-streptomycin combination have been noted. And occasionally, instances say of very florid skin rashes and jaundice have been observed following the administration of novobiocin. But I think that more important that these are the possible countless instances of streptomycin toxicity which may not be obvious.

We know that the dose of streptomycin, the toxicity is additive, and that probably as we administer this material it may do damage to the hair cells in the ear which may not be entirely obvious. And this is the sort of thing, I think, that is the most important thing to try to prevent, in other words, the unobvious instances of toxicity which nevertheless are very likely to occur.

Senator NELSON. I take it—just for the purposes of keeping the record clear—that the answer to counsel's question, have people been injured by the use of these combinations, is the word "unnecessarily," because it was not necessary to use the combinations which you are referring to, is that correct?

Dr. HEWITT. Yes.

Dr. KUNIN. There is no question that this is correct. I would emphasize not only the individual injury, but injury to all of society, not only the individual who received the drug. Because their widespread use have induced the spread of resistant organisms. So that instead of medical practice being simple it is much more complicated now, and many more expensive drugs have to be used because of this widespread practice.

Dr. WISE. I would add that because of implication of broad spectrum that there is a tendency to use them without establishing the etiologic diagnosis, and then interfering with the diagnosis of the infection, placing the patient in a state of therapeutic dilemma, in which only empiricism could then be followed rather than the choice, which could also be considered a hazard.

Senator NELSON. There is another general question that any or all of you may wish to comment on. We have had testimony from a number of distinguished witnesses, pharmacologists, clinicians, on the vast array of drugs under innumerable brand names, making it impossible for any one person to keep track. We might have one compound that has 25 or 30 brand names.

In addition to the panels' conclusions about the lack of efficacy and the hazards of the combinations, there is the problem created by putting togther all kinds of various combinations of antibiotics or any other combinations which makes it impossible for a physician to really manage to keep up to date on what they all mean and how they all ought to be used.

Dr. KUNIN. I would like to comment on that, Senator.

If I were in an industry, and I were in danger of losing my patent with which I have reaped my fortune over many many years and wanted to retain that patent, then I would combine that drug something else so that I have a new propriety agent. This is another way of keeping this within one's own pocket.

There is no question that there is confusion. There is no question that it is very, very difficult to keep up with one or another.

The company that has the best advertising campaign will dominate that market.

Senator NELSON. As to that compound?

Dr. KUNIN. Sure, it will dominate it because he has the most advertising in that particular area. This is the way it is done.

Dr. HEWITT. Could I respond also.

Senator NELSON. Yes.

Dr. HEWITT. I think, however, there is an implication to your question that maybe a large number of names are confusing to the profession. I think in actual point of fact that probably isn't true, and that most doctors recognize which agents are valuable to him in his practice, and even though there may be 12 or 15 agents with proprietary names which belong to the same generic family, he usually becomes familiar with one or two of these and learns how to use them. So that for each doctor, at least, this multitude of names is not necessarily confusing. For example, let's take tetracycline. There is certainly a wide variety of trade names. But by and large I don't think this introduces a factor of confusion to the clinician.

There are a variety of preparations of digoxins for the treatment of cardiac patients. But usually the doctor learns one or two preparations and uses those in his practice.

Mr. DUFFY. If I may, I would just like to find out why the practicing physician is able to distinguish between large varieties of brand names, and yet when we have such a large body of adverse literature on fixed combinations he apparently is unable to distinguish in this case. How do you justify this.

Dr. HEWITT. What I am saying is that the mere presence of a large number of proprietary names is not confusion. The doctor may decide he likes the color of a pill or the coating that is on it, so he chooses, say, a Lederle tetracycline as opposed to Upjohn tetracycline. And he really isn't required to distinguish between those, because he knows really, or at least he assumes that they are really all the same.

Senator NELSON. I was really aiming toward a favorite question. I will recite a couple of instances of what I am referring to.

We have had testimony on the question of requiring that a drug be prescribed by generic name, and that the label carry it, without interfering with the doctor's right to say what brand it might be. On the label it may have the brand, but the generic name would appear also. We have had a number of people testify in support of this concept both from the standpoint of good practice in identifying by generic name, and secondly, as a safety matter. I believe it was Dr. Adriana who pointed out that in the flood in Louisiana 2 or 3 years ago they had people who were ill who had a bottle, the drugstore was under water, it had a few numbers on it, and they had no notion of what they should

give that patient. Dr. Taussig testified here that in the Thalidomide case, long after it was known—it was in the newspapers all over the world what the side effects were—but Thalidomide was still in the marketplace being prescribed in various places, cities in South America, and in Spain, under a half dozen brand names which didn't identify it as Thalidomide. And it continued to be prescribed.

And she said it may still be taken by pregnant women, because the doctor didn't know that the brand name was Thalidomide.

We had a doctor before us who had some reservations about the idea of generic names. We had about 30 brand names for Thalidomide, and I asked him to identify three of them, but he had no notion of what they were. But they were all Thalidomide. I was getting at the question of whether or not we can consider it valuable or not to require that there be a generic name on the lable, and that it be prescribed that way, without interfering with the right of the doctor to name the brand he desires, and excepting in the case where he feels there is a compelling reason for not letting the patient know what compound he is getting.

Dr. HEWITT. I would champion our case.

Dr. KUNIN. I would go a little further. I mentioned earlier that the Albemarle County Medical Society, in conjunction with our pharmacists, have made it a point of medical consideration that there be routine labeling of the name of the drug on prescriptions unless the physician deems it unwise, that this should be a routine practice.

Senator NELSON. By generic name?

Dr. KUNIN. By the name of the compound that is prescribed. We didn't go as far as the generic name, but I think it is a good suggestion.

Senator NELSON. Wouldn't that be what it was if you identified the compound?

Dr. KUNIN. We would identify—let's assume that you have tetracycline. It would be identified on the label. So that no one has to look this up by number. One could easily know that this is a tetracycline. We think this is a very important move, and the pharmacists are very much in favor of this type of development. I think this is very important, and should be done. I think we ought to take the mystery out of medicine.

Dr. WISE. We see very serious adverse reactions from patients who have had combinations of antibiotics knowing it only by the trade name and not recognizing that another combination contains the same ingredient to which the patient is very supersensitive. The physician too perhaps did not recognize that there was such a hypersensitivity to one ingredient.

Senator NELSON. If I understand you correctly, you are referring to something that has been said in testimony before; that is, a patient knows that he is allergic to some particular brand name, it may be penicillin or something——

Dr. WISE. It may be the name of the combination of ingredients of the antibiotic.

Senator NELSON. He may know a single brand name of some drug which has 20 brand names. And the doctor prescribes it by another brand name but——

Dr. WISE. The patient doesn't recognize it.

Dr. HEWITT. I think that is a very valid point that Dr. Wise has raised. And I would like to make it clear that my reference to these

various brand names not being confusion is relating to confusing to physicians. And I think that his point with regard to confusion of patients is probably a valid and important one.

Senator NELSON. Thank you very much for your very valuable testimony.

We will now hear from Dr. Wise.

Did you have a biographical sketch attached to your statement?

Dr. WISE. As to who I am?

Senator NELSON. We usually print whatever background and experience the doctor wishes to put in the record.

STATEMENT OF ROBERT I. WISE, M.D., PH. D., PROFESSOR OF MEDICINE AND CHAIRMAN, DEPARTMENT OF MEDICINE, JEFFERSON MEDICAL COLLEGE, PHILADELPHIA, PA.

Dr. WISE. I am sorry, I didn't attach one. I am the professor of medicine and head of the department of medicine at Jefferson Medical College. I have a doctor of philosophy degree in microbiology from the University of Illinois. I have an M.D. degree. I have served my fellowship training in the field of infectious diseases. I have been participating in research with bacteria and antibiotics since 1937.

Senator NELSON. And you also currently have a clinical practice?

Dr. WISE. I participate in practice. I am formerly the vice president of the section of internal medicine of AMA. And I might say that I am a representative to the AMA on scientific exhibits. I am responsible for the scientific exhibitions in internal medicine at the convention of the AMA. I have been active on the committee of the American College of Physicians on Advertising. And I am a member of the Greater Philadelphia Committee on Medical-Pharmaceutical Sciences which meets to discuss problems of pharmaceuticals, drugs, the FDA and medical education.

Senator NELSON. Thank you.

Dr. WISE. It is an honor to be invited to participate in the hearings before this distinguished committee.

I would like to state that the modern era of therapy of infectious diseases began in 1935 and the many antimicrobial agents developed since that time have provided a potentially curative armamentarium against infectious diseases considered incurable only 35 years ago.

This has been a fantastic development.

May I say as comment that in the beginning when an anti-infective agent is produced there is naturally an empirical evaluation. One has to try, not only in the test tube, but also in clinical problems, to determine the effectiveness of each one. And as the years have gone by, there has developed something more than empiricism, a specificity of relationship between a drug and the cause of each infectious disease.

Many factors influence the concepts and habits of physicians who treat infectious diseases. Medical students, interns and residents are taught principles in the diagnosis and management of these diseases. Representatives of pharmaceutical manufacturers discuss their companies' antimicrobial products with physicians. Medical journals publish reports of varying degrees of excellence on observations of the use of anti-infective agents; advertisements containing statements that

would not be acceptable in a scientific manuscript are printed in the same journals Exhibits at every major medical convention attempt to influence the physician in his choice and use of antimicrobial products. Patients may suggest and demand the administration of an anti-infective drug.

This latter influence has been of great importance in the demand of the patient to be given a drug, even when it was not at all necessary and perhaps even contraindicated.

The physician therefore is pressed by many, many influences in his administration of an anti-infective drug.

I would like to go through the reasons for the rational use of anti-infective agents.

A patient who has indications of infection can be assumed to have a disease caused by one or more of the following: (1) bacteria, (2) viruses, (3) rickettsia, (4) bedsonia, (5) mycoplasma, (6) fungi, (7) other parasites, protozoa, and so forth, or (8) a host of noninfectious agents, which cause fever and those symptoms which are considered to be significant, or coexistent with infection.

The patient should be treated by methods which will eliminate the etiologic agent as rapidly as possible in order to prevent the progression of disease, the development of complications and death, and to decrease morbidity and expense. If adequate therapy is not begun promptly, the disease or its sequela may become irreversible.

It must be emphasized that any bacterial infection is potentially a serious illness which, if it is inadequately treated, may result in death.

This is true of any bacterial infection, that it may proceed to death, which is not as true as some of the other infectious diseases, for example, the viruses. If, for example, the disease is caused by Streptococcus hemolyticus, the possible complications are bacteremia and infection of other areas of the body and may result in the following: acute glomerulonephritis with renal insufficiency, rheumatic fever, rheumatic heart disease and bacterial endocarditis.

Mr. DUFFY. Doctor, how long would it take this course of action to develop?

Dr. WISE. The acute glomerulonephritis and rheumatic fever can occur within a few weeks. It may require a period of years up to, let's say 5 through 15 years for rheumatic heart disease, and bacterial endocarditis may occur after the rheumatic heart disease at any time, as late as 30 years later, all having started with the initial stimulation by the one infection.

Infection with Staphylococcus aureus may advance to bacteremia and the development of metastatic abscesses in the bones and viscera. Pseudomonas and Escherichia may cause bacteremia with acute peripheral vascular collapse, and death. These may spread and eventually cause fatal illness unless they are appropriately treated before becoming irreversible.

Next I would like to discuss the principles that should be used in the rational use of anti-infective agents.

An optimum specific therapy can be selected for these common but malignant bacterial infections only when the etiologic agent is identified or, if identification is impossible at the time the physician sees the patient, then it must be selected when excellent clinical judgment is used to determine the most probable diagnosis.

If the causative agent has not been identified—and I might echo Dr. Kunin's statement, which I like—at least make the effort to do those d agnostic techniques which will provide the answer, and as a result, an ineffective mode of therapy is selected, the infectious disease may advance, remain dormant until therapy is discontinued and then relapse, or a cure may result from the response of the patient's natural defense mechanism.

The latter occurs particularly in patients with virus diseases, whether they rece.ve antibiotics or not, because in that instance the disease itself is limited, and the antibiotics really are not specific and play no role in the curative method, except at the present time I should modify that by saying, there is on the horizon some agents which may change that, hopefully.

The initial use of an ineffective drug or combination of drugs may actually interfere with further attempts to identify the etiologic agent and thus, place the patient in a hazardous situation since further therapy must be selected empirically.

In this situation the physician must rely on his observations and experience in choosing a therapeutic agent. He cannot plan the optimum duration of therapy or anticipate the possible complications of the illness. Morbidity, complications, mortality and expense are increased.

Conversely, when the etiologic agent is identified, the physician can institute specific therapy with an anti-infective agent immediately. He can select a preparation and mode of administration that will better assure adequate concentration of the drug at the site of infection, plan the probable duration of therapy, and foresee possible complications. Under such circumstances, mortality rates, morbidity, complications and expenses are kept at a minimum.

The cure or prevention of infectious disease with avoidance of drug-induced deleterious effects is the goal of antimicrobial therapy; thus, in addition to the harmful effects that may result from the use of an inappropr ate agent, the physician must keep in mind the deleterious effects associated with the use of specific agents. For example, penicillin may cause allergic reactions ranging from relatively mild and reversible reactions such as dermatitis, pruritis and fever, to immediate anaphylaxis and death. Some anti-infective agents can cause deafness, aplastic anemia, hemolytic reactions, hepatic damage and injury to the kidneys. If the normal resident bacterial flora is disturbed, transient micro-organisms may proliferate and produce disease. The overuse of anti-infective agents results in the development of resistance of micro-organisms to a therapeutic agent.

Now, selection of anti-infective agents.

In table 1 are listed the common etiologic agents which produce infectious disease in humans.

I have prepared this table to give a perspective. There are listed the different kinds of bacteria, and there are many of them of different generic names. And each genus has many species. Each one of those bacterial names is the generic name, and there are many species and varieties of each. Each one differs. Each one produces a different kind of disease. And each one reacts differently to the various anti-infective agents that we have.

Some require different concentrations of antibiotics, and some require combinations of antibiotics. At the bottom I have listed viruses and the other etiologic agents which cause infectious diseases.

In table 2 I have attempted to demonstrate the complexity of the anti-infective agents. And it was mentioned by Dr. Hewitt, in the beginning penicillin was effective against gram positive, and streptomycin which was effective against gram negative bacteria. I have listed on the left-hand side antibiotics which we now have that are effective against gram positive bacteria, and in the right-hand column antibiotics which are effective against gram negative, and some of the gram positive bacteria.

I have classified them to show you the number of different penicillins and number of tetracyclines and the number of the cephalosporins and the macrolides.

Senator NELSON. May I ask, do each of the various penicillins and tetracyclines listed, have a specific different use?

Dr. WISE. Under the penicillins one can come to the conclusion that each one has a specific use. Penicillin G certainly has its own use, which is different from the other penicillins. Methicillin has its own use, which is a bit different from the others, such as oxacillin, cloxacillin and Ampicillin. Ampicillin has its own specific advantage over the others. And there would be in a patient a specific type of infection in which the knowledgeable physician would choose specifically the one antibiotic.

My answer to that in regard to tetracyclines, I would say that there is less specificity or differences between all the tetracyclines, one can almost state that they are pretty much alike with some very minor differences.

Does that answer the question?

Senator NELSON. That is what I was trying to get at. Are the various tetracyclines listed simply other names for the same generic, same compound?

Dr. WISE. These are generic names.

Senator NELSON. Each is a generic name?

Dr. WISE. I have used no trade names in this list.

And then I have listed those agents which are used for the fungi, the bedsonia, the rickettsia, and the myoplasma. There may be some additions to this. But this serves as an example to give the committee an idea of specificity in the use of antibiotics.

The anti-infective agents should be selected on the basis of:

(1) Early identification of the microorganism if possible.

(2) In case identification is not possible, therapy should be selected on the basis of clinical evaluation.

(3) Specific treatment should consist of one or more drugs as indicated for the etiologic agent and the characteristics of the disease process in the individual patient.

May I enlarge upon that just a bit. A patient with a staphylococcus infection of the skin, let's say a small boil, could be treated by an oral antibiotic such as one of the semisynthetic penicillins swallowed orally. The goal here would be simply to prevent spread from that small localized site, and it would heal. However, if the same organism was present on the heart valve, or present, let's say, in an abscess in

the brain, one would now be faced with a completely different kind of situation, in which now one would want to know exactly which antibiotic would reach that site, the concentration one would desire there, and now one has to come to a decision as to the mode of administration, the dose that would be used, and the technique to accomplish the desired result.

(4) Selection of the drug or combination of drugs, dose of each drug and route of administration of each drug should be determined in a manner that will result in adequate concentrations of the single drug or multiple drugs at the site of infection with minimum hazards of adverse effects of each drug and result in maximum benefit to the patient.

I have listed some of the commercially available prefixed combinations of the antimicrobial agents and a number of preparations and different dosage forms of each of these combinations on the next page. Just to give one an idea of the extent of this, I have here listed combinations that I think make up 95 different trade names of prefixed combinations.

There is a lack of therapeutic indications for prefixed combinations of anti-infective agents.

I say this because if one goes through the list of bacteria that I have listed on table 1 and asks the question:

What would he use in the treatment of this specific infection caused by this particular bacteria?

There is no logical indication for use of any prefixed combination when they are viewed in light of indications for therapy with single or multiple anti-infective agents.

I want to stress that a bit again. When one thinks of a specific bacterial infection, one does not come up with any indication for any prefixed combinations.

Mr. GORDON. How do you know which is causing the infection? Do you take cultures?

Dr. WISE. By the use of the history, the physical examination of the patient, getting the information one can, and coming to a conclusion as to what is most likely the disease, and then obtaining those specimens from the patient which will give the answer.

Let's say that this is pneumonia, and the physician comes to the conclusion that this is pneumonia. By examination of the sputum, or if the patient with pneumonia has a collection of pus in the thoracic cavity, obtaining that, or by obtaining blood and doing appropriate studies on that, one can determine the specific cause in most instances. If he can't, then he has to resort to his best clinical impression.

There is a lack of controlled clinical studies.

No adequately controlled clinical studies have been conducted to prove the superiority of prefixed combinations over the use of singly administered antimicrobial agents.

Limitation of dose of one ingredient by the toxicity of other ingredients in a prefixed combination of antibiotics.

There are few disease entities, as Dr. Kunin mentioned, which should be treated concurrently by more than one drug. Examples are tuberculosis, bacterial endocarditis caused by streptococcus fecalis, mixed infections caused by two or more different etiologic agents

with differing antibiotic susceptibility, and infections caused by gram negative bacilli before antibiotic susceptibility is determined.

There is no question that subacute bacterial endocarditis caused by streptococcus fecalis—which is a fatal disease, I would say 100 percent when not treated appropriately.

Senator NELSON. Which one is that?

Dr. WISE. Streptococcus fecalis endocarditis. It has been mentioned as a group D streptococcus, as a cause of the infection of the heart valve.

Now, this should be treated with penicillin in a daily dose, which I think we would agree, of 10 to 20 million units of penicillin a day plus streptomycin, concurrently in a dose of one to two grams.

Senator NELSON. That is the only drug, penicillin?

Dr. WISE. At the present time, in a patient with streptococcus fecalis endocarditis, a fatal disease, if he is not allergic to penicillin or streptomycin, this would be the treatment of choice.

Senator NELSON. If he is allergic?

Dr. WISE. If he is allergic to penicillin, one has another choice to go to. I am making the point of flexibility here, which we do not get with prefixed antibiotics.

Dr. KUNIN. We would never achieve the proper proportion with any of the prefixed combinations of penicillin and streptomycin.

Dr. WISE. You have just read my next sentence, Dr. Kunin.

Dr. KUNIN. I am sorry.

Dr. WISE. However, only one of the prefixed combinations of penicillin and streptomycin provides a daily dose of 2.4 million units of penicillin without exceeding a toxic dose of 2.0 grams of streptomycin.

Now, if you were to use that combination, the patient would receive two grams of streptomycin, and at that point it begins to be toxic. And this patient has to be treated for 1 month to 6 weeks. And therefore the toxicity of streptomycin would be so great that one could not use that prefixed combination because the patient would only be getting 2.4 million units of penicillin, and if you tried to give that patient 20 million units of penicillin you would be giving over 10 grams of streptomycin, and therefore, you see, there is no flexibility, there is a limitation to adequate therapy in the example that I have given, which would be the result of the prefixed combination.

There is a lack of therapeutic advantage of prefixed combinations.

The combinations of tetracycline and novobiocin, tetracycline and oleandomycin, penicillin and sulfonamide, tetracycline and sulfonamide, erythromycin and sulfonamide, oleandomycin and sulfonamide afford no therapeutic advantage over single antibiotics, when there is single antibiotic susceptibility, such as is the case with pneumococci, streptococci straphylococci, meningococci, gonococci, vibrios, spirochetes, anthrax, clostridial gangrene, and listeria—and I list these to make a point—that when one looks at the specific cause, there is a drug of choice. And in those that I have mentioned, penicillin, or one of its semi-synthetic preparations, are effective, proven effective with the single antibiotic, single without any mixture of anything else.

Nor in the case of bedsonia, rickettsia and myoplasma in which single effective antibiotics are indicated. The rest of the bacterial infections such as caused by Mimea, Horrellea, and the gram negative nonspore forming rods, require in vitro susceptibility tests to deter-

mine antibiotic susceptibility for specific antimicrobial therapy, if maximal opportunity for cure is to be attained.

The point I am making here is that in most of the bacterial infections, if you recognize the organism, a single antibiotic can be administered and there is no advantage therapeutically to using any prefixed combination.

There are some antibiotics—and there are some infective agents—as to which one we cannot be so predictive, but we must have information which comes from the laboratory in order to guide the physician in choosing a single antibiotic or multiple antibiotics that he is going to use, if he is to achieve maximum cure.

None of these combinations have any effect against viruses, which cause most of the infections in the United States.

Now, the use of unnecessary drugs when prefixed combinations are used.

When a single drug is maximally effective there is no logical reason for the administration of a second drug which adds nothing more to the clinical result.

However, there may be increased risk of adverse drug reactions when combinations of drugs are used, particularly when one of them is unnecessary.

The use of any drug may result in an adverse reaction in the patient. An unnecessary antibiotic in a prefixed combination can result in hazards varying from mild reactions to fatal results. Superinfection resulting during treatment with combinations of antibiotic may reach considerable magnitude.

This means that when one uses more antibiotics there is a greater elimination of the normal bacterial flora that every human carries with him and to which he is in a state of equilibrium. When one gives an antibiotic, the susceptible bacteria to which he is quite accustomed, are eliminated. He then replaces and obtains new bacterial flora which in the environment of the antibiotic which is being used, to which he now may become a victim by infection of a newcomer. This is what we mean by a superinfection. The instances of this are increased, the more antibiotic one uses. One creates what may be termed a biological vacuum when one uses antibiotics, and of course, this has some hazards.

Increased resistance of micro-organisms to antibiotics.

The acquisition of microbial resistance to antibiotics is related to the use of an antibiotic in an environment. The unnecessary use of an antibiotic as occurs with the use of prefixed combinations of antibiotics results in the appearance of resistance strains of bacteria with increased number of superinfections.

The erroneous implication of "wide spectrum" of antimicrobial effect.

Selection of a fixed combination of antibiotics, because there is a wide spectrum of antibacterial activity against a larger group of micro-organisms, indicates a lack of specificity in choosing the most effective antibiotic with a more direct specific effect against the micro-organism causing the disease. This philosophy of therapeutics may result in failure to establish an etiologic diagnosis and failure of cure until more appropriate therapy is selected.

In other words, when you need a rifle you certainly shouldn't use a shotgun. One wants specificity of action directly because of the disease.

In summary:

1. There is lack of indications for prefixed combinations of anti-infective agents.

2. There is lack of controlled clinical studies to prove indications for prefixed combinations of anti-infective agents.

3. When a prefixed combination of anti-infective agents is used here in a limitation of dose of one ingredient because of the toxic concentrations of the other.

4. In most infections there is a lack of therapeutic advantage of prefixed combinations over one specific antibiotic.

5. If one ingredient is unnecessary, there is hazard of increased unnecessary adverse drug reactions including the development of resistant strains of micro-organisms.

6. When a prefixed combination of antibiotics is chosen empirically, there may be interference with further diagnostic techniques. Unless, during the time of that empirical judgment, appropriate tests are in progress.

7. Specific narrow spectrum antibiotics may be more advantageous than a "wide spectrum" combination of antibiotics.

Thank you.

(The complete prepared statement and supplemental information submitted by Dr. Wise follows:)

STATEMENT OF ROBERT I. WISE, M.D., PH. D., PROFESSOR OF MEDICINE AND CHAIRMAN, DEPARTMENT OF MEDICINE, JEFFERSON MEDICAL COLLEGE

SELECTION OF ANTIBIOTICS IN THERAPY OF INFECTIOUS DISEASES

I. Introduction

The modern era of therapy of infectious diseases began in 1935 when Gerhard Damagk introduced protosil, a dye stuff derived from sulfanilamide, which protected mice against fatal doses of hemolytic streptococci. The many antimicrobial agents developed since that time have provided a potentially curative armamentarium against infectious diseases considered incurable only 35 years ago.

II. Factors influencing treatment

Many factors influence the concepts and habits of physicians who treat infectious diseases. Medical students, interns and residents are taught principles in the diagnosis and management of these diseases. Representatives of pharmaceutical manufacturers discuss their companies' antimicrobial products with physicians. Medical journals publish reports of varying degrees of excellence on observations of the use of anti-infective agents; advertisements containing statements that would not be acceptable in a scientific manuscript are printed in the same journals. Exhibits at every major medical convention attempt to influence the physician in his choice and use of antimicrobial products. Patients may suggest and demand the administration of an anti-infective drug. The busy physician is pressed to prescribe.

III. Reasons for the rational use of anti-infective agents

A patient who has indications of infection can be assumed to have a disease caused by one or more of the following: (1) bacteria, (2) viruses, (3) rickettsia, (4) bedsonia, (5) mycoplasma, (6) fungi, (7) other parasites, protozoa, etc. or (8) a host of noninfectious agents. The patient should be treated by methods that will eliminate the etiologic agent as rapidly as possible in order to prevent the progression of disease, the development of complications and death, and to decrease morbidity and expense. If adequate therapy is not begun promptly, the disease or its sequela may become irreversible.

It must be emphasized that any bacterial infection is potentially a serious illness which, if it is inadequately treated, may result in death. If, for example, the disease is caused by *Streptococcus hemolyticus,* the possible complications

are bacteremia and infection of other areas of the body and may result in the following: acute glomerulonephritis with renal insufficiency, rheumatic fever, rhemuatic heart disease and bacterial endocarditis. Infection with *Staphylococcus aureus* may advance to bacteremia and the development of metastatic abscesses in the bones and viscera. *Pseudomonas* and *Escherichia* may cause bacteremia with acute peripheral vascular collapse. Mycobacterium tuberculosis may spread and result in a prolonged and eventually fatal illness.

IV. Principes in the rational use of anti-infective agents

An optimum specific therapy can be selected for these common but malignant bacterial infections only when the etiologic agent is identified or, if identification is impossible, when excellent clinical judgment is used to determine the most probable diagnosis.

If the etiologic agent has not been identified and, as a result, an ineffective mode of therapy is selected, the infectious disease may advance, remain dormant until therapy is discontinued and then relapse, or a cure may result from the response of the patient's natural defense mechanism.

The initial use of an ineffective drug or combination of drugs may actually interfere with further attempts to identify the etiologic agent and thus, place the patient in a hazardous situation since further therapy must be selected empirically. In this situation the physician must rely on his observations and experience in choosing a therapeutic agent. He cannot plan the optimum duration of therapy or anticipate the possible complications of the illness. Morbidity, complications, mortality and expense are increased.

Conversely, when the etiologic agent is identified, the psysician can institute specific therapy with an anti-infective agent immediately. He can select a preparation and mode of administration that will better assure adequate concentration of the drug at the site of infection, plan the probable duration of the therapy, and foresee possible complications. Under such circumstances, mortality rates, morbidity, complications and expenses are kept at a minimum.

The cure or prevention of infectious disease with avoidance of drug-induced deleterious effects is the goal of antimicrobial therapy; thus, in addition to the harmful effects that may result from the use of an inappropriate agent, the physician must keep in mind the deleterious effects associated with the use of specific agents. For example, penicillin may cause allergic reactions ranging from relatively mild and reversible reactions such as dermatitis, pruritis and fever, to immediate anaphylaxis and death. Some anti-infective agents can cause deafness, aplastic anemia, hemolytic reactions, hepatic damage and injury to the kidneys. If the normal resident bacterial flora is disturbed, transient micro-organisms may proliferate and produce disease. The over use of anti-infective agents results in the development of resistance of micro-organisms to a therapeutic agent.

V. Selection of antiinfective agents

In table 1 are listed the common etiologic agents which product infectious disease in humans. In table 2 are listed most of the anti-infective drugs that are available for treatment of the various disease producing micro-organisms.

The anti-infective agents should be selected on the basis of:

(1) Early identification of the micro-organism if possible.

(2) In case identification is not possible, therapy should be selected on the basis of clinical evaluation.

(3) Specific treatment should consist of one or more drugs as indicated for the etiologic agent and the characteristics of the disease process in the individual patient.

(4) Selection of the drug or combination of drugs, dose of each drug and route of administration of each drug should be determined in a manner that will result in adequate concentrations of the single drug or multiple drugs at the site of infection with minimum hazards of adverse effects of each drug and result in maximum benefit to the patient.

VI. The use of prefixed combinations of antiinfective agents

(1) The following is a list of some of the commercially available prefixed combinations of antimicrobial agents and the number of preparations and different dosage forms of each combination.[1]

[1] McCabe, W. R., Clinical Use of Combinations of Antimicrobial Agents. Antimicrobial Agents and Chemotherapy—1967; Proceedings of the Seventh Interscience Conference on Antimicrobial Agents and Chemotherapy, pp. 225–233, edited by G. L. Hobby, Amer. Soc. Microbiology.

Example of prefixed combinations

	Number
Penicillin-streptomycin	20
Tetracycline-novobiocin	3
Tetracycline-oleandomycin	5
Tetracycline-nystatin	13
Tetracycline-amphotericin	4
Penicillin-sulfonanide	22
Tetracycline-sulfonanide	2
Erythromycin-sulfonanide	3
Oleandomycin-sulfonanide	1
Sulfonanide-methenamine mandalate	2
plus	
Tetracycline-analgesic (aspirin)	2
Oleandomycin-analgesic	1
Penicillin-analgesic-antihistamine-vasoconstrictor	3
Tetracycline-analgesic-antihistamine	2
Sulfonamide-pyridium	6
Sulfonamide-scopolamine	2
Methenamine-pyridium	1
Methenamine-scopolamine	2
Methenamine-analgesic	1

Note.—Each of the above 95 prefixed combinations has a different trade name.

(2) Lack of Therapeutic Indications for Prefixed Combinations of Anti-infective Agents.

In the selection of a therapeutic program for any of the etiologic agents, listed in Table 1, there is no logical indication for use of any prefixed combination when they are viewed in light of indications for therapy with single or multiple anti-infective agents.

(3) Lack of Controlled Clinical Studies.

No adequately controlled clinical studies have been conducted to prove the superiority of prefixed combinations over the use of singly administered antimicrobial agents.

(4) Limitation of Dose of One Ingredient by the Toxicity of Other Ingredients in a Prefixed Combination of Antibiotics.

There are few disease entities which should be treated concurrently by more than one drug. Examples are tuberculosis, bacterial endocarditis caused by *Streptococcus fecalis*, mixed infections caused by two or more different etiologic agents with differing antibiotic susceptibility, and infections caused by gram negative bacilli before antibiotic susceptibility is determined.

There is no question that subacute bacterial endocarditis caused by *Streptococcus fecalis* should be treated with penicillin in a daily dose of 10.0 to 20.0 million units plus streptomycin in a daily dose of 1 to 2 grams. However, only one of the prefixed combinations of penicillin and streptomycin provides a daily dose of 2.4 million units of penicillin without exceeding a toxic dose of 2.0 grams of streptomycin. None of the prefixed combinations of penicillin and streptomycin could be used to provide a daily dose of 20.0 million units of penicillin without giving a toxic dose of over 10 grams of streptomycin.

(5) Lack of Therapeutic Advantage of Prefixed Combinations.

The combinations of tetracycline and novobiocin, tetracycline and oleandomycin, penicillin and sulfonamide, tetracycline and sulfonamide, erythromycin and sulfonamide, oleandomycin and sulfonamide afford no therapeutic advantage over single antibiotics, when there is single antibiotic susceptibility, such as is the case with pneumococci, streptococci, staphylococci, meningococci, gonococci, vibrios, spirochetes, anthrax, clostridial gangrene, and listeria in which the penicillins are more effective, nor in the case of bedsonia, rickettsia and myoplasma in which single effective antibiotics are indicated. The rest of the bacterial infections such as caused by Mimea, Horrellea, and the gram negative non-spore forming *rods*, require *in vitro* susceptibility tests to determine antibiotic susceptibility for specific antimicrobial therapy, if maximal opportunity for cure is to be attained.

None of these combinations have any effect against viruses, which cause most of the infections in the United States, nor against the fungi.

(6) Use of Unnecessary Drugs in Prefixed Combinations.

When a single drug is maximally effective there is no logical reason for the administration of a second drug which adds nothing more to the clinical result.

(7) Increased Risk of Adverse Drug Reactions When Combinations of Drugs are Used.

The use of any drug may result in an adverse reaction in the patient. An unnecessary antibiotic in a prefixed combination can result in hazards varying from mild reactions to fatal results. Superinfection resulting during treatment with combinations of antibiotic may reach considerable magnitude. The hazard of neutralization of the effects of one antibiotic by another antibiotic may result in decreased efficacy of therapy.

(8) Increased Resistance of Micro-organisms to Antibiotics.

The acquisition of microbial resistance to antibiotics is related to the use of an antibiotic in an environment. The unnecessary use of an antibiotic as occurs with the use of prefixed antibiotics results in the appearance of resistant strains of bacteria with increased number of superinfections.

(9) The Erroneous Implication of "Wide Spectrum" of Antimicrobial Effect.

Selection of a fixed combination of antibiotics, because there is a wide spectrum of antibacterial activity against a larger group of micro-organisms, indicates a lack of specificity in choosing the most effective antibiotic with a more direct specific effect against the micro-organism causing the disease. This philosophy of therapeutics may result in failure to establish an etiologic diagnosis and failure of cure until more appropriate therapy is selected.

VII. Summary

(1) There is lack of indications for prefixed combinations of anti-infective agents.

(2) There is lack of controlled clinical studies to prove indications for prefixed combinations of anti-infective agents.

(3) When a prefixed combination of anti-infective agents is used there is a limitation of dose of one ingredient because of the toxic concentrations of the other.

(4) In most infections there is a lack of therapeutic advantage of prefixed combinations over one specific antibiotic.

(5) If one ingredient is unnecessary, there is hazard of increased unnecessary adverse drug reactions including the development of resistant strains of mcro-organisms.

(6) When a prefixed combination of antibiotics is chosen empirically, there may be interference with further diagnostic techniques.

(7) Specific narrow spectrum antibiotics may be more advantageous than a "wide spectrum" combination of antibiotics.

TABLE 1

ETIOLOGIC AGENTS OF INFECTIOUS DISEASES

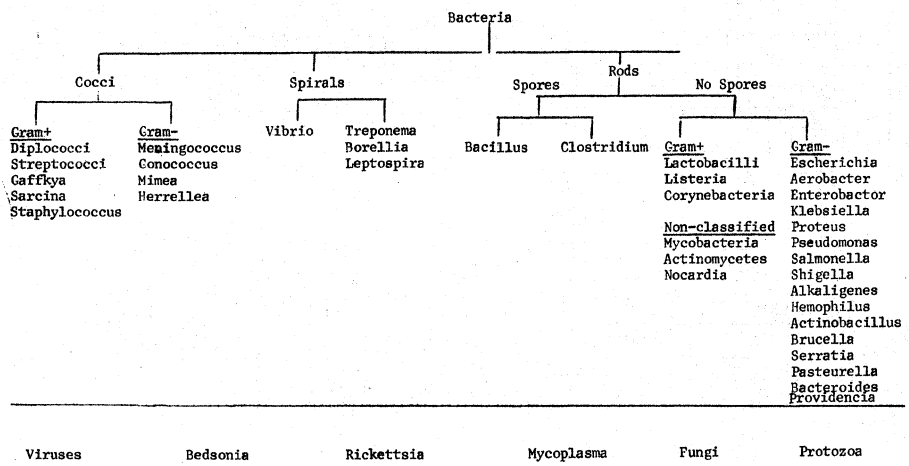


TABLE 2

THERAPEUTIC ANTI-INFECTIVE AGENTS

ANTI-BACTERIAL AGENTS

GRAM POSITIVE BACTERIA

THE PENICILLINS

Penicillin G
Methicillin
Oxacillin
Cloxacillin
Nafcillin
Ampicillin
} Semisynthetic

THE CEPHALOSPORINS

Cephalothin
Cephaloridin
Cephaloglycine

THE MACROLIDES

Erythromycin
Novobiocin
Oleandomycin
Triacetyloleandomycin
Carbomycin

OTHERS

Lincomycin
Vancomycin

GRAM NEGATIVE (& Positive) BACTERI

Streptomycin
Dihydrostreptomycin
Neomycin
Kanamycin
Paromomycin

THE TETRACYCLINES

Tetracycline
Oxytetracycline
Chlortetracycline
Demeclocycline
Methacycline
Doxycycline
Rolitetracycline
Demethylchlortetracycline

CHLORAMPHENICOL

THE POLYMYXINS

Polymyxin B
Polymyxin D (Colimycin)

OTHER AGENTS

Gramacidin
Gentamycin
Bacitracin
Sulfonamides
Nitrofurantoins
Nalidixic Acid
Methenamine

ANTI-FUNGAL AGENTS

Nystatin
Amphotericin B
Griseofulvin

ANTI-VIRAL AGENT (Systemic)

(with exception of Idoxuridine for Herpes simplex, keratitis, there are no clinically effective agents)

ANTI-BEDSONIAL AGENTS

Tetracyclines
Chloramphenicol

ANTI-RICKETTSIAL AGENTS

Tetracycline
Chloramphenicol

ANTI-MYCOPLASMA AGENTS

Tetracycline
Erythromycin

Dr. KUNIN. May I add, Senator Nelson, if you were to extend the number of witnesses from the five or six that you had over these 2 days to 1,000, or 10,000, from the group of experts that deal with these problems, I don't think you would get any different opinion. The unanimity of opinion in this particular area is really tremendous.

Senator NELSON. Does anyone have any other comment he would like to add?

I want to thank you, Dr. Wise, Dr. Hewitt, and Dr. Kunin.

Yours was a very valuable contribution to the hearings that we are conducting on fixed combinations. We will be hearing from the FDA. And then we shall also invite all of the manufacturers of these drugs to appear to respond in any way they desire.

That will recess these hearings until May 20 at 10 a.m., in the Caucus Room of the Old Senate Office Building.

Thank you.

(Whereupon, at 12:15 p.m., the subcommittee was adjourned, to reconvene at 10 a.m., Tuesday, May 20, 1969, in the Caucus Room, Old Senate Office Building.)

81-280 O—69—pt. 12——7

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

TUESDAY, MAY 20, 1969

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

The subcommittee met, pursuant to recess, at 10:15 a.m., in room 318, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senators Nelson, Long, and Dole.

Also present: Benjamin Gordon, staff economist; Elaine C. Dye, clerical assistant; and James P. Duffy III, minority counsel.

Senator NELSON. Our witness this morning is Dr. John Adriani of the Charity Hospital of New Orleans, La.

Dr. Adriani, would you come up to the witness table?

Doctor, your statement will be printed in full in the record. You may if you wish at any time elaborate on any aspect of your statement. I assume that you have no objection to questions during the course of your testimony?

Dr. ADRIANI. No, I have not.

Senator NELSON. Go ahead, Doctor.

STATEMENT OF DR. JOHN ADRIANI, CHARITY HOSPITAL, NEW ORLEANS, LA.

Dr. ADRIANI. At the beginning of my statement I give some of my background. I graduated from the Columbia Medical School in 1934. I trained in surgery at the French Hospital in New York.

I have always been interested in chemistry and drugs. After I got into surgery I realized that advances in surgery would be curtailed unless something was done about the administration of anesthetics. I became interested in that problem.

And at that time there was a man named Rovenstine who trained with Dr. Ralph Waters at the University of Wisconsin who started the department of anesthetics at Bellevue Hospital. I signed up with him, supposedly so I could learn what there was to learn about anesthesia in a couple of weeks.

But instead of a couple of weeks I stayed 5 years, after which I moved to New Orleans, where I am now located at the Charity Hospital. I have charge of the anesthetics department, and have been for nearly 30 years.

In addition, I am associate director of the hospital, second in command. I hold a full professorship in the department of surgery at the Tulane University School of Medicine, and also at the Louisiana State

University School of Medicine. I am a member of the pharmacology department at the Louisiana State University, and teach pharmacology to undergraduate medical students. Incidentally, I have just completed my lectures and am correcting the examination papers now.

I have thus been interested in drugs all these years. My interest in drugs began in anesthesiology and broadened into pharmacology.

Anesthesiology actually is a branch of clinical pharmacology. We use the drugs we require in human beings who are sick. Because of this fascination in the action of these drugs, my interest in drugs has broadened as the years have gone by, so that I have expanded my interest in other aspects of drugs besides anesthetics.

In addition, there has been an expansion of the anesthesiologist's interest in the field of drugs, because multitudes of drugs that we use, caused at times, what we refer to as interactions. When you give two or three drugs you do not know what the combination is going to do. We have adverse reactions sometimes when two drugs are combined. A patient, for instance, may be getting a tranquilizer—chlorpromazine—that is well known, and when one gives him an anesthetic, his blood pressure disappears, and it is hard to restore it to normal with the usual drugs that restore blood pressure. We have learned about some of these various reactions and we are cataloging them as we learn more. We are using drugs in patients all the time and not in animals.

My experience in laboratory work with animals is confined to problems I cannot solve in human beings and studying them in the laboratory and not jeopardizing the patient to find out something I want to know. One area in which I have been interested is in the area of local anesthetics. These drugs can be lethal if they get into the bloodstream. We have done many studies in animals, and the results parallel pretty much those in human beings.

In addition to this experience with drugs I have been a member of the revision committee of the U.S. Pharmacopeia for the past 9 years. We are now in the process of proofreading the 1970 edition of the U.S. Pharmacopeia. I am a member of the Council on Drugs of the American Medical Association, and I have been chairman of this council for about 2½ years. And I am also a member of various pharmacological associations.

When the Kefauver-Harris amendments were enacted, Commissioner Larrick formulated a committee which was known as Modell's—Walter Modell of Cornell University—committee. I was on that committee, which was advisory to Mr. Larrick to help him implement this act. We met here once a month for about 2 years. After that period of time we requested that the committee be dissolved. We thought our mission had been completed, because they finally found what they had been searching for for quite some time, a medical director (Dr. Joseph Sadusk). But I remained on as a consultant.

When Dr. Goddard became commissioner, he finalized a number of committees. One of them is the committee on anesthetic and respiratory drugs. When we say respiratory drugs, we refer to those drugs used to stimulate respiration.

Sometimes when we give too much of an anesthetic, we may want to stimulate a patient to get him to breathe again. These drugs are also used for inhalation therapy for people with lung diseases. This

committee meets periodically. I am chairman. It is consulted regularly by the Food and Drug Administration and is quite active. We met here (D.C.) last Monday (May 12). Some of the material, for which advice was sought, was on the recommendations of the NAS–NRC in this particular category of drugs.

Thus, I have been associated, more broadly, with drugs in the latter part of my life than I was in the beginning.

Most of my professional life has been devoted as an employee of the State of Louisiana. Before that I was at Bellevue Hospital, New York University. Charity Hospital in New Orleans is owned by the State of Louisiana. It is a teaching hospital. All the patients that we treat are indigent. In other words, they do not pay for the cost of their medical care, unless they happen to be emergency cases that are later found to be able to pay. But the majority are people who do not have the means for paying for their own medical care.

We have about 60,000 admissions a year to the hospital. It may have fallen in the last year or two, because we had to curtail beds due to the shortage of personnel. So as far as seeing patients is concerned, I have seen many, and have a wide clinical experience.

I am also engaged in the training of personnel to administer anesthetics. They fall in two categories. One is the physician group that are called anesthesiologists. But there not being enough physicians, and not enough in this particular specialty, we therefore have to resort to the use of nurses. We have a school for the training of nurses. One of the largest in the country. We have as many as 50 enrolled most of the time. Without these young ladies that we train it would be impossible to carry on surgery in our part of the country.

We were successful in having the Louisiana Legislature appropriate $150,000 to initiate a school for the training of surgical technicians. This also comes under my purview.

That is my background. I would like to say that I am not here as the chairman of the Council on Drugs, though I will be happy to answer any questions along that line. I am not representing the AMA. I am here strictly as an individual physician with an opinion on drugs, and as a man who has been teaching the use of drugs, and has been investigating drugs.

Pharmaceutical firms sometimes approach me about investigating a new drug. If I am interested and have someone that can do it—I cannot do it myself, but I can have it done under my direction, I will agree to do it.

On page 5 of the statement that I have prepared I refer to generic names. To me this is a very important item, because if you teach pharmacology as I do, you will find it very difficult to teach material about a drug, to a doctor or prospective doctor, when you have three or four names for a drug.

Now, we have what we refer to as generic or given names. This is a name just like you are Gaylord Nelson and I am John Adriani. These are our names. I might have a nickname or an alias, but that is not my name. Brand names of drugs are aliases. I cannot see why we keep on using these aliases for drug's names.

Drugs, as far as I am concerned, are something that are vital to the health, of not only the Nation, but the whole world. They are an item

just like food; they come in the same category. We have an industry that makes drugs that is given special privilege, being permitted to call a commodity by a name which it really should not have (an alias). An alias is meant to be deceptive or to conceal identify. This is what a brand name does to a drug.

For instance, recently there has been considerable discussion about Panalba. The Journal of the American Medical Association has an advertisement on the back cover. If I were a psychiatrist and not dealing with infectious diseases—we do have infections in surgery—I would not know what Panalba is. Many physicians have no idea what is in Panalba. Yet here is a name appearing in the advertising on the back of the leading medical journal.

Now, the only persons that can do it—there is no scientific group that can do what I am going to propose—is Government. For instance, in medicine we can police ourselves. In the hospital we have a Tissue Committee. If a doctor does unnecessary surgery we can call him and say, "a normal appendix is reported by the pathologist. Explain why you took out a normal appendix." And he has to give a written explanation.

So as physicians we can police ourselves in many ways. But getting rid of brand names is something we cannot do. Now, if you get rid of all brand names and use the generic name, in large type on a bottle, and put underneath it the name of the company that makes it, and if they have a trade name and they want to use it to put that in parentheses in fine print, this is fine. This would not inhibit a physician from prescribing a commodity that the patient should have, nor will it forbid the physician from specifying a particular manufacturer. For instances, if you go to a supermarket and you want tomato soup you can buy Campbell's, you can buy Heinz', you can buy Van Camp's—these are some of the brands. I do not shop any more. I used to. But when I was a boy we had a grocery store, and I remember these brand names. But tomato soup is tomato soup. You can pick your brand. If the Government would decree (drugs are so vital to the health of the Nation) that from now on drugs should be called by their given names, the names that really belong to them and by nothing else—this will not hamper the physican at all. He can still practice the way he wants to. If he has confidence in a particular pharmaceutical firm he can specify that pharmaceutical firm's product. There are certain people that prefer products of one firm over those of another.

For instance, in my own field we buy ether. Ether is made by several firms—Mallinckrodt, Squibb—I don't know whether Merck is still marketing ether, but they did have it—Squibb has labelled across the front of the can "Copper plated." When you seal the can the copper absorbs the oxygen preferentially. No oxygen left in the ether. Some air dissolves in the ether and is sealed in the can. The oxygen is not there to act on the ether, and the ether is preserved. So copper is actually a stabilizer. For that reason, I preferred Squibb's ether. When we open a can we do not have to use it all. We used part of it and then discard it. Since then other firms have found other ways of handling this problem. But I sort of got used to Squibb's ether, because of the copper plating and I prefer it. If I went to an institution

and I wanted to use ether and I had another brand that was marked USP, I would have no hesitation in using it.

Mr. Chairman, I think that the first thing that the Congress really should do—and no one else can do it except the Government—is to decree that all drugs are dispensed and sold under their generic name. Then the doctor would have to know the generic name. Many doctors, including myself, don't know the generic names of all the products they use. I know only the generic names of those that I use all the time. If the use of generic names is mandatory the patient will know them, the pharmacist will know them, the public will know them, and members of the family will know them. If an overdose is inadvertently given, or where somebody takes a drug with suicidal intent, the physician and the toxicologist will know it. And this is, I think, very important.

Generic naming will eliminate, I think, to a large extent one of the arguments that we have been hearing recently concerning advertising. Some drugs will not be advertised if they are sold by USP names and not by brand names. Brand names as far as I am concerned are aliases and deceptive. And being a teacher of pharmacology, and having taught people to use drugs all these years, I find their elimination a very important thing.

So labeling, generically, then, should be compulsory. Instead of having the brand name in large type as is done now—this was instituted when the Kefauver-Harris amendment was enacted—I would do the reverse, have the generic name in large type and have in very small type the brand name if one wants it on the label.

Some physicians will still use the brand name, but when they learn the generic name they will not be using the brand name, because a good many physicians do not care about the brand name, as I told you. If they see USP on the label then they know that these drugs meet certain accepted standards.

Senator NELSON. May I interrupt just a moment?

Doctor, Senator Long of your State has arrived here. He wanted to be here to present you to the committee. So I would allow Senator Long, who is a member and former chairman of this subcommittee, to make his remarks now.

Senator Long, it is very nice to have you here today.

Senator LONG. Thank you very much, Mr. Chairman.

I wanted to be here when Dr. Adriani started. I would have liked to have heard his entire statement and asked a few questions. And if time permits I will do that.

Dr. Adriani is one of our distinguished citizens of Louisiana. And insofar as his views coincide with mine, I assure you, Mr. Chairman, it is only an accident, because I come from the northern part of the State of Louisiana. I did one time live in the city of New Orleans, and I have visited New Orleans Charity Hospital and have seen the magnificent work being done there.

But I really was not familiar with all the fine work Dr. Adriani has done until I happened to look over his credentials prior to his appearance here. He and I have never discussed the matter of drug prices or generic pricing. But I am proud to notice that at New Orleans Charity a fine job has been done in trying to acquire the drugs in the best quality at lowest possible price.

And I am very proud to have Dr. Adriani appear before us today and give us some of those statements that we have had some difficulty in getting from some other members of the profession.

Senator NELSON. Thank you very much, Senator Long.

Dr. Adriani, apart from the confusion resulting from the great proliferation of drugs—I mean, the difficulty in keeping track of them all—are you aware of any instances where the fact that we use brand names has been a safety problem to the patient? For example, thalidomide was in the marketplace in Spain and South America under, according to Dr. Taussig, a number of brand names. Long after the medical community was aware that thalidomide was a dangerous drug, it was still being prescribed under brand names with the physician not being aware that it was, in fact, thalidomide?

Do you view that as a serious problem under the brand name system?

Dr. ADRIANI. Yes. A patient who is sensitive to sulfa drugs may have taken a drug under one brand name, and when he goes to another physician and may get the same product of another manufacturer, under another name. He gets a reaction from it, if he does not know what it is. This is possible, not knowing the identity of the drug.

And this is why I strongly emphasize—the FDA talks about full disclosure on their package inserts, that I am for full disclosure on the label of what is in that bottle.

Here is an example with which I am familiar. A patient went to one physician and was treated by that physician for some time. He did not think he was getting any better. So someone else said, "Why don't you go see my doctor?" He had been given Equanil by this first doctor. The other doctor looked at him and said to himself, this fellow is on the "neurotic side," and I will give him Miltown. So this patient threw away his Equanil and bought Miltown. Miltown is the same thing as Equanil. If meprobamate had been on the label and the patient had seen that label, he would have said "he gave me the same thing the other doctor did." And he would have said, "maybe there is something wrong with me 'upstairs.'" And he would have known that he got the same medicine.

Senator LONG. Assuming he went to a third doctor, that doctor might have given him the same medicine by the honest name, meprobamate, and he would save said, this doctor isn't any better than the other one was. And a fourth doctor might give him Librium, and he might give it by a different name, and he still wouldn't know what he is taking.

But he finally found a doctor who could come up with the correct answer. It just happened that recently I discussed this same problem with the president of a drug company. And naturally he does not agree with your position, Doctor, because he likes to sell by brand names. So I interrogated him on the difference between Librium and meprobamate. And he was arguing for his position. He said, "It is very important that a doctor should know his own patient and know what his patient's problems are and how his patient reacts to drugs."

So I interrogated him on this difference between Librium and meprobamate. He said, if a doctor gave me—I can't recall what, one or the other—the next day I would feel like I had the worst hangover I had ever had in my life; that is the way I would react.

And I said, "How would a doctor know that if he hadn't tried it on me?"

Can you tell me, how would you know that a man would have a very horrible side effect from either one of them without having tried it on him?

Dr. ADRIANI. He would not know if he didn't have the label, if he had not tried it. And there are some people who become very sleepy. For instance, an ally to Librium is Valium. This is a trade name. And this they give to people who have muscle spasm. I know if I take that drug it makes me sleepy.

Senator LONG. Valium?

Dr. ADRIANI. That is a trade name.

Senator LONG. For what, Librium?

Dr. ADRIANI. It is a modification of Librium. I cannot spell the generic name offhand. I should know it. Really I should know it. But I cannot spell it for you. If you asked me to spell that name, I could not spell it correctly. But if the drug had been introduced on the market with the generic name I would know the generic name and would be able to spell it; I would have to write the prescription generically instead of Valium.

Senator LONG. Another thing that bothers me about this thing, Doctor, is that right now I think the drug companies are trying to help pursue this hocus-pocus of never letting the patient know just what it is that he is taking. Some doctors ask, what drug stores do you do business with? I will call the pharmacist down there and you can pick it up.

And the druggist takes the bottle, which is correctly labeled, and he tears the label off and sticks something on there—"This is prescribed by Dr. Jones to be used as directed"—so that you never do know what it is. And why does he tear the label off? Just to keep you from finding out what the Food and Drug people required them to put on the bottle so that you would know what it was.

What good is that doing the patient?

Dr. ADRIANI. It is not doing any good.

I want to tell you, Senator, you know as well as I do what happened in south Louisiana when Hurricane Betsy struck. I was in Philadelphia, and I flew back to New Orleans. I had just bought a new car. They talked, in the press, about cars being rolled over. Fortunately my car was all right, but I noticed others were bashed in.

I got to Charity Hospital. As the waters receded we began to receive patients. They had run out of medicines they were taking, Orinase, insulin, and so on. They had the bottle with no identification of the drug on it except the doctor's name.

If you tried to call the pharmacy you made no contact. because it was under water. The prescriptions were all soaked with water. Besides, when you called you would get a busy signal, because there was no operative telephone connection.

W did not know what drugs those patients were getting. If the containers had been labeled, whatever it was, meprobamate, digitalis, and so on, we could have given them their medicines. What we did was to try to locate the doctor or to figure out as best we could what medication he was getting. This worked a handicap on these people—and us also.

Another Saturday afternoon——

Senator LONG. Doctor, let's just get that straight. At that particular time we must have had to evaculate about 20,000 people, right?

Dr. ADRIANI. Easily, if not more, because the evacuation went on for 3 or 4 days after the hurricane.

Senator LONG. And as you said, a great number of these people had to be pulled out of the water.

Dr. ADRIANI. That is right.

Senator LONG. So here they were taking certain medicines which they needed to take. But with this fraud of not permitting the patient to know what he is taking, and this trade name fiasco, these people did not know what medicine they were taking. They needed it but they didn't know what it was. And you were in no position to find out what it was that they needed, is that right?

Dr. ADRIANI. That is right.

Senator LONG. Now, if we found ourselves at war and had a bomb hit or another Hurricane Betsy, or something of that sort, we would have the same problem all over again, wouldn't we?

Dr. ADRIANI. We sure would.

Senator LONG. And so the patient needs medicine, without it he may be in serious difficulty, might even die, and yet you can't find out what it is because of this farce, this hocus-pocus, this shell game that prevents the patient from knowing what medicine he is taking?

Dr. ADRIANI. I will give you another example. One Saturday afternoon I was in the hospital. A patient was brought in from Raceland with 10 bottles of different colored pills with the name of the doctor but with no identification of the pills. The doctor took out his PDR, and tried to identify them by the pictures in the book. I said, "Call the doctor or the pharmacist to find out and you will know exactly what they are from the number on the prescriptions."

Now, if those medicines had been labeled he would not have been put to that trouble—I may say this, also the (AMA) Council on Drugs when I first joined it, strongly urged that labeling be applied to all prescriptions doled out to a patient. I make this recommendation in my prepared statement—so the patient knows what he is getting. You know, years ago doctors had few drugs and did not know what to use. They used herbs and that sort of thing, and resorted to hocus pocus medicine. Today, we have specific remedies with specific actions. And today patients know about these; they can read, they are not morons.

The opponents of labeling sav they will use the pills again at a later date or give them to friends. This is a lot of nonsense. I am not going to use a pill if it has been on the shelf for a couple of months, because one is not sure of its efficacy.

I had some erythromycin which I carried around in a suitcase. I didn't know that the label had expired. I was advised to take it, but the infection that I had was not going away. I ran out and got a fresh supply. And right away the infection subsided. So there ought to be an expiration date on drugs. There ought to be expiration dates also on the containers given to patients.

You cannot give too much information to a doctor, to a patient, to the family when you prescribe something. You just cannot do it.

There is no such thing as over teaching anybody, from what I have learned.

Senator LONG. In other words, the more you tell a man about what his health problem is, what medicine seems to help him, what the name of the medicine is—and if they insist on selling it by 50 different names, what all the names are, but particularly what the official name of the thing is.

Dr. ADRIANI. Absolutely.

Senator LONG. Suppose he was visiting in some small rural town and he needed to have a particular drug. Perhaps he is nervous, sensitive and needs a tranquilizer. For this reason he has been taking Equanil, a trade name of the drug meprobamate. But the druggist in this town doesn't have Equanil. The physician he goes to see doesn't know other trade names for meprobamate and as a result the man is without needed medication. This is just one illustration of the confusion that results from all these brand names.

It's highly possible that the pharmacist has the drug on his shelf, manufactured by other firms. But the patient and the doctor may well not be familiar with the other trade names for this drug. Further, not one of these firms, though they brag about their company's quality control would dare make the assertion under oath that theirs was a better drug than the other companies because if they did, the other company might sue them successfully.

So, here we are in a situation where the poor patient can't get the medicine he needs, and the whole purpose of the long list of names for this same drug is to confuse and make him pay more for a product that isn't any better, isn't that what it amounts to?

Dr. ADRIANI. It really is.

I was telling Senator Nelson before you came, I have with me a Charity Hospital drug list which we call a formulary. We buy only certain drugs at Charity Hospital. We have a pharmacy committee that makes the selections.

Some of the medical staff send in letters saying, we would like to have you include such and such a drug on the drug list. And they will tell you why. And we look at it and approve, reject, or defer action. A drug (detail) man may see two or three professors or doctors on the staff, and ask to get their drugs in the hospital formulary. These doctors like to be "nice guys"; so they write a letter and say, "will you please stock such and such in the pharmacy." Well, the minute the committee sees that letter it "smells" right away what it is. It defers action on the request. And it never hears about it any more.

We have this list. If a doctor prescribes Equanil, and the pharmacy does not have it, they will call the doctor and say, we do not have Equanil, but we do have Miltown. The doctor would say, OK, substitute Miltown. He doesn't care. The staff will use whatever we have if it is equal.

When I was an intern we had a little book, also a formulary, and whatever was in there the doctor would prescribe. And if they did not have it they would say, we have something equal and as good, U.S.P. The visiting doctor would say OK, go prescribe that.

Once in a while we do have to go out and buy a drug we do not stock. But when we have something that is equal, that is U.S.P., we will buy and use it every time.

The U.S.P. have been doing a good service since 1840 or whenever it was founded. They keep updating their standards. If you look at the U.S.P. that was written 10 years ago and the one that is in use today, in the section relating to the testing of drugs, you will note they have sophisticated methods listed for testing. If it is found out that there is such a thing as generic equivalency that is being talked about they will adopt methods to indicate it. When I read some of these articles about generic equivalency they remind me of some of psychiatrist's treatises—they do not mean a thing. I have yet to see specific instances where there is any well-defined evidence clinically on generic equivalency.

And if it should come to pass that there is, the U.S.P. will include it and they will rewrite their standards. They are not backward. They are an active group.

Senator LONG. Doctor, here is something that happened to me, and I am sure it happens to many others. In fact, I suppose, there are many people who think that they are being done a favor.

My dentist is a good friend of mine, a man whom I respect—you perhaps know him, but I am not going to identify him. But this is a good illustration of what happens. I have a tooth he is fearful might abscess. But he is trying to save it for me. And he succeeds in saving it, so that tooth remains in my mouth a couple of years longer than it would have if he hadn't done such a skillful job of saving it. However, he says: "An abscess might develop. And this could hit you some night when you are overseas at a conference or something of the sort. If that should happen you should have some drugs to help you. I am going to give you two things. One, Darvon to keep the pain under control. And two, Panalba. The Panalba will kill the bacteria, and that will keep that infection under control until you can get back to me or to someone who can help you."

He states that, "The Darvon and Panalba will hold you for about 24 hours. This will help you in the event that this flares up into a painful abscess."

Now the question is—why did he prescribe Panalba? He has a whole drawer full of free samples of Panalba. He hands me some, and says, "just put that in your bag. In case it is not enough I will give you some more." He has been given these as free samples.

So I take the medicine with me. From time to time if it appears to me that the tooth is beginning to act up, I take the Darvon and the Panalba.

Incidentally, this committee has brought to light some facts that I wasn't aware of. And that is that Panalba is a substitute for tetracycline, it is tetracycline with something else in it. So they put something in the tetracycline that I didn't need, that could be harmful to me. The details about the Panalba can be better provided by this committee, because I wasn't here to hear the testimony, but I understand that Panalba was determined by the National Academy of Science to be ineffective.

But here I am loading myself up with Darvon and Panalba because the man left all the free samples. If the dentist had just written down tetracycline and I could have bought all I wanted for 5 cents a capsule—and the six capsules wouldn't have cost me a dollar—if it had been for sale on a competitive basis I would have had all I needed

rather than having something which was not only no better but which was mixed with something that might even be harmful to me.

Now, if the drug companies were required to label the product with its true name to begin with—and the dentist prescribed by its true name—then explained to me, "Look, this is tetracycline, and here is what it does, and this is tetracycline with something else, and here is what it does," the probabilities are that I would have been using a drug more suitable to my problems, rather than just getting all those free samples.

Wouldn't you agree?

Dr. ADRIANI. That is right. You were getting a combination of two drugs, and probably all you needed was the tetracycline. There was no use in exposing you to two. These antibiotics all have hazardous effects. For instance, I have had a loss of hearing, a certain amount, from taking a drug called Kanamycin when I was real sick. Of course it probably did help; maybe it "pulled me through." But it is capable of injuring the nerves to the ear. There are several of these—the streptomycins that will produce deafness. We found out the hard way. We had to try it on some one to find out that they cause a loss of hearing.

All of these antibiotics have some adverse effect. For instance, erythromycin will produce yellow jaundice in some patients. Some of these injure the kidneys. There are a lot of things that we don't know about these drugs. And just dishing them out to people that really do not need them is not good. If you take these fixed combinations off the market, if you take Panalba away, the doctor can still use tetracycline and if he wants to add novobiocin it is still available.

A patient takes two capsules. In this way you give the man the dose of each drug he needs. There is no hardship in doing this. Instead, as in Panalba, the pharmaceutical manufacturer determines the dose instead of the physician.

Senator LONG. Thank you, Doctor.

Senator NELSON. Doctor, at the beginning of your statement you said you were not appearing here as a spokesman or as the chairman of the Council on Drugs for the AMA.

Dr. ADRIANI. No, I am not, I am appearing as an individual.

Senator NELSON. Do you wish to comment on this? Do you know whether the Council or the other members of the Council agree with your position respecting the labeling of drugs?

Dr. ADRIANI. Yes. The Council has gone on record recommending having drugs labeled when they are dispensed to patients, unless there is some medical reason why you don't want a patient to know what he is taking. I see very few instances where this might be the case.

The Council on Drugs also has for many years opposed the use of fixed ratio combinations, in other words, mixing two drugs together and selling them as is being done. We had a council meeting last Friday and Saturday in Chicago. The question of the NAS–NRC report about the fixed ratio combinations of antibiotics was discussed. This is the Council and not the department of drugs. We are advisory, I might point out, to the board of trustees. What position the AMA trustees will take about this I don't know. But I can tell you as chairman of the council that the council unanimously voted to uphold the NAS–NRC on fixed ratio on antibiotics.

They (the NAS–NRC) have 100 or so now that are open to question, and are deemed ineffective. Of course we (the council) have felt this way about all drugs. I feel this way. And I mentioned in my prepared statement a particular drug combination called Innovar which is a narcotic combined with a tranquilizer in a ratio of 50 to 1. How they arrived at this 50-to-1 ratio I don't know.

You have a simile in the statement. If you sell salt and pepper, you can mix both together, in a fixed ratio and all you need is one shaker. And this is the argument drug firms use. One capsule or pill. This is ridiculous, because some people like more salt and some more pepper. If you packed salt and pepper together and put it on the grocery shelf it wouldn't sell. Some might call it "piperosal" and say it is delicious, in a big ad. It might then appeal to somebody who might buy it. This is the essence of what you are doing when you mix two drugs together under a brand name.

When a practitioner in your father's time wrote a prescription, he would write down the ingredients in a certain ratio individualized for each patient. But he wrote the prescriptions.

When I took pharmacology we were also taught pharmacy, with it. We learned incompatibilities—which two drugs you could not mix together.

If one wanted to teach incompatibilities to medical students today how would one do it with this hodgepodge of names we have?

I have in my briefcase—and I showed it to you before the hearing—a list of fixed drug combinations used by the Federal agents in getting evidence for violations of the Drug Abuse Act. They are mostly barbiturates and amphetamines. I asked him for one when I testified in the State and Federal courts against a doctor who was selling amphetamines by the barrel to teenagers and truckdrivers. He said, "there are 4,000 individual items or combinations. How do you expect a revenue agent who does not know medicine to know 4,000 names?" He has to look at this list.

This business of using the real name for drugs also applies to mixtures. The label should indicate it is a mixture. One who looks at the label sees that it is a mixture. If he looks at what is now called Panalba he will say, this is tetracycline and novobiocin. Which one of these is better? Maybe I am sensitive to novobiocin? He may have had a reaction to it before. And he would know. But if he takes Panalba he would not know it if it were labeled with the trade name.

Senator NELSON. I understand, then, that the drug council supports the position of the National Research Council of the National Academy of Science.

Dr. ADRIANI. Oh, yes, unanimously. We made that recommendation and this will go to the board of the trustees.

Senator NELSON. But as of this date the board of trustees hasn't acted on it?

Dr. ADRIANI. I do not know when they will meet again or what they will do about it. But I asked specifically that it be published—we have the AMA News which goes to all physicians—in AMA News. We asked to put it in there so all doctors will know our position.

Senator LONG. That reminds me of the story I heard of a man that came back from South America and told about a dangerous drug he had come across down there.

This thing will kill you. It nearly killed me.

He was asked "What is the name of it?"

And he said "I don't know what it means in English, but in Spanish they call it 'lo mismo, "—which means "the same thing."

Now, that fellow didn't know just what it was he had been taking, but he knew that he took too much of it. A person can find that there are certain drugs that he knows are bad for him, they might be good for somebody else but they are bad for him. And many times if he is buying these things by the trade names he doesn't know it. Isn't that about the size of it?

Dr. ADRIANI. That is right.

Talking about mixtures, I have a bottle here—I was in Portland a month or so ago, and I had a headache, and I bought this bottle of APC's. Everybody knows what this mixture is. It is aspirin, phenacetin, and caffeine. I bought it at the Safeway Supermarket. And it cost 59 cents for a 100. It works just as well as some of the more expensive similar items that you see advertised on TV.

And it indicates what the ingredients are. It says, aspirin, phenacetin, and caffeine. The only objection I have to this label is that I would like to know if the aspirin and the phenacetin and caffeine are U.S.P. They might have been and they omitted it, or they might not. But here is a drug which costs about half as much as some identical brand name combinations that they advertise on TV.

And I say, Senator, that the Federal agencies are derelict in their duty too, in policing some of this advertising. The FDA can control advertising in medical journals but it does not control the advertising of these over-the-counter drugs—this is an over-the-counter drug.

I have an ad here for the committee.

Senator LONG. I would like to ask that that be included in the hearing record. It says, "Who needs a cold" on the top.[1]

Dr. ADRIANI. It says "Who needs a cold?" And it advertises nose drops which are sold over the counter. And this company, Winthrop, is a reliable company. And the brand name—the generic name is phenylephrine hydrochloride, and they have got Neosynephrine, which is a trade name. And it says down here "good for colds."

How do you know you have a cold? I had an uncle that thought he had a cold, and what he had was a coronary. And after about 3 days he died. He had a stuffy nose. And this would be the worst thing that you could give a man for a coronary. He could buy this over the counter. And it says in the directions here, "ask your druggist for Neosynephrine nasal spray or nose drops, he will recommend the proper strength of Neosynephrine for adults or children or infants." This was in McCall's magazine of March 1969.

I told Herb Ley about this, and asked, "Why don't you do something about this?"

He said, "We can't, this comes under the Federal Trade Commission—or one of these agencies. We have no jurisdiction."

You get all of this stuff on TV. You see someone take a tablet, it says, "Dissolves 10 times faster than another, and it is much more effective." And they have ways of appealing to the public. These should

[1] See Appendix III, p. 5256, infra.

be policed. Millions of dollars are spent on this sort of endeavor that the public throws away.

Senator NELSON. Do you know whether the law presently permits any agency of the Federal Government to require proof of efficacy for any over-the-counter drug?

Dr. ADRIANI. No, not that I know of. The only ones that are released on that are the ones that are considered to be harmless, but one is never sure about them.

For instance (referring to APC tablets) it says on here not to take more than six a day, and for not more than 10 days, because they recently found that they may produce damage to the kidney—they are not sure. So they are required to put that label on the package. The FDA requires that. But the FDA cannot stop them from putting this ad in McCall's. This is an over-the-counter drug. If they put that in the AMA Journal they could call up and say, "Hey, that ad does not meet the specification."

The FDA, incidentally, does a commendable job. The trouble is, that you fellows do not appropriate enough money for it, and they cannot get enough help. This is what they need.

Senator LONG. Doctor, it would be easy to raise the moneys for it. We are having real difficulty in raising enough money to provide for the proper inspection of drugs.

I am the chairman of a committee that handles the tax laws—we ought to put a tax on the drugs to cover the cost of inspecting them, to make sure that they are what they are supposed to be. We might make the companies pay for their own inspection.

Now, that brings up another point that concerns me. The big companies claim that they have much better quality control than the small ones, but they complain that FDA loads them down with as much needless inspection, and needless paperwork, as with their small competitors who don't have anything like the quality control that they have—they claim that, I don't know whether it is correct or not. And they will take you to their air-conditioned plant where they filter the air before it comes in, and things of that sort and try to make a great impression on you with the tremendous efforts they expend and the steps they take to assure quality control and they say we have competitors who are not doing these things.

Frankly, I haven't seen the competitors they constantly allude to. I would like to see some in order to ascertain the truth. But many of the large companies make strong assertions. The first thing you know they will start saying here is a guy that's manufacturing drugs in his garage—or worse. They will make as strong a statement as you will let them get away with as to where the fellow might have manufactured the drugs. What would be your reaction to the assertion these major companies (which have very fine plants, air conditioned with filtered air), that drugs sold at the Safeway might have been produced in somebody's garage? How would I know that it had not been produced in a garage, and what would the difference be?

Dr. ADRIANI. You do not. You will have to apply the same law to everyone, and license everyone that makes a drug. If you have a slaughterhouse it has to meet certain requirements. The meat has to be inspected and graded in a certain standard way, whether you are

a big or small establishment. The requirements have to be applied equally.

Senator LONG. You are simply saying if you do it for a slaughterhouse you ought to be able to do it for a drug manufacturer.

Dr. ADRIANI. That is right. You inspect food. This country probably is assured the highest quality of purity as far as foods are concerned. All the food is not always pure, but if poisoning occurs, someone from the Public Health or other service investigates.

We had a few days ago what appears to be an outbreak of an intestinal ailment resulting from food. We had help from the U.S. Public Health Service helping locate the source of contamination.

If pharmaceutical firms are making drugs in the garage, this is like making "hooch" in the backyard, as they used to do years ago. I think everyone who makes drugs should be licensed; every drug individually should be licensed.

There are certain areas in which pharmaceutical firms have done a lot of good. For instance, we used to make our own intravenous solutions at Charity to save money. The commercially prepared material is superior. They have good controls and labs for testing. They do it far better than a hospital can on its own.

I recommended that we get rid of our processing unit and we finally have done this. Pharmaceutical firms have made sizeable contributions in this area.

But if the argument is, that certain companies are being given privilege of not having a license, then I think they have a valid argument. Everyone should meet the same requirements.

Senator LONG. In other words, if I understand you correctly, you said that just in order to provide the drugs more cheaply for your hospital you used to manufacture some of the drugs at Charity, do I understand your statement correctly?

Dr. ADRIANI. No. We used to make solutions that you give by vein. In the old days the manufacturers did not make these and we had to make our own. Hospitals used to buy the whole outfit, the still to make the distilled water, etc. and all that. Then you have to test these solutions for pyrogen, a substance that causes fever. You do this in rabbits. These rabbits have to be trained. You have to have rectal thermometers, and other accessories. This takes skill and expertise. You go to Cutter or Baxter Laboratories you will find that they have real good quality control. I will buy manufactured solutions any time. They do a good job. But, again I say if you have a small firm or if you have a large the same standards should apply to each.

Senator LONG. If I understand what you said, even though you used to manufacture some of these things that you now purchase from manufacturers, when they got into it you were satisfied that they could do a better job, so you preferred to buy it from them?

Dr. ADRIANI. They do a better job in that particular line, yes.

Senator LONG. So when these people come to sell you the product, the Government ought to see to it that all the products they offer you meet the required specifications—the same as those you were required to meet when you were making them yourself. They shouldn't be permitted to put something on the market that doesn't meet these standards?

Dr. ADRIANI. That is right.

Senator LONG. I was told by a major manufacturer that they not only check the drugs they are making and the ingredients going into them to insure good quality control, but they keep samples of everything that is sent out, and they check for deterioration. Further, they know where every package of their product is, so that if they find one of those samples is deteriorating in any way to the extent they wouldn't recommend that it be prescribed, they can take every one of this particular batch off the druggist's shelves and get rid of it, because it is no longer of the quality they would recommend.

Now, if I understand what you are suggesting, you would say that all of them should be made to do that?

Dr. ADRIANI. Yes, everyone. If you are going to sell something—after all, these things can be poisonous they should all meet standards. Of all the things that a doctor can do for you—he can cure you with a medicine, or he can make you comfortable. He does one or both of two things. He does these things with drugs.

Senator LONG. He can cure you, but he can also kill you.

Dr. ADRIANI. There were certain diseases that we cured surgically like doing a thyroid operation. We don't see those done as often. We give medicines that reduce the number requiring surgery.

The concepts of medical practice have been vastly changed by drugs. So drugs are very important and they should not be regarded lightly. And here we are, a society that can put a man into space and go around the moon, and send back a message of good will on Christmas eve, and we cannot standardize the names of one of the most vital commodities that the public uses to remain healthy. There is nothing more vital to a nation than its health.

Senator LONG. When I was practicing law a standard joke among lawyers, when they discussed the difference between the legal profession and the medical profession, was that the doctor can bury his mistakes. That is something a lawyer can't do, it is on the record when we make a mistake, and we have to pay for it.

But the potential of drugs both to help or hurt—many times isn't it true that a doctor has to make a decision, for example, where a person is suffering from more than one malady, which requires that the doctor give him something to help one aspect of his illness, which, in turn, may hurt him in another. The physician has to decide which of the patient's maladies takes priority, so that he decides to treat the one that is the greatest hazard to his health at any given moment.

Dr. ADRIANI. That is right, you have to choose which is the lesser of the two evils. I allude to that in my statement, I say that one of the things that is really being studied now quite intensively, that is of interest to all of us is drug interactions—how does the presence of one drug in the body influence the action of another.

We know that this happens frequently. And there are many recorded instances. As a matter of fact, Colonel Moser, at Walter Reed, has written a book on this particular subject. He was able to collect enough information on drug interactions to write a big, thick book, "The Diseases of Medical Progress," diseases induced by drugs. If one tried to write a factual book on generic equivalence—one could not write a pamphlet the size of my prepared statement.

Mr. GORDON. You testified that eliminating brand names would improve medical practice.

Dr. ADRIANI. It certainly would. It would improve medical practice, it would facilitate the dissemination of drug information, and it would facilitate the teaching of pharmacology, and it would increase the safety as far as the public is concerned.

Senator LONG. Could I ask one more thing that is very important that I have been troubled about in dealing with this subject.

You mentioned Neosynephrine. I thought that was a complicated enough name. But you tell me that Neosynephrine is a trade name. Would you mind telling the generic name for Neosynephrine?

Dr. ADRIANI. The generic is phenylephrine hydrochloride. Phenylephrine is not too hard to pronounce. This is one problem that you will probably encounter.

Senator LONG. Here is a thought that occurs to me. I can understand how in trying to develop a product that you could come up with some sort of compound which might result in a word 20 syllables long that would be almost impossible to pronounce. Why can't we work it out so that once the FDA determines that a drug is safe and effective—why can't we then give it a name that could be pronounced more readily?

Dr. ADRIANI. I agree with you. I make a comment in my prepared statement about the naming of drugs. Do you know how it is done now? It is done by the USAN Committee. The AMA has a representative from the Council on Drugs who works together with a man that is a chemist, a full-time employee of the AMA. Then the U.S. Pharmacopeia has one; the National Formulary has one; the FDA has one; and one is selected at large.

You see these agencies are working together. This is what we need. More cooperation instead of fighting each other. All including the drug industry ought to work together. We need the drug industry, you can't abolish the industry. We need the AMA. It is the largest medical association in the world. They have done a lot for world medicine as I point out in my statement. The USAN get together and pick names of new drugs. I advocate putting the chemical names in fine print on the back or side of the label. What the USAN tries to do when they pick names is to imply the chemical nature of the drug in the name.

Well, most doctors do not know chemistry. I teach pharmacology. When I put chemical formulae of a drug on the board, the students shudder. Doctors do not like chemistry. They do not have to know the formula of a drug to prescribe or use it. I would rather know what it does than the formula. If you put the chemical name on the label these fellows on the USAN will try to simplify the names. Some of them, as you point out, are jawbreakers, and they will have to be simplified. And this is one of the reasons why brand names have taken such a hold. Doctors use brand names because they are simple and a lot easier to pronounce and spell. They find using the brand names easier than putting down generic names.

We need simplification, but that will come only with time. You cannot do it over night. But you can overnight require—and I think it is the first big job that the Government has to do is to standardize the names of drugs and get rid of all the aliases, and make it a law that they put the real name in big print. They can then put the brand

name below it in fine print down so that the fellows who are living today and who will die off tomorow can use brand name if they must. When they are gone, the trade name will be forgotten. And doctors will be free to prescribe the way that they want to even with this change.

The minute you start telling a doctor that you cannot do this or that, he is going to "holler." You know that. One thing doctors resent very much is somebody trying to tell them to do something, particularly when that person is not a doctor. That is a peculiarity of the members of the medical profession.

Senator LONG. Doctor, one thing does bother me about all this is that some one is putting out an awful lot of misleading, confusing information.

Now, my daughter married a young man whose father is a doctor. And he is a few years older than I. You perhaps knew him—Charles Moseley. It was difficult enough for me to find time to educate the Senate about something like this, much less to educate my cofather about the matter.

The good Lord called him home recently without us getting together on the matter. Every time I turned around he had the idea that I was doing something to destroy the practice of medicine—that Congress was trying to tell the doctors what they should prescribe. I think if the three of us could have sat down and discussed the problem we wouldn't have any difficulty with Charles Moseley. Did you know him?

Dr. ADRIANI. Yes.

Senator LONG. He was a highly regarded general practitioner in Baton Rouge, La.

Why must someone insist on putting out all this information to the effect that some of us in Congress are trying to tell doctors how to prescribe—when in truth all we are trying to do is to see to it that the patient, the doctor, and the pharmacist can easily identify the very medicines they must rely upon. We are making every effort to see to it that the public is not defrauded or denied the kind of treatment it deserves when illness occurs.

Dr. ADRIANI. I make it pretty clear in my prepared statement, Senator, that when requiring labeling you give the doctor the option of requesting not to label if he feels it should not be on the prescription. Also, the labeling on the container should have the brand name in very fine print to deemphasize the brand name. Some doctors are used to, or know only, the trade name and you do not want to create confusion. You do not want to interfere with a doctor's prerogative of practicing medicine the way he sees fit.

Senator LONG. Recently I walked into a drugstore and asked for a bottle of Maalox. They had Maalox No. 1 and Maalox No. 2. Not having a doctor there to advise me I asked the lady behind the counter, "What is the difference between Maalox No. 1 and Maalox No. 2?"

She replied, "One tablet has just twice as much Maalox in it as the other, that is the difference."

I asked, "Isn't that a big price to pay for it?"

She said, "You are a fool to pay it, there is the same thing there for half the price."

I said, "How do you know?"

And she said, "Read what is says on the label."

I did and the list of ingredients on the two products read the same—one selling for half the price of the other.

Dr. ADRIANI. Most of them are mixtures of milk of magnesia aluminum oxides or calcium carbonate. You can write them down "dirt," because that is where they get them, out of the ground.

It is really a mixture of clean dirt. That is what they really are. Limestone, calcium carbonate, they get them out of the ground.

Senator LONG. You say it is limestone?

Dr. ADRIANI. Yes.

Senator LONG. The same thing you make cement out of?

Dr. ADRIANI. Yes. You can take it and pulverize it, and if you have a "sour stomach" or too much to eat or drink, it will neutralize the acid in your stomach just like Maalox No. 2.

Senator LONG. If companies were required to put on the bottle the generic name in letters equally as big as the trade name, then the person could look at the two and decide whether he wanted to buy twice as much, because somebody puts the name Maalox on it, or whether he would buy the other product at half the price.

Offhand, do you know what company manufactures Maalox?

Dr. ADRIANI. Rorer, I believe.

Senator LONG. But as a practical matter can you give me any assurance that their Maalox is any better than the same product made by some other company?

Dr. ADRIANI. No. But they sure sell a lot of it in Louisiana.

Senator LONG. By pushing that trade name?

Dr. ADRIANI. By pushing the trade name. At Charity they get the doctors to use the drug. They give them whole lots of samples. The doctors get to using it and then continue to prescribe Maalox. Instead of Maalox you label it "mixture of" and name the ingredients. You could go to a drugstore—and many of them are like supermarkets—and you could walk through and say, here is so and so's mixture and it has the same ingredients and is 10 cents cheaper than another firm's mixture. You could shop. I saw an editorial written in a medical journal, which said, if you let the patient know what he is getting he will shop around. The editorial said this would be objectionable.

Why shouldn't they shop? My wife shops. She goes from one store to another to buy groceries and meat. Why should I not go around and shop? And if I see that this has aspirin phenacitin and caffeine all ingredients USP for 59 cents, why should I pay a dollar and a quarter for Excedrine or whatever brand they advertise on TV?

And again I would like to say you had better clean up that TV and newspaper advertising. The FDA cannot do it. It is beyond their jurisdiction. They can "police" the medical advertising, but they cannot do anything about the advertising on over-the-counter drugs, and all this malarkey about Geritol and "tired blood."

Senator LONG. Doctor, when I see a TV program and see that it is being paid for by American Telephone and Telegraph Co. I am pleased to see that because, I know that that is part of my telephone bill, and when I pay my telephone bill I am paying for that program.

I know that it is not hurting me. It is not doing me any harm at all. It is a disgrace to let the television media be used to misinform the

public, especially with respect to over-the-counter drugs or cigarettes.

For example, here is a beautiful girl standing out in driven snow puffing on a cigarette suggesting that the smoke going into her lungs is just as clear as the air on top of the driven snow. And here is Miss Lung Cancer. Every time she talks about how she loves her cigarette, "me and my Winstons," and that sort of thing, it suggests that you are going to be more attractive or beautiful, or that the girl might give you a date if you will smoke that cigarette. To suggest that it will make you sexier, more desirable, and more attractive, if you smoke this one product or another is, to me a disgrace to America. If we will permit the Federal Communications Commission to do what their conscience requires, they will put a stop to this type of advertising.

These ads on aspirin also are getting pretty ridiculous. For example, they say—this particular product has twice as much pain killer as aspirin—what does this mean, really?

Dr. ADRIANI. It doesn't mean anything to anybody, it is just a meaningless term. You cannot measure pain.

Senator LONG. It says it has twice as much pain killer—I would like to find out how they justify that kind of thing. I think you will find that that same company manufacturers two aspirin tablets, one, two and a half grains, and the other five grains. When they say this one has twice as much pain killer as ordinary aspirin, do they mean the big capsule?

I think that is what they mean.

And then they say that this gets into your bloodstream more quickly. Would you mind explaining that? How does one kind of aspirin get into your bloodstream quicker?

Dr. ADRIANI. It depends on whether you take that aspirin before or after you eat. How fast it gets into your blood stream depends upon the state of your stomach, how much acid is in it, how much fluid, how much food—no one knows how fast it gets in there. Both you and I could take the same aspirin tablets, and maybe my blood level will go up quicker than yours, even though we both have empty stomachs. No two people are alike.

Senator LONG. Is Anacin an APC tablet?

Dr. ADRIANI. That is right.

Senator LONG. If you were to decide whether to give a patient an aspirin tablet or an APC, what would be the factors upon which you would make your decision?

Dr. ADRIANI. Some people cannot tolerate aspirin, it bothers their stomach. And this does not. Otherwise I would give him the aspirin, because there is some question about the phenacetin producing injury to the kidney. We know aspirin does not. The best thing you have for people with arthritis is aspirin.

And getting back to aspirin, you see it advertised as St. Joseph's Aspirin or Bayer's Aspirin. This is perfectly all right, because both firms are selling aspirin, and one is saying that ours is better than another's. You believe it, just like you believe Campbells soup tastes better than Heinz's. If you want to believe that, that is fine.

Senator LONG. But aspirin is aspirin and APC has phenacetin and caffeine in it?

Dr. ADRIANI. It has phenacetin, a drug that is supposed to produce injury to the kidney. This is a pain relieving drug too. It is a coal tar drug.

Senator LONG. It is a pain relieving drug, but it puts a burden on the kidneys?

Dr. ADRIANI. So they think. There has been a lot of dispute about it. Over a long term usage it might injure the kidney.

Senator LONG. Does it have caffeine in it?

Dr. ADRIANI. It has caffeine in it. This tablet has a half a grain.

Senator LONG. You say that particular capsule has a half a grain?

Dr. ADRIANI. Yes.

Senator LONG. Is that a special APC capsule?

Dr. ADRIANI. No, this is pretty standard formula. It is two and a half grains of aspirin, two and a half grains of phenacetin, and half a grain of caffeine.

Senator LONG. My impression is that the caffeine tends to keep you awake, doesn't it?

Dr. ADRIANI. It tends to stimulate you with the idea that maybe the aspirin and the phenacetin tends to make you drowsy. I have never been convinced that there is any evidence to the effect that these drugs do so. I think if you leave the caffeine out that it would not make any difference.

Senator LONG. Assuming that it stimulates you, if you are getting ready to go to bed at night it would be better to take aspirin than APC?

Dr. ADRIANI. If you are one of those people, people who cannot tolerate caffeine because it keeps them awake. You take two of these and you get a grain of caffeine which would be about what you would find in about three-quarters of a cup of coffee.

Senator LONG. About three-quarters of a cup of coffee?

Dr. ADRIANI. I would say that. I do not remember exactly the caffeine content, but that would vary with the brand of coffee.

Senator LONG. So that is equivalent to about two-thirds of a cup of coffee?

Dr. ADRIANI. Yes.

Senator LONG. If you take a couple of these, then you have got two-thirds of a cup of coffee?

Dr. ADRIANI. You get a stimulant effect from it.

Senator LONG. It might keep you awake?

Dr. ADRIANI. There are people that are kept awake. I think a lot of it is in the mind. Some people can go right to sleep after taking coffee.

Senator LONG. Then it might be good to have both, if you get up in the morning it might be well to take an APC, because if you have a cold a little stimulation might tend——

Dr. ADRIANI. Someone that cannot tolerate coffee, would see this on the label, and would say, "I am not taking that, it has got caffeine in it." I know someone at Charity that cannot take this because the caffeine bothers him. He takes aspirin and something else. I have forgotten what the combination is. I emphasize in my statement, that what we want—what the public and the medical profession should have is full disclosure, all the information you can give. You cannot give too much information.

Senator LONG. Here is one other thing that major drug companies just love to use as part of their standard selling pitch, and that is if you buy from a small manufacturer, that these small manufacturers have been known to compress their ingredients into tablets so hard that they go right through the body without ever dissolving at all. Do you have information on this subject? How can we know when we are buying an aspirin or some other tablet whether it is going to dissolve in the body?

Dr. ADRIANI. I have seen tablets of inferior grade drugs go through a patient and not be absorbed. But if you license every pharmaceutical firm, and every drug, you will obviate this. And I also advocate in this statement, that if a drug is made by another firm, the packaging firm should label from whom they bought it. Some big manufacturers buy drugs from someone else and then put a brand name on it, and say "we make our own." They may import it from Europe. If you require them to indicate where the drug was made, and who made it, then the patients will know it was repackaged and they gave it a fancy name. Let's take an example and—this is just an example—Equanil. They could import the drug in bulk from some place and give it the name Equanil. If you made them say it was manufactured by such and such a firm or manufactured by the laboratory that dispenses it—Wyeth, I guess—then you will know that that company made it. But you do not know they tell you, "we have factories," when actually they do not have and they may be buying the stuff in other parts of the world.

Senator LONG. So if you make it mandatory that the actual manufacturer be identified, then the person buying the product is much better informed than when he merely knows who put the drug inside the bottle?

Dr. ADRIANI. Yes. For instance, the aspirin in this tablet is USP. If they have in parentheses what company made it, this would tell me where it came from, from Germany or Russia or Czechoslovakia or elsewhere.

I know a doctor that was giving his mother Cortisone for an allergy. She shopped around, and found a product that was being shipped in from Mexico that cost less. She broke out in a rash. This was supposed to relieve her allergy.

He finally said, "what are you taking?"

She said, "I bought this cheaper drug." It was an impure drug imported into the country and she did not know it because the label did not indicate the source.

I am not saying that there isn't such a thing as cheaper drugs at all. But some of these firms that say that I am holier than thou, are not as holy as they tell you. If you make them indicate where and by whom the drug was made, then they could say, I am holier than thou if this be the case.

Senator LONG. Like APC from Russia with love, I would be careful about taking that one, if it is all the same I might prefer to try something else. I wouldn't want to reflect on those people particularly. But people would like to know.

Dr. ADRIANI. I generally feel that people should know.

Senator LONG. I don't know of anybody that would argue much against that.

Dr. ADRIANI. Why not? After all you go to a doctor for information. If a man has cancer should you or should you not tell him? Sometimes you talk it over with the family and they say, we would rather you not tell him. But you have to inform the patient of all the facts.

Senator LONG. So you think that if some company stamps a tablet together so hard the tablet won't dissolve in the body, the FDA ought to be checking on such situations?

Dr. ADRIANI. That is right. And if they indicate it meets U.S.P. standards and they compress the tablets so that they are too hard the FDA can say, you are not meeting U.S.P. standards and the FDA can hold them for misbranding.

Mr. DUFFY. Doctor, if I could return to a statement that you made a while back about NAS-NRC studies, you said the Council endorses these studies.

Dr. ADRIANI. Yes, sir.

Mr. DUFFY. Did they have access to these studies at some point?

Dr. ADRIANI. No. Those are in our minutes and they go to the board of trustees. We have requested that our statement be put in AMA News. This is generally available, the AMA News. I gave Mr. Gordon a copy of the Medical AMA News. It had something in there about the article that didn't get published, NAS–NRC study and the editor's statement as to why it didn't get published. So if the council's action is published in there, it would be available. Otherwise, the Council minutes go to the board of trustees. And from then on I don't know exactly what happens. They are filed away, I guess.

Mr. DUFFY. Are you saying, then, that the Council did not have access to any of these minutes?

Dr. ADRIANI. We have access to the minutes, but they are confidential.

Mr. DUFFY. So that you did have an opportunity to read them and review them?

Dr. ADRIANI. No, we don't disseminate them, they are confidential material.

Mr. DUFFY. We are trying to determine, Doctor, on what basis your council endorsed these studies. Did they have adequate access to the studies in order to form their opinion.

Dr. ADRIANI. They go to the basis of long standing policy in the AMA that fixed ratio combinations of drugs are irrational. This applies also to antibiotics. They are not an exception. There are one or two exceptions. "The pill," for instance, has been shown to be necessary in combinations—but there are very few. You can make a generalization about fixed ratio combinations of all drugs. This has been the practice, that we do not recommend fixed ratio combinations.

Mr. DUFFY. In other words, in endorsing the NAS-NRC study, the Council merely reiterated a prior position?

Dr. ADRIANI. Yes, we reiterate a prior position. But we also know that the National Academy of Sciences and the National Research Council are composed of people that are well known or have a status in scientific circles. I served on one of the subcommittees of the National Research Council, a subcommittee on surgery, for nearly 12 years. I think a term is 6, but somehow or other I just went on until finally Dr. Cannon said, "we hate to retire an old work horse, but it is now time."

The recommendations that we make are based on data. I have personally read these studies, and the argument they gave, and the references, and so on. And I have had access to them. Other council members may have not. But most of them are more informed than I am. And they are familiar with them. A mixture is not good. You are exposing a patient to something that he may not need. These are not innocuous drugs by any means (the antibiotics).

Mr. DUFFY. I think we understand the arguments, Doctor. I am just trying to understand the foundation for the statement.

May I ask you just one other question. I think your statement was that you were aware of the documentary evidence and material that was used in arriving at this conclusion. In your opinion does your council's endorsement of this material give it any greater weight?

Dr. ADRIANI. I don't quite understand you.

Mr. DUFFY. Does the fact that your council may have read this material briefly, and agreed with it, make it any more valid than the actual research?

Dr. ADRIANI. You mean if we had access to the material to study it? I do not believe it really would. I think they would come to the same conclusion that I have come to in reviewing these. We are reiterating the general premise is that all of the fixed combinations are irrational. Even something like this (referring to bottle of APC's) is not rational—there are some combinations that are here and have been here for a long time. You could leave out phenacetin. And a lot of people are just given that without the aspirin. This is a combination that somehow got into general use. And once something has gotten into general use it is hard to stop it. And it has just gone right on. The combination has been with us a long time.

If you look at the National Formulary they have one that is called Alkaline mouthwash. It is just as good as the mouthwashes you buy for a dollar and a quarter. The council reiterated its previous statement, the standard they have had, that the AMA does not review or include in its monographs of new drugs, in its reference books any combinations of drugs. And they further go on the premise that mixing antibiotics is a hazardous thing, because these drugs are more dangerous in many ways than other drug combinations.

Mr. DUFFY. Thank you, Doctor.

Senator NELSON. Just to pursue that for a moment, do any of the members of your Drug Council serve on any of the five antibiotic panels?

Dr. ADRIANI. The membership of those panels is secret, with the exception of the chairman. And I don't know whether they do or not. They have not revealed their identity.

Senator NELSON. They will be published?

Dr. ADRIANI. They will be published? We probably will find some council members on there. I am pretty sure that some council members have served because you will find that members of the council serve other committees they have been on the USP and N.F. and other groups. As a matter of fact, I was on the USP long before I got on the council on drugs.

Senator NELSON. To put this in proper perspective, isn't this the situation. The drug council came to the conclusion many years ago that fixed ratio combinations were not efficacious, and that it was irrational to prescribe them, is that right?

Dr. ADRIANI. That is right.

Senator NELSON. And then based upon the amendment, the Kefauver-Harris amendment which required the FDA to review the drugs for efficacy, the National Research Council of the National Academy of Sciences came to the same conclusion that the drug council of the AMA had come to many years ago, and in effect endorsed the same position that the drug council has taken for years, is that right?

Dr. ADRIANI. That is right. That has been the position. I make this point in my statement even with some of the new drugs when I mention that the fixed combination of the narcotic and the tranquilizers, Innovar, that has just come on the market, INA 50 to 1. How did they arrive at the 50 to 1 ratio? I was telling Senator Nelson this morning that when this drug combination was a number we evaluated it at Charity Hospital. I was reluctant to evaluate it, because I wanted to have each individual drug available and give the patient the proportion that he needs. Some may need more narcotic and some more tranquilizers. And they finally provided each drug individually. They gave us the material to investigate. I was not impressed by this material, because the patient got rigidity of the muscles. Then they submitted a new drug application (NDA) and finally got it approved, and it come on the market. After it came on the market they started to promote it. My own staff thought I was old fashioned, because I refused to use it. They said, "the old man is obstructing progress. Here is a new drug, and everybody says it is good." They got their information from the detail man. But the old man had seen the product when it was a number and knew all about it.

Senator NELSON. It is correct, is it not, that Dr. Dowling preceded you as chairman of the drug council of the AMA some years ago? [1]

Dr. ADRIANI. Yes. Dr. Harry Dowling was chairman when I came on the council. He served 3 years—you cannot serve as chairman for more than 3 years. Incidentally, every one on the council is reappointed once a year, so you are never sure if you are going to get back on.

After that, Dr. Simeone was elected chairman, he had 1 year more to serve. He is a surgeon, and he is now up in Rhode Island. He is a very fine doctor, and very knowledgeable. He served a year as chairman.

Then Dr. Sol Sherry took it over. He found the duty too heavy, and he resigned.

I became acting chairman and then chairman and I have been chairman the last year and this year.

Senator NELSON. Do you recall that Dr. Dowling wrote a very distinguished paper on fixed combinations in 1957?

Dr. ADRIANI. Yes. I do not remember the exact reference, but I think that was the year. It was an editorial or a paper on the subject of fixed combinations.

Senator NELSON. I have here an editorial which I want to include as an appendix to this record run in the AMA's Archives of Internal Medicine in April of 1957. I will quote excerpts from it and ask that the editorial be printed in full. The authors, all distinguished doctors

[1] See statement of Dr. Dowling, Appendix VII, pp. 5269–5272.

of medicine, Dr. Harry F. Dowling, Dr. Maxwell Finland, Dr. Morton Hamburger, Dr. Ernest Jawetz, Dr. Vernon Knight, Dr. Mark Lepper, Dr. Gordon Meiklejohn, Dr. Lowell Rantz, Dr. Paul Rhoads signed the editorial, which was printed in the Archives of 1957.[1] And in that editorial, in the Archives of Internal Medicine of AMA they state "there can be no question that the trend toward promotion of combination preparations of this type is a dangerous one."

Then further on in the editorial they state:

> There are no data of experience which would justify the employment of any fixed combination of two antibiotics in a single ampule or a single tablet or a capsule for systemic use. It is our firm conviction that the promotion and sale of such combinations should be discouraged until and unless arequate data from controlled clinical investigation justify this practice, and then only with respect to definite combinations for specific purposes.

That was in 1957. In your judgment, would that editorial still stand as an accurate description of fixed combinations?

Dr. ADRIANI. Absolutely.

Senator NELSON. I have to go to an executive committee meeting of the Labor and Public Welfare Committee for about 10 minutes on a vote. I am sure Senator Russell Long will have some questions, and perhaps committee counsel, as well.

I have something I want to pursue on this question of fixed combinations and advertising of fixed combination in the journal.

I might ask this question before I go. In view of the position of the drug council and the editorial in the AMA Journal for 1957, and then in view of the appearance before the Kefauver committee in which the council again criticized the use of fixed combinations, and the fact that the AMA witness testified that the AMA Journal expected to phase out any advertising of fixed combinations in some relatively brief period of time, and in view of the position of the National Research Council recommending that all fixed combinations be taken off the market on the grounds of either inefficacy or a health hazard, how can the AMA justify running ads that promote fixed combinations in the journal at the same time its physicians, all the scientific community in this country as well as the council agree that these drugs are inefficacious and in many respects expose the patient to a health hazard since simultaneously he is being exposed to a drug that he doesn't need.

Dr. ADRIANI. I do not think the AMA can justify it. The procedure for preparing the journal is for certain people to take care of certain aspects. The advertising is handled by a different department. None of the advertising is in any way supervised by the Council on Drugs. I do not want to go into details because I do not want to speak for the council on that point. But there are various persons in medical circles and on the council who are unhappy about the advertising.

Now, the American Medical Association derives a good part of its income from advertising. I might point out that the American Medical Association has actually put world medicine where it is through its efforts, and largely through its Council on Medical Education.

Many years ago medical schools in this country were "diploma mills." I remember them as a boy. The AMA "cleaned house." The medical

[1] See Appendix I, pp. 5251–5252, infra.

schools were rated A, B, and C. When I started medical school there were two or three grade C schools. They went out of business, and the grade B schools became grade A. Now all the schools are grade A.

These schools are inspected by the American Medical Association. They have faculties of men from other schools to form committees to inspect them.

This applies to internships and residencies and all training programs, they are inspected by the American Medical Association. This is a costly venture, you know. You gather a group of people, fly them to a particular city, and put them in a hotel, and pay for all the paperwork that is required. In addition, the AMA publishes the journal and carries on other business and correspondence, et cetera. From being on the residency review committee for anesthesiology I know the Council on Medical Education has field inspectors that go around every 2 years inspecting intern and residency programs. So this income is very essential to the association. It boils down to this, I would say, that the AMA needs every dollar it can get, to remain in the black.

Senator NELSON. I raised this question before with the editor of the New England Journal of Medicine, Dr. Ingelfinger, and Dr. Annis, and others. It still seems to me to raise a puzzling credibility issue when one of the most distinguished medical associations in the country, maybe in the world, maintains that not only are the antibiotic combinations inefficacious but that there is also a health hazard in prescribing them. Yet, they are, at the same time, willing to accept ads that promote them. As a matter of fact the advertising and promotion is more successful in persuading doctors to use them than the text material in the JAMA or the other journals in dissuading them. Doesn't that seem to you to raise a kind of a credibility question? Isn't there a great distinction given to an ad advertised in the journal? Isn't that a kind of an imprimateur of the approval in effect to the physician who sees the ad?

Dr. ADRIANI. Well, the only answer that one could give to a question like that is that the position taken in doing this is indefensible. One cannot defend it. All I can say is that if you have the scientific members of your association writing and saying that fixed combinations of drugs are bad, and you have the management particularly the lay people accepting advertising, and there is no consultation between the scientific groups in the association and those who pass on advertising and what they are publishing scientifically for their physicians is in conflict with what is in the advertising—this is indefensible.

I could not defend this for the American Medical Association. I am however not speaking for them. But you are perfectly right. This is ironical. The association needs money. I have always contended that they use the income from advertising for a good purpose. That money is well spent.

I have always felt that there ought to be another source of funds for this particular thing. It is an important function. It is important to the public. It is important to the students who go to medical school, and those who enroll in teaching programs, and in internships and in residencies. It is paid for by dues of most of us who are members.

The dues are rather high. The bulk of the cost is made up by dues. I do not know what the sources of all the income of the AMA are, but

I know that if they tried to raise the dues that there would be quite a "howl."

The American Medical Association solicits money from doctors to donate to medical schools. They donated a check last week from the Louisiana State Medical Society. It was a small amount. It was insignificant. I do not feel that we as physicians should finance this type of endeavor out of our own pockets. Lawyers do not "chip in" to build courthouses. And lawyers do not chip in to go around and inspect law schools and give bar exams and all of that. But doctors do.

Senator NELSON. I agree with you, I think that the function of inspecting medical schools and hospitals to see that they meet appropriate standards should be paid for out of public funds, and performed by the qualified people.

Dr. ADRIANI. Our council is writing a drug reference book. The budget for the drug department last year was close to a million dollars. This drug reference book should be given away to each doctor but we are not going to be able to give it away, because it is going to be expensive to produce. And yet we hope to have a compend on drugs that a doctor can refer to quickly. And incidentally, speaking about combinations, we list the combinations and what is in them. But we have put down "not recommended" on all the combinations in the part of the book that is finished to date.

Senator NELSON. I have raised this question before. But it seems to me the acceptance of an ad which is contrary to the scientific evidence and known position of the Drug Council compromises them in a way that they really ought not to be. And I raise the question about this close relationship between the manufacturers of drugs and the medical societies through the advertising they take. It seems to me that in subtle ways it takes away from medical societies the responsibility they have for being tough critics of bad medical practice when they are in effect endorsing in a magazine the drugs that they know shouldn't be used. I don't know whether you want to comment on that or not.

Dr. ADRIANI. I was on the editorial board of our specialty journal, Anesthesiology, for 9 years. The advertising was policed by one of the members of the editorial committee. There was a period when something happened. I think right after the Kefauver-Harris amendments went into effect, when the advertising fell off substantially in all journals, including ours. We as editors did not care. But our board of directors did. They were concerned that the income was falling off. And I said, "well, you will have to get it from some other source." And that was the attitude I took about that journal.

There is no question about the fact that an advertiser can cancel out an ad. If they are the ones that are providing your income—if I am paying you a salary, I have control over you. I hold the aces and you hold the deuces. In this particular case if a pharmaceutical firm does not like what someone does, and they have an ad, they can say, we will cancel the ad. And this means a loss of income. I feel personally that this is a bad position to be in. I would get out of such a position in some way. This is my own personal reaction. I do not approve of being in that position at all. I do not like to have someone with a knife poised in my back saying, "if you do not do such and such a thing we will stab you." I like to have the aces in my hand.

Senator NELSON. Just pursuing for a moment the close association between the medical societies and the industry, were you aware that the AMA is an associate member of the Pharmaceutical Manufacturers Association?

Dr. ADRIANI. No, I just heard that. It came as a surprise to me. I did not know they were a member of that organization.

Senator LONG. How do you get to be a member?

Senator NELSON. Associate member.

Dr. ADRIANI. I did not know that. I do not know why they should be an associate member.

Senator NELSON. Do you think that is generally known among the Drug Council members?

Dr. ADRIANI. Among the council? No. Unless this testimony becomes public—they will know it then. But I would wager to say that none of them know it. I am hazarding a guess though. Because it came as a surprise to me I imagine that if you took a poll among the members of the whole association that they would be surprised to hear this sort of thing too.

Senator NELSON. You have covered your statement in general.

Do you want to present that part of your statement that you haven't covered as of now?

Dr. ADRIANI. I think I had gotten to the labeling on the over-the-counter drugs. I think they should get no preferential treatment as far as full disclosure is concerned.

I think that if you make mandatory generic naming of all drugs, that this would reduce the total number of compounds available, and it would not hurt the public one bit. I think it would help the pharmacist. They would not have to stock as many items. They would not have to have five different combinations when maybe one combination would be the one that sells.

The matter of generic equivalency, I think, is something that I would come right out now and say is a lot of nonsense. Who really knows anything about it? And if it turns out that there is such a thing as generic equivalency, I think that the U.S. Pharmacopeia which is a pretty solid organization will give it due consideration. They have done a commendable job, and they will change the standards as required when facts become available. So will the National Formulary. These two groups can be leaned on. It is hard to test it, actually. When they talk about generic equivalency, they mention blood levels. You can give a patient who has asthma an antihistamine and it will do no good because even though it circulates in the blood it is not getting into the cells where the trouble is. So a blood level does not necessarily indicate how effective a drug is. In testing you measure the blood level in a normal individual, and it is not going to tell you anything about what the drug does to a sick person.

The proof of the pudding is in the eating. Of course if you really want to do it, the right way would be to infect some one with a disease and give the drug to see if it works. We cannot do that kind of experimentation obviously. Animal studies cannot be transferred to individuals. So generic equivalency is one of these nebulous things. A lot has been said about it, but there is very little concrete evidence that is useful at this time. If it should turn out that there is indeed a

difference beween one product and another, and if a licensing law is in effect for each drug, and every manufacturer is compelled to abide by the same standards, and label the product U.S.P. or N.F. with the generic name, you will have taken care of the question of generic equivalency.

This is something for the future, which should not stop progress in generic naming. Naming the drug generically should not be confused with the ongoing debate of so-called therapeutic equivalency.

Senator NELSON. In your extensive experience with drug and drug testing and clinical treatment of patients, have you ever run across a case in the literature of controlled studies which show that drugs that meet U.S.P. or N.F. standards were not equivalent therapeutically?

Dr. ADRIANI. Let me give you an example of an experience that I had about 15 years ago.

We inject a local anesthetic into the spinal canal to produce spinal anesthesia. I think everyone knows what spinal anesthesia is. One of the most widely used drugs for spinal anesthesia is pontocaine made by Winthrop, a good drug. The patent expired on this drug. It became available generically. The generic name is tetracaine hydrochloride.

So a salesman from another firm approached me and said, "look, the State of Louisiana is paying 33 cents per ampule for pontocaine. How would you like to have it for 15 cents?"

Senator LONG. Would you mind repeating the price?

Dr. ADRIANI. He said "you are paying 33 cents for an ampule of Pontocaine. Now, it has gone off the patent. It is available as tetracaine U.S.P."

And I said, "We will buy it if you will sell it to the hospital for 15 cents an ampule."

And so I instructed our Charity pharmacist "the next time you put pontocaine out on a bid specify tetracaine U.S.P."

So he did. And we stocked it. This preparation came in a solution, 2cc solution per ampule. The Winthrop preparation was a powder.

Well, the resident doctors I had with me at that time said the stuff does not work. I laughed, because I had used the same material when I was at Bellvue many years ago. Winthrop dispensed in solution form at that time. And so as they used it the complaints and failures disappeared. About two and a half years passed. The residents had finished their training and we had a new group. The Winthrop man came around and said, "I know that you like the powder. Would you be willing to pay 16 cents an ampule for it?" I said "Yes; I will write a letter specifying why I want the powder." I wrote and we shifted to the powder at the 16 cents per ampule.

The new residents familiar with the solution and not the powder said, "that darned powder is no good." I laughed. Now we have both, and at the same price. Each works equally as well. The price was halved.

So you see what competition does. Tetracaine in U.S.P. works just as well as pontocaine-Winthrop; and I could spend a day talking about similar instances.

Senator NELSON. So you have not in your experience run across proven cases where two drugs meeting U.S.P. or N.F. standards were not equivalent?

Dr. ADRIANI. That is right, I have not. I would like to have a demonstration from anyone who has bona fide evidence. They can make fancy curves plotted on logarithmic paper, but they mean little or nothing. The proof of the pudding is in the eating. The question is when you give a patient a drug, does it make him well? How does he respond?

Senator LONG. Have you been in charge of buying drugs for New Orleans Charity while Dr. Bernhardt was in charge of Charity?

Dr. ADRIANI. I have not been in charge of buying. I stay away from finances.

But ordering drugs, yes. There are certain drugs that I want. If I think a particular commodity is better than another I requisition it. Sometimes the lowest price is not necessarily the lowest bid.

Senator LONG. In deciding what drugs to buy, you were in charge of it while Dr. Bernhardt was the head of New Orleans Charity?

Dr. ADRIANI. Yes.

Senator LONG. What is his first name? I should know it.

Dr. ADRIANI. Robert.

Senator LONG. He is regarded as one of the outstanding heart specialists in America, is he not?

Dr. ADRIANI. Yes. He is retired now. He is not doing much. But he was one of the finest clinicians in the city; yes.

Senator LONG. My uncle Earl who was Governor of Louisiana several times, thought that Dr. Bernhardt was just about the finest doctor anywhere in America. And I would take it that you had no quarrel with him about the way you were buying the drugs at New Orleans Charity?

Dr. ADRIANI. No.

Senator LONG. Did he agree with the practices?

Dr. ADRIANI. I have here a bid list showing how drugs are bought. They are bought under a State contract. Then we have this formulary which we follow at Charity.

Senator LONG. Dr. Ochsner is in New Orleans. He has a very fine clinic, just as fine a clinic as anywhere in America. Is there any great variation in their buying practices and yours at Charity?

Dr. ADRAINI. No; we always buy on bid, the lowest bidder.

Senator LONG. And they buy it about the same way you buy it?

Dr. ADRIANI. Yes; except that now the State has gone into central purchasing. They make a contract with a particular firm for a year to supply a particular drug. For instance, Demerol made by Winthrop (the trade name) is bought using the generic name neperagane. The patent has expired. Wyeth had the lowest bid on Meperidine so we buy this drug from Wyeth.

Senator LONG. Do I understand you to say that the State of Louisiana is not doing central purchasing for both you and the hospitals?

Dr. ADRIANI. No. Just for all the State hospitals.

Senator LONG. So the State is not doing central buying for all the State hospitals?

Dr. ADRIANI. They enter into a contract with a firm. They deliver a particular item to New Orleans. We pool all of our needs and we get a lower price that way.

Senator LONG. So to get better prices the State will buy for all of the State hospitals and ask for one bid so as to get the advantage of a big order?

Dr. ADRIANI. That is right. They enter into a contract for 1 year. If our pharmacists need more aspirin, they will put in a requisition. The local jobber will deliver the item to Charity. It doesn't have to come from Baton Rouge, Shreveport or other places.

But in order to save money we have a restricted formulary. There are certain drugs that are not in it. You mentioned Darvon. You could have taken this stuff—APC—and it would have done you as much good. But Darvon is still on patent. You pay a lot more for it than you do APC. We don't have it in our formulary. We found that this APC works just as well.

Senator LONG. In other words, you don't have it there because this product works just as well?

Dr. ADRIANI. That is right. When we have a request for a product, and the pharmacy committee feels it is not a justifiable request, we turn it down, and it doesn't get into the books. The doctor uses whatever is in this book.

Senator LONG. What if there are complaints by somebody who thinks that a particular drug should be in the book?

Dr. ADRIANI. They write a letter to the pharmacist. We have a meeting of the pharmacy committee. If the committee feels the request is justified, we will let him use the drug in his area. There may be a drug that we don't have that a patient has to have. We get a special request and buy it. We okay such drugs on an ad hoc basis.

Senator LONG. But the private hospitals use similar buying practices, do they not?

Dr. ADRIANI. They have one problem in the State hospitals we do not have. We have a full time staff and they have no interest in anything except the patients. If a doctor looks in the book and sees meprobamate he says okay. He doesn't care whether it is made by Wyeth or Wallace. In a private hospital the doctor would say, "I want Equanil," and he will specify and get that because his patient is a private patient.

And the sister or the superintendent of the hospital has to give it to him. But they put the extra cost on the patient's bill. So it is no "skin off the back" of the administrator. Somebody is paying for the patient. But here, if we don't have Equanil, no one is going to holler. Meprobamate is meprobamate.

Senator LONG. But if the State is paying for it—your attitude is, we know that it is not a bit better than the other firm's product, and we are not going to pay more than the low bid?

Dr. ADRIANI. This is what we do. We have a pharmacy committee. It is made up of visiting staff members. I am on that committee. And we look at an item and say accept it or we defer action. If a drug is good the minute it comes out we list it in the book. We know something about drugs.

I advocate in my statement that the policing can be done by the medical profession itself, it can be done at the local level.

Senator LONG. Did you say it can be done at the local level or cannot be done at the local level?

Dr. ADRIANI. It can be. We do it on a local level in our hospital.

Senator LONG. And you are in favor of it being policed at the local level?

Dr. ADRIANI. Yes. The doctors can do it themselves, because we always say, if you don't do it, then somebody else is going to do it for you. Some policing is important, and the medical profession can do it.

Senator LONG. Just what local level do you mean, the State level or the city level?

Dr. ADRIANI. Right down at the hospital itself. At Charity, we have a pharmacy committee. We have this drug list book. We update this book periodically.

Senator LONG. But take that hospital on the north shore of Lake Pontchartrain, they don't have many doctors, and they don't have a large staff, just a few people there. Are they in a position to do that same thing, or would it be better to have somebody do it for them?

For example, I don't know how many doctors they would have at that Covington Hospital, but it couldn't be very many. What would you recommend for St. Tammany Parish?

Dr. ADRIANI. You see, there is a commission called the Joint Commission for the Accreditation of Hospitals. Everybody wants to be approved by the joint commission. You have to be approved if you want to collect medicare money. And that "green stuff" talks. In order to be approved you have to have a pharmacy committee. If they would make these committees more active, as I say in my statement, then they could police drug utilization in a hospital better.

One of the things that ought to be brought out again is about the overuse of chloramphenicol. You can find out from the pharmicist that Dr. Blank is using five times as much chloramphenicol as someone else. You can call him in and say, what are you using this for?

The pharmacist called me one day and said, "You know, we used $3,000 worth of plasmanate this month." This is a product made from plasma, where it has been pasteurized.

We checked and we found that three resident doctors on the surgery service had used all this. I called them and said, "You are overusing this product and have to have an OK from me every time you want it."

And so we stopped its overuse. This policing can be done at the local hospital level, and at the county society level.

I make a statement that I don't think any doctor should own any stock in a pharmacy or a pharmaceutical house. This is a conflict of interest. When I signed up as a consultant for the FDA I had to submit a list of the stocks I owned, and swear that I did not own any stock in any pharmaceutical firm.

Senator LONG. In other words, the doctor ought to be in a position where he has no financial advantage in giving one product over another product?

Dr. ADRIANI. Absolutely.

Senator LONG. So he ought to be in a position like that of Caesar's wife, where he is totally above suspicion, whether he is giving you one firm's drugs or the other firm's drugs?

Dr. ADRIANI. When you go down to buy a suit, you can buy whatever brand suit you want. You are buying the suit and make the decision. If I give you a prescription to buy a drug you need I make the decision; you are paying for the drug. And if I say, "Use Squibb's," or some other firm's product then I am making a decision as to whose product you

will buy and pay for. If I own stock in Squibb and Squibb is making the drug, then I just cannot help it—everybody is human, and the next thing we will recommend the use of Squibb's.

But if I did not own any stock in that firm it would not make any difference whose drug I might select.

Senator LONG. Many times I suspect that this practice of free samples is being used in a way that you may not be familiar with, and which is not in the public interest.

One of my good friends who owned a drug store had a relative who was a doctor. And after a while he discovered that his doctor friend was giving away his free samples to all his golfing friends and his well-to-do friends with whom he mixed socially, as well as his relatives, but that he was not giving the free samples to the poor people who really couldn't afford to pay for them.

This fellow got in touch with that doctor relative of his and said, "Now, you have got to stop that." He said, "You are cheating me out of my money. You are prescribing for poor people who can't buy the drugs while you are giving your free samples away to your rich friends who can afford to pay for them. Now, if you are my friend, from now on, you will proceed to give those free samples to the poor, and you will give the prescriptions to those people that can afford to pay for those drugs at my drugstore."

I have the impression that this practice of leaving free samples with doctors is a subtle way of affecting their honest judgment. And sometimes one gains the impression that a doctor tends to prescribe the drugs of the company that gives him the most free samples. That in itself sometimes works out to be a matter of taxing the poor for the benefit of the rich—it tends to work out that way in most cases.

Who gets the free samples? It is the doctor's friends, his social group, his relatives.

Dr. ADRIANI. Yes, because those are the doctor's patients. Most doctors do not see charity patients in their offices unless they have somebody that is "broke." The free samples that we get at Charity are given to the patients, but they are indigent. If you give a private doctor free samples—like the dentist who gave you novobiocin, he cannot sell them. So he gave you the sample. He could have written a prescription.

But you can take care of the sample situation if you make all names for drugs generic. Then no salesman is going to give you meprobamate. What has he to gain by giving you the meprobamate? Competitors sell it too.

You see, you are tackling the problem backward. The problem you have to attack is to have uniform naming of drugs. Then you would limit the advertising. Getting rid of the advertising is like shooting at the sails of a boat in order to sink it. You must shoot at the bow or the stern, at the waterline, if you want to sink the boat.

You are hitting the wrong thing when you pick at the advertising. If you give these drugs and mixtures of drugs real names, they will stop giving away samples, they will stop advertising, unless they have a good reason for advertising. So the place to begin, I am suggesting, is in mandatory generic naming.

You will also get the prices down because you will have healthy competition.

Senator LONG. In other words, until you do this you never can have real, honest competition for business among these manufacturers?

Dr. ADRIANI. You are not going to "lick" this problem until you name all the drugs by their given names and get rid of the aliases. Drugs should be called just like every other commodity on the market, by its name. Why should the drug house have preference?

Senator LONG (presiding). I think you are 100 percent correct. Is there any other point you would like to make? Mr. Gordon is going to ask a few additional questions. If there is some point that you want to highlight, I would suggest you do that. Otherwise, I am going to ask, if Senator Nelson doesn't object when he gets back, that your statement be printed in full exactly as you prepared it, at the end of today's proceedings.

Dr. ADRIANI. You will find, Senator, that those who are sincerely interested in this problem, those who teach, those who stock drugs, those who buy them, and so on, will be delighted to see a uniform nomenclature. You have a good group naming drugs (USAN). You have got a Government representative, a USP man, an NF man, and one from AMA. They can attack the problem of "jawbreaking names".

Mandatory generic naming will give the smaller firms, if they want to qualify, the chance to complete with the larger ones. The small business can compete.

The corner grocery is still here with us, because they give service and stay open until 10 or 11 o'clock at night and the others close.

This is the basic plea I am making. The advertising does not concern me at all; nor the fact that the AMA accepts advertising. They need money. They are not going out having a good time with that money, they are using it for a good purpose. If the advertising is curtailed and does not pay for AMA activities then another way must be found to subsidize them. It is a very important venture. And the AMA are the ones that should keep on doing what they started.

Senator LONG. You say in your concluding statement:

> In advocating uniform nomenclature I am not castigating or opposing the pharmaceutical industry. One must remember that the pharmaceutical industry operates in a manner similar to any other industry and its primary goal is profits. It has, however, a greater responsibility to the public than any other industry.

And then you go on down here to say in your statement:

> I am sure that you have information from your hearings which indicates that some pharmaceutical firms have been ruthless, have fixed prices, and have committed acts which have not been in the public's best interest.

Some time ago I was discussing that matter with a major drug manufacturer who, so far as I know, was one of the "white hat" boys. The firm, so far as I know, has never done anything ruthless or corrupt or against the public interest, although, of course, it likes to use brand names.

And he said that he thought in fairness his firm could never have been accused of being a pirate, or a corruptionist, as some people in the industry have been accused of being.

I said, "You may quote me when I make this statement. Let me just give you a few examples." And I proceeded to list him a few examples.

And he did say, out of courtesy to people in a similar business, that he didn't see fit to pass judgment on those competitors of his who had been found guilty criminally in courts on prosecutions that I advocated or Mr. Gordon here, my staff assistant, urged me to advocate, where these people had tried to avoid criminal prosecution by being permitted to plead nolo contendere, meaning I will not defend myself.

If they had been permitted to get away with that, we would not be getting this big refund that we are getting in Louisiana and other States and municipalities because these people overcharged us on tetracycline in a worldwide conspiracy.

Dr. ADRIANI. That is right.

Senator LONG. So I spelled out some of these examples where these people are victimizing the public, thousands of people, and damaging and destroying their health by engaging in conspiratorial practices for money.

This man would not undertake to defend those kinds of practices for a moment, I am sure. In fact, I think he was surprised to know that those people had been criminally convicted of that kind of conduct.

Dr. ADRIANI. I read it in the paper. And I know Gremillion has instituted proceedings to recover the money. I do not know how many millions it is.

We were overcharged by this conspiracy. And I know that conspiracies have occurred. And I know errors that have been made in packaging, and so forth. I know in almost every one of these instances they say they are not true.

One of the things you have heard is that the drugs are important. If the labels all indicate where and by whom they are manufactured, the public will know.

Senator LONG. One of these days I am going to join with a few colleagues who might be willing to do it and contribute a few dollars out of my own pocket to establish an award for people who have done something to help their communities. And I am particularly interested in the field of health research and better health for people.

If Gaylord Nelson can afford it, he might be able to make a contribution to it. And there are some other Senators up here who would be interested in this sort of thing. Senator Hart has been interested in this sort of thing, and a number of others. And assuming that I am successful in creating the kind of award I think should be created, one of the people that I think would be nominated, at least suggested, if I had anything to say about the nomination, would be Dr. Ochsner of New Orleans.

I think he has done a great deal in developing techniques for surgery for cancer, and he is undoubtedly responsible for prolonging the lives of people, not only by his own operations, but by the techniques that he has developed which has enabled other doctors to go forward, multiplying his effectiveness. And I think some day it will be my pleasure to nominate you for what you are doing here in trying to help people get the best drugs at reasonable prices.

I think your statement supports what you stated in your prepared text to the effect that:

> I am strongly biased in my views on matters pertaining to drugs and my bias in this regard is 100 percent pro-patient only pro-patient.

I just wish every doctor had the same bias you have for the patient. And I think when they have reviewed your statement you will find a lot more who will share the same bias.

Dr. ADRIANI. I hope so, Senator. This is a very important problem. A patient will come to Charity, and we will give him a prescription. He does not have the money to buy what we prescribe. I remember one poor elevator operator, who was given a prescription for Orinase. It cost $14. The man was getting $200 a month and could not afford to buy it. I got Social Service to take care of it. They had been given some by Upjohn, a supply to give away.

I am a member of the Greater Cancer Association of New Orleans. We have a $12,000 fund to buy drugs for cancer patients. And one of the things that we have not worked out is a system of out-of-the-hospital provisions for drugs for patients. When you get them in the hospital, fine, you can give them all the drugs you want. But outside there is no provision made for them. And this is where a lot of these samples go. And it should not be that way. There should be some better system. One of the points in the Prescription Drug Task Force Report is how to implement this.

I do not know. I talked with Dr. Young, Commissioner Bonin's assistant. He says, "Louisiana will spend a million dollars a month on drugs for just on a handful of welfare patients." And that is a lot of money, $12 million a year for drugs, let alone other things.

Senator LONG. It is an outrage to make the poor people pay 10 or 20 times more than is necessary. And it is equally an outrage to put taxes on me or any of our other citizens to pay 10 or 20 times too much.

I can recall when I was a young lawyer practicing down at Baton Rouge, La., and a member of the junior chamber of commerce—or Lions Club. And we would get out there on the street corner and pretend we were Santa Claus, and help poor people pay medical bills, or fight cancer, and things of that sort.

But it is disgusting, when you take the Santa Claus costume off, to see some fellows getting rich stealing about half of that money when it was supposed to be for the benefit of the poor.

Serving humanity ought to apply to drug manufacturers just like everybody else. I want them to make a profit. And I think they do make a profit. I want them to make a good, honest, fair profit, no less than the average for all manufacturing by any means.

But the idea of letting them engage in practices to victimize the public which no other industry is permitted to do is pretty ridiculous.

Dr. ADRIANI. They are granted special privileges by allowing use of brand names. No other industry is allowed to do this. You call an automobile an automobile. You call a suit a suit. You don't give it a phony name. But when you buy a drug, then you get something like Panalba—I happen to be dwelling on that all the time—or Neosynephrine. You will have to get after these people and stop this.

The public should be told of the ill effects, and they should not be allowed to have misleading advertising in newspapers, TV, and magazines.

There is nothing that Commissioner Ley can do. As I said before, he is "hard up" for help. Where are you going to employ a doctor for $19,500, except some fellow that is too old to work, or is sick, or is a drug addict, or has other problems.

You cannot get first-class people. To get a first-class man at the top and an inadequate staff to assist him is just like having a good general with soldiers that do not know how to shoot. He (FDA Commissioner) ought to get more backing from Congress.

Mr. GORDON. I have a few miscellaneous questions.

I notice that you are on the advisory board of the Medical Tribune, which is known as a so-called throwaway sheet. How long have you been on it?

Dr. ADRIANI. Since they started it.

Mr. GORDON. What do you do?

Dr. ADRIANI. Well, I will tell you. This is an advisory board. They used to call it an editorial advisory board. Dr. Albert Sabin, who is a fairly outspoken fellow, who developed the polio vaccine, said at one of our meetings "we are not an editorial board," and we more or less criticized the material.

Mr. GORDON. You mean you critcized each particular article?

Dr. ADRIANI. Yes; at first we did. We saw an article that was offensive——

Mr. GORDON. Do you go over each article?

Dr. ADRIANI. No. We just go over different ones and give them ideas as to what subjects they might pursue.

Mr. Gordon. How about advertising.?

Dr. ADRIANI. Well, we have complained about some of the advertising. Some of the advertising we thought is insulting to the intelligence of a medical doctor. We have been critical of that.

I will tell you one of the reasons why I stayed on. I had word from somebody to get off the board. I was pressured to get off (when it was first organized). And I said, I will be darned if I get off. And Al Ochsner was pressured by the same group.

Senator LONG. The same group pressured Dr. Ochsner to resign from the board?

Dr. ADRIANI. Yes, both of us. And we decided to stick it out. It meets once a year. And we get nothing for it. It is strictly advisory. You can take all these ads and complete it. And you have material in there that is a little bit on a higher plane than what you see in the coverage of a medical meeting by the lay press.

And I will tell you what it does. It reports on the proceedings of meetings, and fairly quickly, so that you can read about a paper that was in Czechoslovakia, or Prague, or Berlin, or Paris, or San Francisco, and it highlights some of the papers.

Mr. GORDON. Do you think that it is possible that your name and the name of Dr. Sabin and Dr. Dameshek and others, big names, are used as a sort of——

Dr. ADRIANI. Do I think they are using our names?

Mr. GORDON. Yes, using your names. Do you think that is possible?

Dr. ADRIANI. I expect there might be something to that, yes. You will find that in other things, too. Somebody will come along and, say, you are well known in the city of New Orleans, and you can help us with our fund-raising campaign for our high school, or something of that sort. So you lend your name to these ventures. And I suspect that there might be some of that here. But they actually do call a meeting, and they seek our advice, and they do follow our sug-

gestions. There were a lot of things that we did not like, and they have been cleaned up. I think we have helped them, actually.

And if you took the advertising out of this, it still would be a useful periodical. There is information in it that a physician can use.

Senator LONG. Doctor, I am going to take the liberty of making your statement part of the Congressional Record, with an appropriate introduction by me, because I think that this statement should be widely distributed. To me, it makes better sense, and is more strictly motivated by the public interest than any statement I have heard in the pharmaceutical field in the years I have been working on the drug problem myself.

I was the predecessor of Senator Nelson on this drug study, but I got busy with tax matters, and he wanted to see what he could do in this area.

So I believe that what you are calling for is something that the public will understand. I think the public will understand this. This matter involves two things: One, that neither as taxpayers or consumers should we be robbed in the price that we pay for products. The industry should compete for the business. Two, the industry should not be selling the public a low quality product or a product that is injurious rather than helpful to health.

Now, on these points I think that you are eminently correct. We may find some differences of opinion about the size of print that we should use for trade names. I see that you wouldn't let them put the trade name in any size bigger than one-eighth the print used to say what the drug actually is.

I think that might be a little strong. Maybe one-quarter might be more appropriate. We might differ somewhat on things like that. But as far as your principal arguments are, I have to say they are correct.

And I want to thank you for your service to humanity, and your testimony here.

Dr. ADRIANI. May I add one thing. Government agencies have advocated, and some others have advocated, a drug reference book. The American Medical Association has undertaken the writing of a drug reference book. This is being written by the full-time employees at AMA headquarters, with the supposed supervision of the council. The council is composed of people who go up there three or four times a year, and serve free.

When I became chairman and started to investigate I was displeased with the progress that was being made. I told the board of trustees in January, at the rate that the staff has been working, we expected to have this book out by June 1969. My grandchildren—but no one in this generation might use it. That "shook" them up. They appointed a committee of council members to expedite the publishing.

I am chairman of the ad hoc committee to get this book out. Instead of going out and getting somebody else to write one, and then giving it away—I think the Government could give this book away like a PDR is given away. Nobody would buy a PDR if it were sold.

I am the chairman of the council—I might not be after this meeting—but at least I have taken that assignment. I intend to see this book out even if I have to write it myself.

Senator LONG. If you will make it available to us I think you can count on our help.

Mr. GORDON. The hearings are recessed until next Tuesday, May 27. The room will be announced later.

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

STATEMENT OF DR. JOHN ADRIANI, CHARITY HOSPITAL, NEW ORLEANS, LA.

Mr. Chairman and Members of the Committee, it certainly is a compliment to me, who is familiar with so little of the vast fund of available information on drugs, to be invited to appear before this committee. You do me honor by indicating that I may be of assistance to you. The accumulation of knowledge pertaining to drugs over the past several decades has been so phenomenal that no single individual, be he a practitioner of medicine, pharmacologist, pharmacist or other persons whose primary interest is drugs, can be expected to know all of the important details concerning all drugs available for use in the treatment of disease.

I preface my remarks to the committee with the statement that I am strongly biased in my views on matters pertaining to drugs and that my bias in this regard is one hundred percent pro-patient and only propatient.

BACKGROUND AND QUALIFICATIONS

I am John Adriani of New Orleans, Louisiana. I am a Doctor of Medicine who graduated from the College of Physicians and Surgeons of Columbia University in 1934. My speciality has been surgery, but my interests have been diversified since I began medical practice. I majored in chemistry before entering medical school and gave strong consideration to becoming a chemist and concentrating my interests in drug chemistry before I finally decided to study medicine. I also had training in physiology under the renowned Doctor Homer Smith at New York University. My contact with surgery made me aware of the woeful lack of knowledge of the action of anesthetics and the primitive methods of administering these drugs which existed in the early 1930's. The methods were nearly as primitive as they were in 1842 when ether was first introduced as an anesthetic.

Anesthetics are drugs which are used to carry a patient halfway to eternity and back. Obviously, these drugs are lethal and the responsibility of administering them is great. The science and specialty of anesthesiology has developed as a result of the recognition by a few physicians three decades ago of the importance of the actions of these drugs and of the knowledge of their proper administration.

An anesthesiologist is one who uses and studies pain relieveing drugs in patients. An anesthesiologist must also posses broad knowledge in matters pertaingin to other types of drugs because the speciality encompasses the use of drugs which are either antagonists and overcome the effects of anesthetics or are used as adjuncts to augment the effects of anesthetics. In addition, some drugs are used prophylactically to prevent unanticipated and unwanted side effects. Another point of importance is that patients who require anesthesia often are taking drugs prescribed by personal physicians, internists, and other specialists to treat diseases not directly related to the surgical disease for which they are hospitalized. An example would be the use of digitalis in a patient to treat existing heart disease, reserpine for the treatment of the high blood pressure which caused the heart to decompensate, a diuretic, which facilitates the elimination of salt and prevents accumulation of water in the tissues, quinidine to make the pulse regular, a tranquilizer to prevent excitement and apprehension, a vasodilator to prevent anginal pain. an anticoagulant to prevent clotting in the vessels of the heart and brain, and insulin to control diabetes. It is not uncommon to find a patient who needs an operation having all these conditions and receiving all these drugs. How these drugs interact with those prescribed by the anesthesiologist and surgeon is a matter of great importance. Little is known about many drug interactions and the subject is now becoming one of intensive study.

The anesthesiologist is, in essence, a clinical pharmacologist who is knowledgeable in the behavior of many drugs. He is familiar with their use in human beings who are ill and who are under treatment. His knowledge of drugs stems from their actual use in patients and not merely from information gathered in studies from normal human volunteers or from animals.

My experience in matters pertaining to drugs has been quite diverse, encompassing research in pharmacology, testing of new drugs, the teaching of pharmacology for over thirty years to undergraduate medical, dental, and post-doctoral students. In addition, I am engaged in the training of nurses to administer anesthetics, gases and mists for treating pulmonary (lung) diseases.

I have been a member of the Council on Drugs of the American Medical Association for six years and Chairman from the latter half of 1967 to date. I have been a member of the Revision Committee of the U.S. Pharmacopeia for the past nine years and was a member of the panel on anesthetics of the Subcommittee on Scope of the U.S.P. ten years before I was made a member of the Revision Committee. I have been a consultant to the Food and Drug Administration since 1963 when the Kefauver-Harris Amendment was first implemented. I am now also Chairman of the Advisory Committee to the FDA on Anesthetic and Respiratory Drugs.

For the past nine years I have been Associate Director at Charity Hospital of New Orleans, Louisiana, in which capacity I have gained considerable insight into the budgetary problems concerning the care of the sick and the cost of medical supplies, particularly drugs. I have also been a member of the Pharmacy and Therapeutics Committee of Charity Hospital, serving in the capacity of pharmacologist.

My entire professional life as a physician has been devoted as a salaried employee in tax-supported institutions (Bellevue Hospital, New York, and Charity Hospital, New Orleans) in caring for those unable to finance their own cost of medical care. I have no private practice except occasional consultations, testifying as an expert in medicolegal matters, or the treatment of special cases referred to me for problems pertaining to pain. I submit this résumé of my activities to you and to your committee, Mr. Chairman, to apprise you of the areas of my interest and experience and background in matters pertaining to drugs.

TOPICS REQUESTED TO BE DISCUSSED

I am appearing by invitation as an individual physician, representing no organization or institution. My statements reflect my own thinking and opinions and are not to be construed as reflecting opinions of any organization or institution with which I am associated. I have been asked to express any general views I may have on drugs, but specifically to comment on antibiotic combinations, antibiotic overuse, and particularly the overuse of Chloramphenicol.

GENERIC NAMING

The problems of drug utilization and prescription methods are complex and are increasing in complexity as the number of drugs introduced into therapeutics increases. The situation can now be described as nearly chaotic. No semblance of order can be made of the existing chaos until all drugs and combinations thereof are designated by given, common, or generic names and not by proprietary, or brand names. Proprietary or brand names are, in essence, aliases. An alias, no matter how used, tends to confuse or to be deceptive. An alias is intended to conceal the true identity of whatever or whomever is being designated by an alias. The use of brand names for drugs serves no constructive purpose; on the contrary, the practice hampers rational drug utilization, rational prescribing and dissemination of drug information. Brand names should be abolished. The public's best interests will not be served until this is done.

It is a function of the government to do for the people what the people cannot do for themselves. No private group or scientific organization possesses the capability or is empowered to institute reforms in drug nomenclature which are so sorely needed. Obviously, then, this is something that the people cannot do for themselves. Government, therefore, must intervene and act in the public's behalf. The record of the U.S. Government in assuring the public that food products supplied to a consumer are pure and properly labelled is commendable and is known to all. The citizens of no other nation on earth have the assurance that food products which enter interstate commerce are safe, as does the citizenry of this nation. Foods are dispensed by their given names and not by aliases. The brand and the name of the vendor or producer is inscribed on the dispensing container to permit the consumer to purchase the commodity of his choice and preference. It is difficult to understand why drugs, which are equally as important, if not more important than food, to the health of a nation and well-

being of the public are permitted to masquerade under aliases. In essence, the pharmaceutical industry is being granted preferential treatment by being allowed to distribute drugs using brand names, since no other major industry preparing merchandise for human consumption is granted similar special privileges. The reasons given are that merchandise of one manufacturer varies in quality from that of another and that to do otherwise interferes with the physician's prerogative or prescribing a drug of his choice. It is ludicrous to conceive that items so vital to the public health are distributed by brand names, under the guise that to do otherwise would be interfering with the physician's prerogative of selecting the product of a manufacturer which he deems best for his patient. The arguments which have been advanced for justifying the practice of using brand names are not only illogical and superfluous, but even puerile. If it is the object of the pharmaceutical industry to promote ignorance and to confuse not only the physician, but the public as well, the use of brand names effectively accomplishes this purpose. The prime motive, if one gives the matter thoughtful consideration in using aliases for drugs, is to promote sales, to establish monopolies and to stifle competition of rival manufacturers.

GENERIC LABELLING

It is my belief that carefully and thoughtfully prepared legislation should be adopted, advocating *that compulsory labelling of prescription drugs* dispensed either in bulk to pharmacists and physicians or prescription drugs dispensed in individual packages *be done by generic, or common names.* By "common names" I refer to names that are shorter or better known than the generic name. Aspirin is a more common name than the generic name—acetylsalicylic acid. The generic labelling should appear in large, bold-faced type on the label, wrapper, container, brochure and all other identifying devices or documents. The brand name of the manufacturer, if such a drug has a brand name, should be in parentheses beneath the generic name in type no larger than one-eighth the size of the type used for the generic name of the drug. Interposed between the generic name of the drug, in type no larger than that used for the manufacturer's name and the brand name but large enough to be easily legible, should be interposed the chemical name of the drug.

A pharmacist who dispenses to a patient, on a prescription from a physician, a portion of the contents of a drug packaged in bulk should be required to label the package of the drug so dispensed to the purchaser with the generic, or common name of the drug. If the physician has specified dispensing a drug of a particular manufacturer, the manufacturer's name should be indicated in parentheses below the generic name, in order that the physician, as well as the patient, will know whether or not the specified item has been supplied. The labelling on the container given to the patient should be omitted if the physician indicates "do not label" on the prescription.

NAMING OF MIXTURES AND COMBINATIONS

Mixtures of drugs would be designated as Mixtures. For example, the mixture now available as Coricidin would be labelled as Chlorpheniramine. Asprin and Phenacetin Mixture. The brand name Coricidin would not be included in the labelling. Instead, the name, Chlortrimeton, since it is a proprietary ingredient, would appear in parenthesis in type one-eighth the size of type used to name the ingredients of the mixture beneath the name of the ingredient Chlorpheniramine, together with the manufacturer's name. The labelling of mixtures should also carry the chemical names of each ingredient, in fine print, with the generic or common name in parentheses and the amount of each ingredient in each tablet, capsule, or unit of liquid measure should be indicated in both milligrams and in grains. The latter stipulation would not be a requirement of the labelling applied to the package dispensed by prescription to a patient. These are of interest primarily for the pharmacist, pharmaceutical chemists, or the toxicologist in the event this information is required in cases of poisoning, homicide, determination of purity or biologic assay. An expiration date should be indicated for drugs which have expiration dates.

LABELLING OF OVER-THE-COUNTER DRUGS

Producers of "over-the-counter drugs" are likewise enjoying special privileges which are far from being in the public's best interest. As a matter of fact, the surveillance of the firms packaging over-the-counter drugs is not as close as that

of firms packaging prescription drugs. The FDA has no surveillance over claims of efficacy of over-the-counter drugs made in advertisements, in newspapers, magazines, telecasts, etc., and Federal agencies empowered to take action seldom do so.

Pharmaceutical firms which package a prescription drug which may also be sold over the counter in certain dosage forms often make claims in advertising in newspapers and nonprofessional magazines that would not pass the scrutiny of the FDA. I am thinking specifically of Neosynephrine, packaged by Winthrop, in the form of nose drops, which is available over the counter, which, in lay journals is claimed to be effective for "colds." The labelling of over-the-counter drugs should follow the same pattern as that of prescription drugs and the advertisements should be as informative concerning full disclosure and efficacy as prescription drugs.

REPACKAGING OF DRUGS

Drugs dispensed by "repackaging firms" should indicate the source of each ingredient, that is, the name of the manufacturer from whom each chemical was purchased. The same requirement should apply to firms distributing a repackaged drug under a brand name or to mixtures. The large manufacturing firms who buy drugs from other firms should indicate on the package that they did not make the drug, by indicating its source, in the same manner as required of the "repackaging houses."

In addition, the American Medical Association should indicate in its code of ethics that physicians should own no stock or interest in any pharmaceutical firm, repackaging firm or pharmacy, and insist that this be enforced at the county society level. No conscientious, ethical physician who lives up to his oath should object. The patient is at his mercy and purchases what he specifies and there should be no conflict of interest.

IMPACT OF GENERIC LABELLING

Should one ask, "Will such a change in labelling as is being proposed be in the public's best interest?", the answer will obviously be, "It will." If one asks, "How?", the answer would be, "Everyone will learn and know the real name of a drug"; the physician, the pharmacist, the nurses who take care of the patient, the pharmacist's attendants and the relatives. Pseudonyms and aliases ultimately will disappear, without one bit of harm to the public.

Will physicians be restricted in their prescribing prerogatives if such a plan were placed into effect? The answer is, "not at all." The physician will still be able to prescribe the drug he chooses, manufactured by the firm he prefers and in which he has confidence. He still will be able to prescribe in the dosage form he chooses and has always used in prescribing the drug. If, for medical reasons, a physician does not wish a patient to know the identity of a drug, it will still be his prerogative to request this.

Pharmacists will still be required to supply to a patient a drug a physician requests, made by the manufacturer that the physician indicates and prefers. An ethical pharmacist will not substitute an inferior drug, as has been argued that he might do by those who feel that the brand names protect the patient and protect the physician's right to prescribe as he sees fit. If a physician does not object to labelling, the patient is then told what he is to receive and can insist that the pharmacist supply exactly what is prescribed and what the patient is paying for. Patients may be able to shop and obtain a drug at its lowest cost.

The days of mystery in medicine are over. Medicine is a science as well as an art. Patients are not morons. They read, and they are becoming more knowledgeable, and there is no reason for not disclosing all pertinent information to everyone for the proper and safe use of a drug. By using a standard name for each drug, full disclosure will be provided for all persons involved. The chemically oriented physician will have the chemical name. The pharmacist, the pharmaceutical chemist, the toxicologist and the physician who have become accustomed to using brand names will have them at their disposal should they wish them, but in time they will be de-emphasized and brand names hopefully will disappear. Existing hospital formularies can be abbreviated and new ones prepared in hospitals where none now exist. Pharmacists will find that in due time physicians' prescribing habits will change and they will need fewer items on the shelves.

GENERIC EQUIVALENCY

The arguments for retaining brand names prescribing have been shrouded and wrapped in that nebulous cloud referred to as "generic equivalency." The paucity of convincing and well-documented data of clinical significance causes one to suspect that this situation has been grossly exaggerated. Should a product of one pharmaceutical firm be chemically equivalent and more effective biologically, then this would be a selling point which a pharmaceutical firm could use in its advertising. The firm could, with justification, capitalize upon this point in its advertising and utilize it as a reason for selecting the drug of that particular firm. The firm thus could boast that its product is superior and has this advantage over that of competing firms. Considerable stretch of the imagination is required for one to see the justification for the use of an alias for designation of a product merely on the basis of generic equivalency. For example, should ether be prepared by Squibb be found to be biologically and clinically more effective than that of competitive manufacturers, and I doubt that it would, a physician who is aware of this would request ether—Squibb. In the event Lidocaine U.S.P. prepared by Astra were demonstrated to be biologically and clinically superior to products distributed by a competing firm, this wold not necessarily interfere with a physician's choice to prescribe Lidocaine—Astra instead of the alias, Xylocaine. Neither would there be interference of the physician's prerogative to prescribe the product he deems most effective clinically, if indeed he can make such a distinction, and the best interest of the patient will still be served. The question of generic equivalency has been "ballyhooed" with both scientific and pseudoscientific data, so that it is virtually impossible to determine what is fact and what is fancy. The situation is almost laughable. Much is said about crystal size, the effect of binders and mordants, coating, etc. This all sounds impressive and has some basis of fact, no doubt, Mr. Chairman, but no one has said what happens to one of these elite "non-generic brand name drugs" when it is introduced into the stomach of a patient, the contents of which are not known, the acidity of the juices in the stomach are not known and other variable factors which are bound to exist are not known. What happens to one of these pills or capsules after they are introduced into the stomach and are followed by a martini, potato chips, shrimp remoulade, turtle soup, a steak, potatoes, some wine, salad and dessert. If a drug is readily soluble, the chances are excellent that chemical equivalency equals biological and clinical equivalency.

One cannot deny that in some cases biologic potency may vary from one product of one manufacturer to another or even from batch to batch of a given drug by a given manufacturer, but how much is known about all of this which is factual and clinically significant? It appears to me that no one has given this matter much thought over the years and now the matter is being called to the attention of the scientific community and we are becoming aware of something that only time will prove whether or not is important. The effectiveness of a drug taken before breakfast may differ from that of taking the same drug before lunch or before supper or at bedtime, or from one day to the next. Such variable factors as fever, the presence of other drugs, hydration and liver and kidney function may influence the efficacy of a drug. Generic naming must not be confused with generic equivalency. The two terms are distinct, separate entities and not synonomous.

ACCEPTABLE STANDARDS

Standards formulated by the U.S. Pharmacopeia, the National Formulary and other agencies are acceptable, reliable standards and should be adhered to at this time until additional well documented information is available, at which time these agencies and scientific groups can revise their standards. As time passes we will no doubt learn more about the so-called "biologic equivalency" and its clinical importance. The standards will then be modified in accordance with our added knowledge, but until such a time the present-day standards are adequate.

There must be a beginning to make order out of chaos, and now is the time to effect changes. The vociferous displeasure which will be voiced will be intense but it can be readily parried by asking, "Is what is being done in the public's best interest?" How can full disclosure of all details pertaining to a drug be anything other than in the patient's best interest?

COMPLEXITY OF GENERIC NAMES

The greatest objection and difficulty that one will encounter in attempting to establish uniform nomenclature of drugs will be the complexity of some of the generic names which have been assigned to drugs. This is a matter that will have to be resolved with time. Some names undoubtedly will have to be simplified. Chlorpheniramine, mentioned in the description of Coricidin, is a name that borders on the complex side. There is a tendency among physicians to abbreviate names or use "nicknames." For instance, cyclopropane is usually referred to as "cyclo" by anesthetists. Muscle relaxants are facetiously referred to as "arrow poisons." In the case of the muscle relaxants, for example, Decamethonium is the generic name for Syncurine and Succinylcholine is the generic name for Anectine or Sucostrin. Tubocurarine is a non-patented generic name for Curare and should be retained. These generic names are not difficult to pronounce or spell.

The purpose, Mr. Chairman, in my recommending that the chemical names be included on the package and in the other types of labelling is that one wishing to know the chemistry would have it available. The United States Adopted Names, a committee composed of members of the U.S.P., N.F., Council on Drugs of the AMA, and the FDA, now attempts to incorporate in the name an indication of the chemical nature of the drug. If it were known that the chemical names are required on the labelling, perhaps the USAN would be more inclined to adopt the simpler names and not attempt to follow a chemical type of nomenclature.

LICENSING SYSTEMS

A code of good manufacturing practices and other criteria with a licensing system and registration for all individual pharmaceutical products is essential. All drugs would then meet the same standards. This, of course, would be imposing the same requirements on all firms manufacturing drugs equally and would do much to solve the problem and obviate the objection which allegedly exists that some drugs are chemically equivalent but not biologically equivalent. This is not an impossible problem to resolve.

FIXED RATIO COMBINATIONS

Physicians have, for years and years, used drug combinations. They will continue to use drug combinations in the future. I see no end to this practice. It is reasonable and logical in some cases. There is a difference, Mr. Chairman, between *combinations* and *fixed ratio combinations*. Combinations are essential and not necessarily objectionable. However, there are objections to the use of *fixed ratio combinations* because no two individuals respond in the same manner to a given drug. The argument advanced in the use of *fixed ratio combinations* is that a patient then would receive all the medication in one tablet, capsule or teaspoonful of solution or injection. The use of *fixed ratio combination* is as logical as selling combinations of salt and pepper in fixed proportions. I am sure that if pepper were combined with salt in a fixed ratio and sold on the premise that one would require only one shaker on the table instead of two the product would have limited sale. Individual tastes vary; some people would like more salt and less pepper and vice versa.

The same principle applies to drugs in combinations of fixed ratio, particularly when they are dissimilar chemically or therapeutically. I have in mind a particular fixed ratio combination which has been recently introduced on the market under the brand name of Innovar. This is a mixture of a new narcotic of great potency, Fentanyl, and a new "tranquilizer," Droperidol. The narcotic causes rigidity of the muscles and interferes with respiration. The tranquilizer has the capability of paralyzing the nerves supplying the blood vessels and causing a fall in blood pressure. The combination is packaged in a ratio of fifty parts of the tranquilizer to one part of the narcotic. When this combination is used, certain individuals overreact to the narcotic while others overreact to the tranquilizer. Such a mixture of fixed proportions is illogical. It has been promoted and, because of its newness, detailed information of its pharmacologic properties is lacking or it has not as yet drifted down to the practicing physician through the normal and unbiased drug information channels; that is, from physicians who actually are familiar with the drug and recognize its side effects. When an N.D.A. of a new product of this sort is approved by the FDA, the "detail men" are the first to acquaint the physician with the product. The package insert, in these

cases, provides all of the required available information but this is not sufficient because in many cases the drug has been tested by individuals whom we facetiously refer to as "testimonial writers." Seasoned researchers are not interested in testing drugs in the manner proposed by a sponsoring manufacturer. The data on the N.D.A. applications is not always obtained from research of the highest quality. Side actions and other adverse effects often remain virtually unknown until a drug is subjected to widespread general use or is studied carefully by seasoned researchers. When a drug is first introduced, we are not fully aware of its actual usefulness and limitations. It is only with time and sad experiences that a drug finds its proper niche in therapeutics.

ANTIBIOTIC FIXED RATIO COMBINATIONS

Some fixed ratio combinations of antibiotics and chemotherapeutic agents available on the market are deemed ineffective in certain cases, from data studied by the Review Committee of the NAS–NRC. Inasmuch as the physicians and other scientists on these committees are knowledgeable in their fields and not biased. I would accept their recommendations. In instances where they say that a fixed ratio combination is not effective, this combination should be withdrawn from the market unless supplementary data of proof of efficacy is supplied by a manufacturer. Withdrawal of mixed ratio combinations of these types does not hamper the physician from using combinations. A physician will still be able to prescribe two or three drugs in quantities to suit an individual patient. Antibiotics and chemotherapeutic drugs are far from innocuous drugs. Each type is capable of producing sensitization, kidney, liver, and in some cases nerve damage. Where fixed ratio combinations are used, only one ingredient may be effective but the amount in the mixture is insufficient. The physician may increase the dose if the response is good but not as great as anticipated. It is thus possible for the amount of the ineffective agent to be increased above the toxic level and cause harm to a patient.

CHLORAMPHENICOL

I have been asked to comment on the use of Chloramphenicol (Chloromycetin). Chloramphenicol is a valuable drug and certainly nothing should be done to curtail the intelligent use of the drug by knowledgeable physicians in instances in which it is indicated. It not only would be difficult to legislate when a physician should or should not use Chloramphenicol, but such a step would be ill advised. There is no doubt that there has been and probably still is some abuse of the drug. This appears to be decreasing. There are, however, other drugs in other categories that are equally as hazardous as Chloramphenicol but in other ways. They, too, are used thoughtlessly and indiscriminately in certain cases.

PHARMACY AND THERAPEUTICS COMMITTEES

The hospital pharmacy and therapeutics committees required by the Joint Commission on Accreditation of Hospitals in accredited hospitals could manage the problem of proper drug usage quite effectively. These committees, however, should be strengthened and be more active than they now are. Their scope should be broadened to include the reporting, not only of adverse reactions, but a review of a drug utilization and promotion of drug education to the hospital visiting staff. The premise upon which the Joint Commission for the Accreditation of Hospitals bases its requirements of accreditation, as far as the medical and surgical visiting staff is concerned, is that the visiting staff governs itself. The philosophy that the staff governs itself can be workable. It is effective in certain, but not all, hospitals, Tissue committees are quite effective in most hospitals in preventing unnecessary surgery. Utilization review committees which review duration of patient stay and hospitalization likewise have been effective; therefore, the same principle could be applied to drug utilization. The pharmacy and therapeutics committee could challenge a physician for using a drug such as Chloramphenicol in situations where it was not indicated or for administering the drug without performing the proper bacteriologic and sensitivity studies. Legislation is not the answer to this problem. The solution must be by education and self-regulation by the medical profession. The use of drugs presenting hazards similar to Chloramphenicol could be "policed" in a similar manner.

ROLE OF THE AMERICAN MEDICAL ASSOCIATION

I realize that the American Medical Association has, over the years, differed with Congressional leaders and governmental agencies in its views concerning the dispensing of health care to the public. I prefer not to say that I agree or disagree with the pronouncements that have been made by the Association because I must admit that I am not familiar with both sides of the story in some cases. I have either heard or read biased sides presented by physicians or read biases presented by the government in the news media. Therefore, it is difficult for me to have strong feelings one way or the other in this matter. Again, when in doubt, I apply the rule which serves as my guide—"Is what is being proposed in the best interests of the public?". I would like to emphasize, Mr. Chairman, that medicine, as it is practiced today, is the best in the history of the world. It would not be in the state of development that it is today had it not been for the American Medical Association. Many years ago Abraham Flexner submitted a report on the deplorable status of the various medical schools in the United States. Following the presentation of this report the American Medical Association took the initiative and established uniform standards of medical education in this country. We then surpassed the rest of the world as far as medical standards of medical education and medical practice are concerned. The American Medical Association is a scientific body which can, if it wishes, assemble scientific and medical talent of the highest calibre. The association has and must have a political superstructure. The part of the medical association that the public knows is the "political portion," which is a small portion. After all, the American Medical Association is a democratic organization. It is organized and operates in many ways as does the Congress or the various State legislatures. It is governed by an elected House of Delegates. The actions of the Congress, as depicted in the press, sometimes appear absurd. Likewise, the actions and resolutions of the American Medical Association may appear to be ridiculous and ill conceived to one on the outside looking in who does not know all the ramifications involved in a decision. The portion of the American Medical Association that one does not see is the conglomerate of scientific councils and other divisions not involved in medico-political affairs. The Association may be likened to an iceberg, one-eighth of which protrudes above the water. This portion is the political portion which the public sees.

The functions of the American Medical Association of which the public is not aware are the scientific functions. This is the portion likened to the iceberg which is beneath the water. The Council on Medical Education, which inspects and approves medical schools, internships, residencies an dpostgraduate programs, a costly and important undertaking, is a little-known body of the Association which serves the best interests of the public. The Council on Drugs, of which I am a member, is promoting the formulation of drug utilization policies, adverse drug reaction reporting and dissemination of medical knowledge to physicians. The activities of the Association are financed to a large extent by physicians' dues and voluntary contributions and to a lesser extent from income from advertising in periodicals published by the Association.

I may appear to be idealistic and naive in making this statement, but I believe the governmental agencies should take into their confidence and work closely with the various scientific bodies of a national stature, including the AMA, and attempt to cooperate and work jointly for the benefit of all. Any legislation which is hastily passed, ill conceived, is restrictive and appears to encroach upon the physician's prerogative to make decisions and to practice medicine as he deems best for the patient will be construed as punitive and will arouse resentment and resistance. A frustrating situation will be created and the main goal, namely, providing the best health care possible for the public which both the government and the American Medical Association are obligated to provide, will not be attained.

THE PHARMACEUTICAL INDUSTRY

In advocating uniform nomenclature I am not castigating or opposing the pharmaceutical industry. One must remember that the pharmaceutical industry operates in a manner similar to any other industry and its primary goal is profits. It has, however, a greater responsibility to the public than any other industry. The patient does not make the decision as to which and whose drug

is to be bought. The physician does. The industry should remember this fact but does not always do so. If the profit incentive is removed, then expansion and progressive development of the industry will be stunted and this would not be in the best interests of the public. I am sure that you have information from your hearings which indicates that some pharmaceutical firms have been ruthless, have fixed prices, and have committed acts which have not been in the public's best interest. Nonetheless, the pharmaceutical industry has also contributed its share to the progress of medicine in this country. We need an active and vigorous pharmaceutical industry. There should be regulation of the industry but such regulation should be nonrestrictive in nature. It should create a more competitive environment than now exists and permit a firm to expand and progress and to develop significant and better products and not duplicate products. Any restrictions which are placed upon a firm that remove incentive will not be in the best interests of the public or the medical profession. Restricting monopolistic practices will, of course, encourage competition which is healthy and which is in the best interests of the public.

The question, Mr. Chairman, then is not should we abolish brand names and use generic names, but when? The sooner the better. It can be done, and it will be a step forward in medicine.

I think I have said enough, Mr. Chairman; thank you.

(Whereupon, at 12:50 p.m., the subcommittee recessed, to reconvene at 9:30 a.m., Tuesday, May 27, 1969.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

TUESDAY, MAY 27, 1969

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

The subcommittee met, pursuant to recess, at 9:30 a.m., in room 318, Old Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senators Nelson and Dole.

Also present: Chester H. Smith, staff director and general counsel; Benjamin Gordon, staff economist; Elaine C. Dye, clerical assistant; and James P. Duffy III, minority counsel.

Senator NELSON. Our witness this morning is Dr. Herbert Ley, Jr., Commissioner of Food and Drugs, Consumer Protection and Environmental Health Service of the Public Health Service.

First let me say that we periodically make it clear that any drug company that has any product or any action of its own discussed before this committee is welcome with a high priority to come before the committee and discuss any aspect of its drugs or its operations before this committee. And we repeat, that has been the policy of this committee from the beginning, to give first priority to drug companies to respond to any criticism made of them before the committee.

Through their representative, we specifically invited the Upjohn Co. to come. On May 14, 1969 I sent a letter to Mr. Joseph Stetler, president of the Pharmaceutical Manufacturers Association, in which I said:

DEAR MR. STETLER: A long standing policy of our hearings, publicly and frequently announced, is to give the first opportunity to be heard to any firm whose products or policies have been discussed before the subcommittee. As you know, we are now conducting hearings on drug efficacy studies on fixed combination drugs conducted by the National Academy of Sciences National Research Council. The purpose of this letter is to inform you that if you or any of your members would like to appear before our committee to discuss these studies you are welcome to do so. Arrangements to testify are to be made by contacting Benjamin Gordon, the Committee's Staff Economist.

Sincerely yours,

GAYLORD NELSON,
Chairman of the Monopoly Subcommittee.

No companies have requested thus far to appear, nor has the Pharmaceutical Manufacturers Association. But I want to make it clear to them that they are welcome to appear and discuss the issues that are pending before the committee.[1]

[1] A letter was received subsequent to the hearings and appears as Appendix IV, p. 5257, infra.

We are very pleased this morning to have the Commissioner of the Food and Drug Administration, Dr. Ley, before the committee. He has a long and distinguished career in public service, and a national reputation of high repute.

And we are pleased to have you here this morning, Doctor, to discuss the fixed combination of antibiotic drugs.

You may present your statement as you please. All of it will be printed in the record. If at any time you wish to elaborate on anything in the statement, feel free to do so. I assume you have no objection to questions?

Dr. LEY. None whatsoever.

Thank you, Mr. Chairman.

STATEMENT OF DR. HERBERT L. LEY, JR., COMMISSIONER OF FOOD AND DRUGS, CONSUMER PROTECTION AND ENVIRONMENTAL HEALTH SERVICE, PUBLIC HEALTH SERVICE, U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE; ACCOMPANIED BY WILLIAM W. GOODRICH, COUNSEL, OFFICE OF GENERAL COUNSEL; DR. JOHN JENNINGS, ACTING DIRECTOR, BUREAU OF MEDICINE, FOOD AND DRUG ADMINISTRATION; AND DR. PAUL BRYAN, DIRECTOR, BUREAU OF MEDICINE TASK FORCE, FOOD AND DRUG ADMINISTRATION

Dr. LEY. Before I begin I would like to introduce the members of the staff of the administration whom I have brought with me.

On my left is Mr. William Goodrich, of the Office of the General Counsel of the Department of Health, Education, and Welfare.

On my right is Dr. John Jennings, Acting Director of the Bureau of Medicine of the Food and Drugs Administration.

And immediately behind him is Dr. Paul Bryan, who is head of the task force that is responsible for the drug efficacy study implementation.

We welcome this opportunity to join in the discussion, which was started before this committee 3 weeks ago, about combination antibiotic drugs, the review of their effectiveness by the National Academy of Sciences-National Research Council Drug Efficacy Study Group, and the follow-up steps that FDA is required to take to remove these products from the prescription drug market.

Let me begin with two general observations. First, we are most fortunate to have had the assistance in the effectiveness review of medical scientists of the stature of the witnesses who appeared before this committee earlier. These five panel chairman, as I'm sure the committee noted, are not cloistered academicians aloof from the realities of treating infectious diseases. To the contrary, they have been and are now working at the frontiers of the treatment of the most complicated of infectious diseases. Their contributions, which led to their selection as panel chairmen by the NAS/NRC, clearly establish their excellent qualifications to make efficacy judgments for this class of drugs.

Second, we cannot overemphasize the importance of the drug efficacy review in terms of better patient care. The implementation of

the panel recommendations with respect to the combination antibiotic drugs will not only eliminate some unnecessary risks in therapy, but will help to return antibiotic treatment to the realm of rational therapeutics.

Specific treatment for bacterial infections was not available to the physicians until the late 1930's, when the sulfonamides were first introduced. Before that, only bed rest, cold compresses, and similar palliatives were available to deal with even infectious diseases.

The sulfonamide drugs of the 1930's were the first effective chemotherapeutic agents employed systematically for the prevention and cure of a variety of bacterial infections in man.

Numerous derivatives of sulfonamides were synthesized and tested for their clinical value in various bacterial, protozoal, and viral diseases. Sulfapyridine produced dramatic results in pneumococcal pneumonia and, for a brief period, it was the agent of choice in this disease. In 1938, sulfathiazole replaced sulfapyridine as the preferred sulfonamide because of its higher therapeutic index. Sulfadiazine soon replaced sulfathiazole and has retained a prominent position among the sulfonamides ever since. Two methylated derivatives of sulfadiazine were soon introduced into therapy.

In 1941, English scientists discovered that penicillin was effective against staphylococcus and streptococcal infections. A vast research program was initiated in the United States to produce this antibiotic and, by the spring of 1943, penicillin was available for the Armed Forces of this country.

Although numerous antibiotic agents have been produced since penicillin was discovered, this drug it still the most widely used for the treatment of infections. In the years since the first crude product was obtained from fermentation vats, chemical manipulation of the penicillin molecule has produced a large number of natural and semisynthetic congeners, and several new penicillins have become important therapeutic agents.

Penicillin itself, however, is generally ineffective in the treatment of infections due to gram-negative organisms. And I think it might be appropriate to mention that in the infectious disease field agents are broken down into groups on the basis of staining principles. The gram-negative organisms are those organisms that are usually associated in gastrointestinal infections and things of that type. The gram-positive, of which the pneumococcus is a good example, are involved in respiratory infections to a very high degree, and in skin infections. This fact stimulated the research for antimicrobial agents effective against such bacteria. In 1947, streptomycin became available after it was shown to inhibit the growth of the tubercule bacillus and a number of gram-positive and gram-negative organisms in vitro—that is, in laboratory tests—and in vivo, in animals and in man.

Dihydrostreptomycin was produced the same year. It had about the same degree of antibacterial activity as streptomycin, but its use is fraught with a high risk of producing irreversible deafness.

The development of the tetracyclines followed penicillin and streptomycin. The discovery of these agents was the result of a system screening for antibiotic-producing organisms of soil specimens collected from many parts of the world. The first of these compounds, chlortetracycline, was introduced in 1948. Two years later, oxytetra-

cycline became available and, in 1952, tetracline—that is the basic chemical entity of both oxytetracycline and chlortetracycline—came into use. In 1959, demethylchlortetracycline became available for general use.

The tetracyclines are effective against rickettsia, a number of gram-negative and gram-positive bacteria, and the agents responsible for lymphogranuloma venereum, inclusion conjunctivitis and psittacosis. These are somewhat exotic diseases, but nevertheless represent, in large portions of the southern United States for the first two, and across the whole country for the last, significant disease problems in this United States.

The tetracyclines, because they were active against some types of infections, therefore became known as broad spectrum antibiotics. Although claims have been made for the superiority of some tetracyclines over others, their chemical, antimicrobial, pharmacological, and therapeutic properties are, with some exceptions, very much alike.

Senator NELSON. You say claims have been made for the superiority of some tetracyclines over others. What are you referring to?

Dr. LEY. Mr. Chairman, in the differences among tetracyclines the spectrum of activity is essentially identical for all. There are differences in performance and absorption and in the amount of tetracycline required to produce a given blood level among the various chemical manipulations of the tetracycline complex. So that the differences are chiefly in the mode or quantity of administration, so that with one product you may be able to maintain blood level after starting therapy by taking only one tablet a day, whereas with another product you may have to take several tablets or capsules several times a day to achieve the same blood levels.

Senator NELSON. Are they compounded in different ways with a specific purpose in mind?

Dr. LEY. No. The tetracyclines as a group have only excipients or inactive materials compounded with them, as we have discussed so far in the testimony. There are differences in the formulations, but these differences have no relationship in general to the way the product performs.

Senator NELSON. So in terms of the production of the drug, that is, the combining of excipients, this isn't done for the specific purpose of reaching a certain blood level at a certain time to meet a certain disease circumstance, and another one compounded in a different way to sustain a different blood level at a different time for a different disease situation, you are not saying that?

Dr. LEY. No, Senator. The changes in formulation that are characteristic of this group of drugs considered so far are simply changes that have been established by the various manufacturers to either stimulate killing or to provide greater stability for the active material in the capsule.

Senator NELSON. And your conclusion is that, with some exceptions, they are very much alike. What kind of exceptions are you referring to?

Dr. LEY. The exceptions are essentially all in the area of dosages required to achieve a given blood level. In terms of therapeutic response they are identical.

Senator NELSON. Does the blood level in any one of these circumstances make any difference in terms of the treatment?

Dr. LEY. It does make a difference in terms of treatment. Our knowledge of the exact relationship of a blood level to a cure in the disease process is very elementary today. But we do know that a product that is introduced should produce a blood level within a certain range of levels. So that the objective with any one of these tetracycline materials is to tailor the dose to the patient to achieve blood levels within a certain range. And this is a very important part in the manufacturers' establishment of the proper dose of the product for a patient in the investigational phases.

Senator NELSON. But then each individual manufacturer would provide his own instructions as to what dosage to prescribe; is that correct?

Dr. LEY. That is correct.

Senator NELSON. And there aren't any clinical studies, did I understand you to say, that would prove that one particular blood level achieved by one brand product was any different in its effect from the drug level achieved at a particular time by another product; is that correct?

Dr. LEY. As long as the blood levels are roughly comparable there is no difference in clinical response.

Senator NELSON. Please continue.

Dr. LEY. Other antibiotics also became available in this period of postwar discovery—chloramphenicol, which has been the subject of discussion in this committee in past hearings, erythromycin, the cephalosporin, oleandomycin, triacetyloleandomycin, neomycine, paromomycin, kanamycin, polymixin-B, colistin, bacitracin, lincomycin, and many others.

Senator NELSON. These hearings have covered the area, not completely, but fairly extensively, of the promotion of the use of drugs either by detail men, by literature, directives sent to doctors, or by advertising in the medical press and the medical journals.

And the question has been raised here a number of times by witnesses and by me about the nature and the character of the promotion used by the drug companies.

I think this is the appropriate place in the record to insert a rather disgraceful example of the promotion of drugs. I have a letter from the Veterans' Administration hospital at Madison, Wis., from Dr. William R. Merchant—whom I do not know—who is director:

DEAR SENATOR NELSON: Knowing of your interest in the price of drugs I thought that the enclosed advertisement might be of interest. This is one of the most brazen unethical forms of advertisement that I have seen carried out by a pharmaceutical company. In my role as the director of the Veterans Administration Hospital I would not accept such a remuneration, but in talking with my other colleagues we agreed that this would be highly unethical for a private physician. I share with you the feeling and wish that this kind of expenditure would be taken off the price of drugs. I have returned the original check to the company, and enclose a copy of the letter that I wrote to Mr. Wimbley of the Marketing Research Department. Also enclosed are Xerox copies of both sides of the check.

I would like to take this opportunity to thank you for the support you have given the Madison Veterans Hospital. And if there is any way we can be of service I hope you will call upon us.

And he enclosed an advertisement for Lincocin. This is the ad and the literature that was sent. And there is also enclosed a $5 check dated April 11, 1969, the Upjohn Co., made payable to the order of W. Merchant, M.D., the sum of $5, void 60 days after date, the First National Bank & Trust Co. of Kalamazoo, Mich., signed by C. J. Swope. Inserted in the ad it says:

You will find a $5 check in your mail piece, because the cancelled check from you and a few selected other doctors will provide an efficient measure of how many doctors were exposed to this particular mail piece with a minimum of inconvenience to you. Please be assured that a check made out to you appears only in the mail piece received by you. Before you cash or deposit the check please answer the brief questions on the back. The information generated by this survey will be used to help us improve our communications with you and your fellow physicians.,

Thank you.

THE UPJOHN COMPANY.

P.S.—If you have any questions regarding this survey please write to Charles L. Wimbley, Marketing Research Department, The Upjohn Company, Kalamazoo, Michigan.

I just insert this in the record at this point. I think it speaks for itself. And I think it raises some very serious ethical questions. But if it does nothing else, it raises the price of the drug. And the consumer will have to pay for it. I won't draw any conclusions about the ad or ask you to. I think it speaks very loudly for itself.

(The documents follow:)

VETERANS' ADMINISTRATION HOSPITAL,
Madison, Wis., April 17, 1969.

Mr. CHARLES L. WIMBLEY,
Marketing Research Department, The Upjohn Co.,
Kalamazoo, Mich.

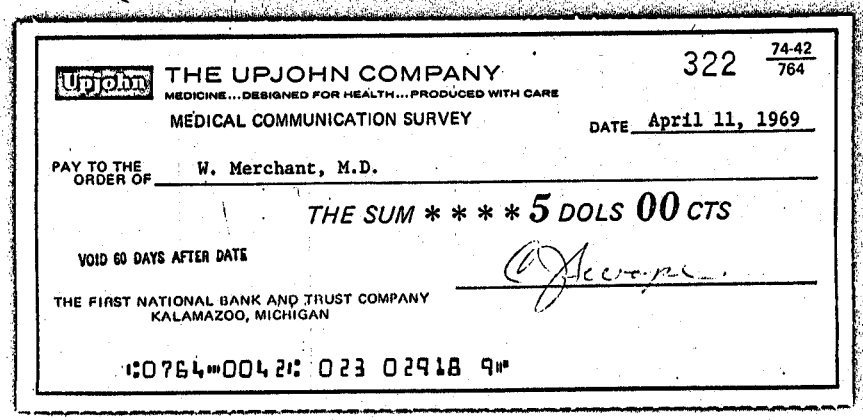
DEAR MR. WIMBLEY: Enclosed is a check made out in my name for the sum of $5.00, which apparently was to be given to me for taking part in some type of medical communication survey.

In the first place, I am the Director of the Veterans Administration Hospital at Madison, Wisconsin, and under no circumstances could accept such remuneration. In the second place, even if I were a physician in private practice, I would consider it most unethical to accept such a sum. I do not think that this form of advertising or survey can help the image of your drug firm.

Sincerely yours,

WM. R. MERCHANT, M.D.,
Hospital Director.

FACE:



REVERSE:

1.) WHO FIRST DISCOVERED THIS CHECK?

a.) _____ YOURSELF

b.) _____ SOMEONE ELSE

IF SOMEONE OTHER THAN YOURSELF DISCOVERED IT, PLEASE ANSWER QUESTION NUMBER TWO.

2.) WOULD THIS MAIL PIECE ORDINARILY HAVE BEEN PASSED ON TO YOU IF THERE HAD BEEN NO CHECK IN IT?

a.) _____ YES

b.) _____ NO

in pneumonia and other bacterial infections of the respiratory tract

special delivery

rapidly absorbed: peak serum levels at 30 minutes after I.M. administration; in 2 to 4 hours after oral administration

widely diffused: significant drug levels demonstrated in the majority of body tissues (including fluids and bone)

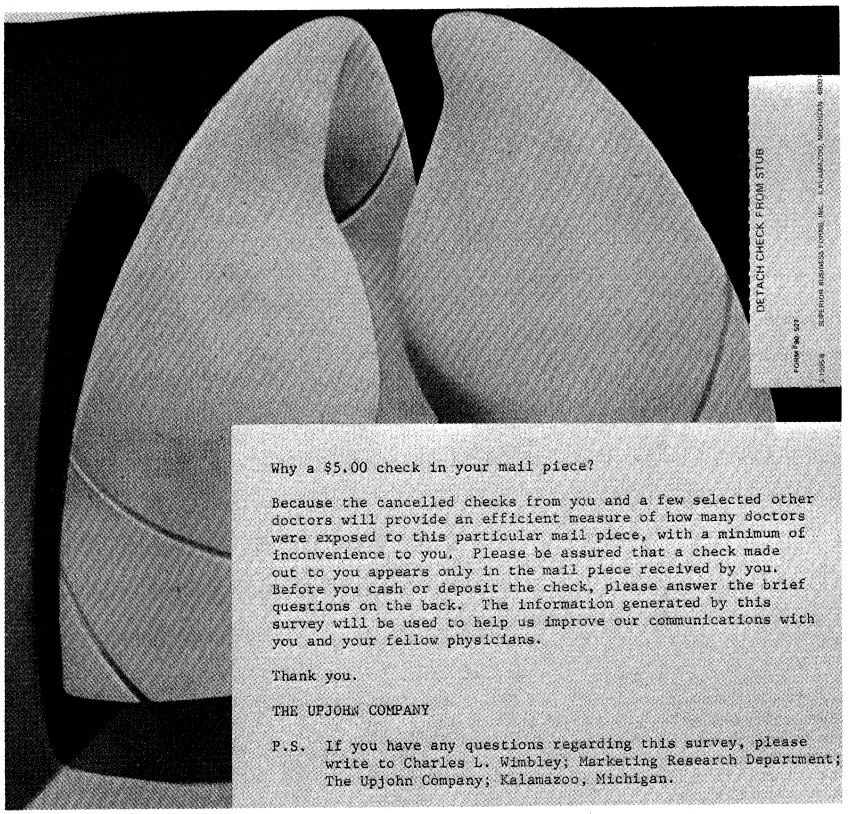
Lincocin (lincomycin hydrochloride monohydrate, Upjohn) is indicated, subject to appropriate culture and susceptibility studies, **in infections caused by susceptible gram-positive organisms, particularly staphylococci, streptococci and pneumococci**—pathogens responsible for the majority of infections seen in daily practice. Lincocin should not be used for the treatment of viral or minor bacterial infections.

The most common side effect with Lincocin is looseness of stools or diarrhea. Cases of severe and persistent diarrhea have been reported, some with blood and mucus, at times necessitating discontinuance of the drug. This side effect has been associated usually with oral but occasionally with parenteral therapy.

And when the infection is severe, parenteral Lincocin may be preferable. Patients have demonstrated excellent local tolerance to intramuscular administration; reports of pain following injection have been infrequent.

■ 500 mg. capsules ■

Lincocin®
(lincomycin hydrochloride monohydrate, Upjohn)



Why a $5.00 check in your mail piece?

Because the cancelled checks from you and a few selected other doctors will provide an efficient measure of how many doctors were exposed to this particular mail piece, with a minimum of inconvenience to you. Please be assured that a check made out to you appears only in the mail piece received by you. Before you cash or deposit the check, please answer the brief questions on the back. The information generated by this survey will be used to help us improve our communications with you and your fellow physicians.

Thank you.

THE UPJOHN COMPANY

P.S. If you have any questions regarding this survey, please write to Charles L. Wimbley; Marketing Research Department; The Upjohn Company; Kalamazoo, Michigan.

Senator NELSON. Go ahead, Doctor.

Dr. LEY. Combination therapy with antibiotics began almost as soon as two such agents became available.

As new antibiotic entities were developed, their use in combination preparations was quick to follow. Shortly after streptomycin was developed, it was mixed with penicillin and recommended for use in situations in which the cause of the infection was not readily apparent. This was followed in 1950 by the use of penicillin-sulfonamide combinations for the enhancement of the antibacterial action.

In the same year, penicillin was combined with dihydrostreptomycin for use, in the words of some of the promotional material for the product:

> * * * in the treatment of peritonitis, mediastinitis, brain abscess or conditions in which the causative organisms cannot be identified * * * mixed infections, common in the respiratory or urogenital tract * * * [and] for prophylaxis in surgery * * *

I would add parenthetically that this combination has been off the market for several years.

In 1952 penicillin was marketed in combination with APC and antihistamines. For those who have not had close contact with the medical profession, APC is aspirin, phenacetin and caffeine—a sort of glorified aspirin. This combination was recommended for the relief of symptoms and the prevention of complications of the common cold and other acute upper respiratory infections.

In 1955, tetracycline was combined with vitamins.

Senator NELSON. What was the rationale of that combination?

Dr. LEY. I have no information which would lead to any statement of rationale for this combination, Mr. Chairman.

Senator NELSON. Is that still in the marketplace?

Dr. LEY. That or a similar product is currently in the marketplace, but we have recently initiated action to remove it.

Senator NELSON. In the sentence before you mentioned that in 1952 penicillin was marketed in combination with APC and antihistamines and, recommended for relief of symptoms and the prevention of complications of the common cold and other acute upper respiratory infections. By whom was it recommended for that?

Dr. LEY. By the manufacturer.

Senator NELSON. Were there any scientifically controlled studies that indicated that it had any efficacy at all for this purpose?

Dr. LEY. To the best of my knowledge, the scientific studies in support of this claim were extremely limited if present at all. I have no personal knowledge of this file, but I would point out that this was 1952, 10 years before the enactment of the Kefauver-Harris amendment.

Senator NELSON. At which time proof of efficacy was not necessary?

Dr. LEY. That is correct.

Senator NELSON. Is that still marketed?

Dr. LEY. Dr. Jennings informs me that he believes this product is still marketed today.

Senator NELSON. So 18 years have gone by, or almost 18 since it was marketed in 1952. Are you aware of any well-controlled studies as of this date that indicate that this drug has efficacy?

Dr. LEY. Absolutely none, Senator.

Senator NELSON. The company has produced none for the FDA?

Dr. LEY. Absolutely none.

Senator NELSON. Thank you.

Dr. LEY. In 1956, tetracycline appeared in combination with APC and the antihistamine, chlorothen citrate. The original labeling for the product read:

> * * * for the palliation and treatment of the common cold and for the relief of the symptoms such as headache, muscular aches and pains, prevention of secondary bacterial infections, and relief of mucus and nasal discharge accompanying such a cold.

Later that year, a competitor combined tetracycline with glucosamine, APC, and the antihistamine, buclizine hydrochloride.

Senator NELSON. Are there any well-controlled studies which indicate that these two combinations are effective for the purpose for which they were promoted?

Dr. LEY. Absolutely none.

There is one reservation in that although the efficacy requirements were not formally established for drugs as a whole, there were requirements for demonstration of efficacy of a sort for antibiotic compounds. In this case the requirements were oriented specifically to the antibiotic component, so that it had to have available adequate evidence of efficacy for it as an antibiotic. But there was no requirement for data to support the elaborate claims for relief of mucus, and so forth, and so on, for the other components of the product. So that the antibiotic situation has been somewhat unique in that there has always been a minimum requirement for efficacy data to support the efficacy of the antibiotic portion of such components.

Senator NELSON. But not for the APC?

Dr. LEY. Not for the APC. Mr. Goodrich.

Mr. GOODRICH. This was limited to five antibiotics until 1962, when Congress brought all of the antibiotics under the effectiveness requirements. I believe between 1950 and 1962, a large number of these antibiotics were introduced through the new drug procedures in which proof of effectiveness was not required.

Dr. LEY. In 1956, a combination of tetracycline and oleandomycin was marketed in capsule form under the trade name Signemycin.

In 1958, a combination of tetracycline and novobiocin was introduced to the medical profession under the trade name Panalba.

In 1960, tetracycline and amphotericin-B were combined and marketed under the trade name Mysteclin-F. This drug was represented to provide simultaneous antimicrobial therapy and antifungal prophylaxis.

And again, for general awareness, a fungus is an infectious disease organism somewhat like bread mold capable of causing infections in man, but a little different than the ordinary bacteria and the streptococcus or staphylococcus.

Senator NELSON. Is there anything to be gained from a therapeutic standpoint in administering these two drugs in fixed combinations in administrative dosages?

Dr. LEY. No, in my opinion there is not any justification for a fixed combination of these two products. There may be on occasion justification for separate administration of such drugs as amphotericin-B

in the control and treatment of functional combinations of antibiotic therapy. But as a fixed combination, no.

The immediate commercial success of many of these antibiotic combinations was remarkable. Mysteclin-F and Panalba have been among the 200 most prescribed drugs since 1961. Signemycin was on this list in 1961, 1963, and 1964.

Senator NELSON. How would you secure your data on the most widely prescribed drugs?

Dr. LEY. Senator, we have to utilize the listings provided by industry. There are several services which provide measures in terms of number of prescriptions or number of dosage units or number of dollars involved in the sale of a particular drug over a year's period. One of the most widely known of these is the Gosselin survey, with which I am sure you and your staff are familiar.

Senator NELSON. The thought occurs to me, batch testing wouldn't give you any indication, would it?

Dr. LEY. The certification which these products undergo before they are released to the market will give you a figure for the total volume of product that has been transmitted by the manufacturer to his distribution system. They will not necessarily give you an accurate measure of the amount sold during a year.

Senator NELSON. Are you satisfied that the surveys that are done such as Gosselin that list 200 most widely prescribed drugs are reasonably accurate listings.

Dr. LEY. These surveys, Senator, are performed on the basis of an elaborate sampling procedure, and are generally dependable. As you are quite well aware, however, even such elaborate sampling services as the Gallup poll have failed to predict certain political outcomes in an election. But in general this type of sampling is very good. It is the best we can come up with.

Senator NELSON. Thank you.

Dr. LEY. Other antibiotic combinations that I haven't previously mentioned also made this "best seller" list of drugs with some frequency. For example, Pentid-Sulfa made the list six times, Ilosone-Sulfa and Tetrastatin five times each, and Declostatin four times.

The efficacy of these antibiotic combinations in practically every case was supported almost solely by in vitro studies; that is, test tube type" evaluations comparing combination preparations and single entities. These tests generally showed that the combinations produced increased antibacterial activity, with organisms exposed to the combination building up resistance at a slower rate. But, in general, there was a striking lack of data from carefully controlled, critically evaluated clinical studies to test these drugs in the treatment of disease. In short, the evidence of effectiveness was inadequate in terms of today's legal requirements.

The type of "substantial evidence" now required to support efficacy claims was defined in the Kefauver-Harris drug amendments of 1962. These amendments not only provided that new drugs marketed thereafter must be proven effective, as well as safe, but also authorized a review of the efficacy of all drugs, including antibiotics, introduced from 1938 to 1962.

Even while this legislation was being considered by the Congress, concern was expressed by some medical leaders about the use of combination antibiotics. As a result, the FDA convened a panel of experts in 1963 to evaluate the prophylactic use of antimicrobial agents in combination with analgesics, antihistamines, and other drugs.

This panel concluded there was no acceptable evidence that any antimicrobial agent is of value in the treatment of either the common cold or any viral infections except those caused by certain large viruses.

I might elaborate very briefly here. The certain large viruses referred to are the group of psittacosis, lymphogranuloma venereum, and inclusion conjunctivitis, or trachoma. These are quite different from the flu or influenza or the common cold viruses, against which antibiotics have absolutely no effect. So that one should not confuse this phrase, "certain large viruses," with disease processes with which anyone in the room is familiar.

The panelists also concluded that antimicrobial agents are of no value—and should not be used—for the prevention of bacterial complications in patients with common colds who are otherwise healthy.

Senator NELSON. You are only taking a limited type of case, if I understand it correctly; one in which it is the doctor's judgment in the case of a particular patient whom he has taken care of for some time that it would be wise for him to administer it as a prophylactic to avoid the possibility of some bacteria attacking the patient in this particular circumstance; is that what you are saying?

Dr. LEY. That is right.

When prophylactic therapy of respiratory infection is justified, the panel said that only antimicrobial agents relatively free of inherent toxicity should be used. This recommendation precluded the use of chloramphenicol, triacetyloleandomycin, and sulfonamide products.

The panel generally did not favor fixed combination products containing antimicrobials. With regard to combinations of antimicrobials with antifungal agents to suppress monilial—and monilial is a specific type of fungus—overgrowth, the panel considered it acceptable to permit a statement to the effect that such combinations may effect a diminution in the fungal population, if it was also stated that the combinations had not proved therapeutic value against fungal infections.

Mr. GORDON. If there is no proof of therapeutic value, why wasn't this drug taken off the market instead of just changing the label?

Dr. LEY. Mr. Gordon, you must remember that this panel—and I am paraphrasing the panel recommendation—met in 1963, essentially at the time that the drug amendments went into effect. So that their comments have to be weighed in the light of the absence as of that time of an effective means of pressing for efficacy data. Now, subsequently in my statement I will explain the approach that the agency has taken to close this gap in the scientific information supporting drug products as a group.

Senator NELSON. But is it not correct that the panel back in 1962 was proceeding after the passage of the Kefauver amendment which requires proof of efficacy? Is that correct?

Dr. LEY. I believe the panel met in the intervening period between the passage of the bill and the date it went into effect.

Mr. Goodrich, would you fill in the details here?

Mr. GOODRICH. There was a lagtime, Senator, between the enactment in 1962 and 2 years later, October 10, 1964, when the new effectiveness provisions went into effect. This panel did recommend changes in the labeling for these combination products. The statement will show in the next paragraph that those changes were made. The particular one discussed here is Mysteclin-F, I take it, or that type of product which has not been acted on until quite recently.

Senator NELSON. But the law was in effect, and it provided, as I recall, that the companies were given 2 years in which to produce controlled studies to prove efficacy; is that not correct?

Dr. LEY. Quite right. And after the passage of the 2 years, in October 1964, the agency had the legal authority to move ahead. It did not move ahead until 1966, when Dr. Goddard obtained the assistance of the National Academy of Sciences to review the effectiveness, and in effect there was a further lag on our part of that 2 years.

Senator NELSON. The fact is, though, that the Congress amended the statute—in October, was it?

Mr. GOODRICH. October 10, 1962, when it became effective, with a 2-year lagtime for review of effectiveness.

Senator NELSON. So it is now 6½ years after the act was passed; is that correct?

Mr. GOODRICH. Yes.

Senator NELSON. On October 10 this year it will be 7 years. So all companies have had 6½ years' notice and opportunity to produce well-controlled studies that meet the statutory requirement to prove efficacy of the drugs; is that not correct?

Dr. LEY. That is perfectly correct, Senator.

As a result of the proposal and the comments received, significant labeling changes were made. The recommended dose of the antibiotic was increased to therapeutic level and a labeling statement was added recommending that the patient be switched from the combination drug to the antibiotic alone after fever and other symptoms had subsided.

The action of these medications for colds, however, was just a small step in dealing with antibiotic combinations. Many other combinations remained to be considered as part of the overall review of the efficacy of pre-1962—and subsequent to 1938—drugs. Moving forward with this gigantic task was one of the first problems that confronted Dr. Goddard when he became Commissioner of Food and Drugs in January 1966.

Senator NELSON. So there was a 2-year period in which the Food and Drug Administration was not taking any action under the law?

Mr. GOODRICH. May I say one thing on that. Dr. Jennings reminds me that the first thing we did was to require in 1964, soon after the effectiveness provisions came into effect, an initial report from the drug companies on the products they marketed certifying that the claims were supported by the clinical experience with the drug known to the company. In other words, this step called on the companies to make a self-appraisal and to eliminate unwarranted claims.

Senator NELSON. And when was this?

Mr. GOODRICH. This was in 1964, soon after the effectiveness review provision took effect. Now, the companies did make the initial report in many instances. Some, however, refused to make the report, contending that their drugs had somehow become old drugs, and not subject to the effectiveness review. So, in that respect, the agency did move. But the independent review of effectiveness on our part did not begin until the NAS–NRC support was obtained.

Dr. LEY. Dr. Goddard concluded that the review of drugs marketed between 1938 and 1962 should be conducted by outside experts of the highest distinction whose evaluations would more likely be accepted by both the medical profession and the pharmaceutical industry.

In the spring of 1966 he asked the help of the National Academy of Sciences-National Research Council to undertake the review. After successful negotiations, a contract was signed with the Academy in July 1966. I cannot overemphasize the importance of this agreement. The Academy had the capability of bringing to this work some of the best medical and scientific minds in the country. No other organization could have brought greater objectivity, expertise, or authority to this landmark study. Paramount in the decision of the Academy to do the job was its realization of the importance of the project for the advancement of drug therapy and consequent benefit to the public.

Mr. DUFFY. Doctor, if I may, I am somewhat puzzled by your statement regarding the objectivity of the NAS–NRC panels. Considering the testimony of some of the witnesses from the Council before this committee I think it is fairly well substantiated in the record that the conclusions that were reached were conclusions that at least the witnesses testifying before this committee could have reached and did reach before they actually went through the process of arriving at their panels decisions.

Dr. LEY. The facts upon which the panels based their recommendations were three in number. On the next page of the statement you will find that the judgments of the panels were based on the following criteria: Factual information that is freely available in the scientific literature; (2) factual information that is available from the FDA, from the manufacturer or other sources. There was a very elaborate mechanism provided for each manufacturer to submit to the Academy what in his opinion were the most significant and important data in his files supporting the efficacy of the drugs; (3) as the last basis of judgment, on the experience and informed judgment of the members of the panel.

The conclusions reached in the form of recommendations on each drug product, or its stated indications by the panels are essentially a group opinion on the part of all the members of the panel, six in number. The members of the panel had access to every bit of material that were provided by the manufacturers to the panel. It was the manufacturers belief that this data completely supported the efficacy of their products.

The panels evaluations, based on these three factors, I think were reasonably objective. We did, however, permit a third category consisting of the informed judgment of the panel members in terms of their own clinical experience as one of the elements upon which to base the final recommendation. I believe there was every reason to

say that the process was objective. Furthermore it did involve the firms and their body of information to as great a degree as the firm chose to involve themselves.

May I continue, Mr. Chairman?

Senator NELSON. Let me say this. I understand each one of these distinguished panels offered to the company whose product was involved the full opportunity to prove the case with demonstrated examples of scientifically controlled studies pursuant to the standard established in the statute under the Kefauver-Harris amendments; is that correct?

Dr. LEY. That is absolutely correct.

Senator NELSON. And these companies 5 and 6 years after the law was passed, and in some cases 10 and 15 years after they started marketing the drug, were unable to produce for the panels, for their review, scientifically controlled studies; is that not the fact?

Dr. LEY. This is correct with many of the drugs considered. With other drugs the panels did reach the judgment that the data presented supported efficacy. But in speaking of the combination antibiotics, the panel, after reviewing all the material that the manufacturer had been able to collect over this period from 1962 until roughly 1966, when it was submitted to the Academy——

Senator NELSON. My question was addressed only to those fixed combinations that the National Academy concluded did not meet the statutory standard of efficacy. And as to that, adequately controlled studies were not produced.

Dr. LEY. Adequately controlled studies were not produced.

Senator NELSON. And as I understand it, the recommendation of each of the five panels on the fixed combination antibiotics was unanimous?

Dr. LEY. That is correct.

Senator NELSON. Isn't it also correct that the scientific community, involving those who were expert on the use of these various drugs, concluded a good many years ago that fixed combinations were not efficacious?

Dr. LEY. There were many members of the scientific community who concluded and spoke very vigorously that fixed combination antibiotics were an illogical and irrational therapeutic tool as early as 1952.

Senator NELSON. Do you recall a 1957 article by Dr. Dowling, who is past chairman of the AMA Council on Drugs, in which he took this position?

Dr. LEY. Yes, sir.

Senator NELSON. I think I have already put this in the record. But are you aware that the AMA Journal itself has editorialized very strongly against fixed combinations over a period of years?

Dr. LEY. I am aware of that.

Senator NELSON. I think this would be an appropriate place to put in the record a memorandum by Dr. Max B. McQueen of the FDA. This point was made before the Fountain committee on May 13, and presented to the Fountain committee at that time, but it did not receive much notice. Are you familiar with the memorandum from Dr. McQueen, to Dr. Paul Bryan respecting the studies that your inspector, Roy Sanberg, obtained from the Upjohn Co. files on March 7, 1969?

Dr. LEY. Yes, sir.

Senator NELSON. I would ask that the whole memorandum be printed in the record.

(The document follows:)

U.S. MEMORANDUM

APRIL 29, 1969.

To: Dr. Paul A. Bryan, DESI.
From: Dr. Max B. McQueen.
Through: Dr. Alan Smith, DAD.
Subject: "Panalba" (novobiocin-tetracyline hydrochloride) Review of records obtained by FDA inspector, Mr. Roy D. Sanberg from the Upjohn Company on March 7, 1969.

Submissions Nos. 1, 2 and 3

There were two groups of letters to The Upjohn Company that were reviewed. In group #1 approximately 75 physicians and dentists reported favorably on the action taken by The Upjohn Company and the use of Panalba. In group #2 approximately 30 physicians reported they did not favor the combination drugs including "Panalba". In group #3, were letters to the company from physicians, laymen and drug detail men (Upjohn), all of which were unanswered by the company at the time of the inspection. There were twenty (20) letters commending the company and *praising* "Panalba," and one reply from a physician condemning the company's stand on combinations. This distribution of "pro" and "con" seems to follow the pattern of previous letters from drug firms to physicians with greater response in favor of the company than government regulation concerning drugs.

Submission No. 4

There are eight adverse reactions included in this submission as associated with "Panalba" from 1966 through 1968. Six cases are diagnosed as urticaria and one (1) case of jaundice. The one case of aplastic anemia occurred after one course of "Panalba" and three courses of chloramphenicol.

Submission No. 5

This section of the material collected during the inspection consists of separate documents of blood levels and clinical studies related to the novabiocin-tetracycline hydrochloride combination from 1957 to 1969. These will be discussed in order of their appearance in the assembled records.

1. This is a randomized clinical study of 62 cases of oral and upper respiratory tract infections conducted by Bennett W. Billow, M.D. (date not indicated). Thirty (30) cases were treated with Panalba and 32 with a placebo (drug entity not given). No laboratory diagnosis was given. Results are stated as 18 responding satisfactorily to Panalba an 19 to placebo. Ten (10) improved on Panalba and 10 on placebo. There was no change in 2 on Panalba and 5 on placebo. This clinical study would be classed as "cannot be evaluated" by present evaluation standards.

2. Reports of four (4) crossover studies comparing various "Panalba" dosage forms with novobiocin alone and tetracycline alone. These studies clearly indicate the marked depression of novobiocin serum levels to sub-therapeutic levels when given in combination with tetracycline. (These reports are dated May 18, and 23, July 21 and August 17, 1960).

3. This report of one crossover study dated November 14, 1960 comparing novobiocin and tetracycline serum levels alone and levels of both after "Panalba" re-confirm the marked depression of novobiocin levels and moderate lowering of tetracycline serum levels with the combination drug when compared to each component drug given separately.

4. This is a report of a double blind clinical study submitted by Bennett W. Billow, M.D. using tetracycline alone and the "Panalba" combination. There were 25 cases in each group (each stated to be moderately to severely ill) with a pneumonia treatable with a tetracycline. Quoting the investigator, "Results of our investigation and laboratory studies unequivocally proved to use there was no difference between 58 M and 57 M, clinically or laboratorywise. There were no toxic reactions in either group. The rapidity of action, as well as therapeutic results, was practically the same in both studies."

In addition to the above study, five patients from each group had 4 bloods drawn—a total of 40 blood specimens. Serum activity in undiluted serum and three dilution were tested against five bacterial species. The results showed no appreciable difference in vitro activity of serum from patients treated with tetracycline alone and those treated with the novobiocin-tetracycline combination.

5. This report consists of clinical studies from three investigators who submitted a total of 106 cases. The majority of cases were upper respiratory infections, many with negative cultures or normal floura reported. Of the patients treated with "Panmocin" (tetracycline hydrochloride) response was rated as good to excellent in 38 individuals, compared to 36 so rated after treatment with Panalba (novobiocin-tetracycline hydrochloride).

7. This clinical study of 44 patients in the pediatric age group was conducted by James A. Dugger, M.D. during March and April 1960. The patients were diagnosed as respiratory infections (pharyngitis, otitis media and bronchitis) and soft tissue infections (paronychia—2 cases). All were treated with "Panalba" drops in doses ranging from 50 mg tetracycline and 25 mg novobiocin T.I.D. to 100 mg tetracycline and 50 novobiocin T.I.D.

Comment: These were clinical diagnoses, no laboratory diagnosis is reported. therefore proper evaluation of the treatment results cannot be made

8. This report consists of an eight volunteer cross-over study using single doses of tetracycline hydrochloride 250 mg, 125 mg novobiocin, 250 mg tetracycline hydrochloride and 125 mg novobiocin in drop and granule dosage forms. Serum from all bloods drawn at 2–4–6 and 12 hours failed to inhibit growth of two strains of staphylococcus aureus—1 resistant and 1 sensitive. The combination drugs rated no better than the tetracycline alone.

9 and 10. Reports of a clinical study submitted by Charles H. Fish, M.D. on the comparative therapeutic effect of tetracycline versus tetracycline and novobiocin in 38 children with shigellosis. The protocol and controls are considered satisfactory. Results were good in all cases however 8 cases treated with tetracycline are reported as relapses versus 2 relapses of those treated with the combination.

Comment: These findings cannot be explained since novobiocin is of *no* therapeutic value in shigellosis.

11. This report gives results of a 8-man, 4-way crossover blood level study comparing tetracycline-novobiocin drops, tetracycline-novobiocin drops, tetracycline-novobiocin granules, tetracycline and novobiocin. Tetracycline values were approximately the expected however novobiocin levels were erratic and very low.

Conclusion: The tetracycline 250 mg/2.5 ml and novobiocin 125 mg/2.5 ml combination should be considered unsatisfactory from this particular crossover study.

12. This mouse toxicity study shows no synergestic toxicity of an equal part tetracycline-novobiocin mixture.

13. This letter is a supplemental report on the use of "Panalba", "Albamycin" and "Albacillin". No pertinent information is presented for the purpose of this review.

14. This report concerns a crossover study of 10 subjects given 2 capsules containing 250 mg each of tetracycline phosphate and novobiocin the first dose. Five days later the subjects were crossed over and given 4 capsules 500 mg each of the two drugs.

Comment: Both tetracycline and novobiocin serum levels are depressed.

15. This summary of a clinical study of 425 individuals treated for a variety of infections (except 75 individuals with normal knee joints used as controls in the study of knee joint infections). The study is in the form of a testimonial and cannot be evaluated. Since this study was reported in 1957 by Dr. Murrill M. Szucs, it is doubtful if any copies of his actual studies still exist.

16. This is a testimonial letter from Dr. Jack Weiner reporting on results of treatment of one case of cystic acne and suppurativehidradenitis. No comment necessary since complete details of the case are not included. Dated January 1957.

17 and 18. Communication from Dr. Arthur P. R. James to Dr. Dugger of Upjohn Labs. concerning treatment of acne with novobiocin-penicillin and tetracycline-novobiocin combinations. #18 consists of 92 case reports of dermatologic cases (clinical diagnosis only). These cannot be evaluated under present requirements.

19. This is a duplicate of report #9.

20. This report dated February 17, 1969 gives the results of a blood serum level study after single doses of—

a. One "Albamycin" capsule (novobiocin sodium) 250 mg

b. Two "Albamycin-T" capsules (novobiocin sodium, 125 mg and tetracyclinic HCl, 125 mg)

c. Two "Panalba" capsules (novobiocin sodium 125 mg and tetracyline phosphate comples, 250 mg)

d. Two "Panalba" capsules Revised (novobiocin sodium micropellets, 125 mg and tetracycline HCl, 250 mg)

Note: This report has been submitted by Upjohn as a part of IND 5517.

Discussion: This study shows again the low novobiocin serum levels (approximately 35%) obtained with the present marketed combinations "b." and "c." when compared to the standard "a." (100%) containing novobiocin alone in the same 250 mg dose. The "Panalba" capsules Revised with novobiocin sodium micropellets give serum levels which approach (85%) the 100% of the "Albamycin" capusle.

Conclusion

For approximately ten years it has been observed from blood serum level studies that the "Panalba" (novobiocin and tetracycline) combination results in markedly lowered and occasionally zero blood serum levels of novobiocin and the tetracycline serum level is slightly lowered. This would serve to defeat any purposeful effectiveness the two drugs may have had in combination and certainly leaves a great doubt whether this combination has ever been more or even as effective as tetracycline alone in the spectrum in which tetracycline is expected to be effective.

MAX B. MCQUEEN, M.D.

Senator NELSON. Also I would ask if you could supply us with the study they made. Is it a very bulky one?

Dr. LEY. The actual volume of the comments on this—this is a summary memorandum of the review of the individual records, and may represent a mere summary of the total information available. The information, Dr. Jennings tells me, runs to two volumes, which would be about 4 inches of paper.

Senator NELSON. I would just like to read into the record an excerpt from Dr. McQueen's report and then ask a question or two. These reports, as I understand it, were obtained by your inspector from the files of the Upjohn Company, is that correct?

Dr. LEY. That is correct.

Senator NELSON. And they had not been supplied voluntarily by the Upjohn Company to the FDA?

Dr. LEY. That is correct.

Senator NELSON. And these were reports of studies made by the Upjohn Company itself, or whomever they selected to make the study, is that not correct?

Dr. LEY. They utilized, I think, exclusively physicians outside of Upjohn to perform the clinical investigations.

Senator NELSON. So these are Upjohn's own reports, studies on its own drug Panalba. Here is an excerpt from Dr. McQueen's report:

Reports of four crossover studies comparing various Panalba dosage forms with novobiocin alone, and tetracycline alone. These studies clearly indicate the marked depression of novobiocin serum levels to subtherapeutic levels when given in combination with tetracycline. These reports are dated May 18 and 23, July 21 and August 17, 1960.

Would you like to comment on the meaning of that statement?

Dr. LEY. The meaning of that statement, Senator, is that when you compare blood levels of patients given tetracycline and novobiocin alone, against those receiving the combination of tetracycline plus

novobiocin, the novobiocin blood level in the patient who receives the combination is less than the blood level observed in the patient who received the same amount of novobiocin alone. It is markedly depressed.

Senator NELSON. The language here is that in that test the novobiocin serum levels went to subtherapeutic levels.

Dr. LEY. In all fairness I must say that I would have phrased this somewhat differently. Our knowledge at this time, Senator, of the exact relationship between a blood level and a therapeutic result in a patient is very, very poor. So that I would have qualified that to apparently subtherapeutic levels. It is a minor point. But I think it is important to make it for the record. The fact is that the level decreased markedly, to the degree that there is reasonable doubt that the novobiocin in the combination was therapeutically effective in the patient. With that I would certainly agree.

Senator NELSON. Then this continues:

This report of one crossover study dated November 14, 1960 comparing novobiocin and tetracycline serum levels alone and levels of both after Panalba, reconfirmed the marked depression of novobiocin levels and moderate lowering of tetracycline serum levels with the combination drug compared with each component drug given separately.

He concludes, as I understand it, then, that it reduces the level of the tetracycline too.

Dr. LEY. To a much lesser degree, I would agree with that one qualification.

Senator NELSON. Now, quoting further:

This is a report of a double blind clinical study submitted by Bennett W. Billow, M.D., using tetracycline alone and the Panalba combination. There were 25 cases in each group, each stated to be moderately to severely ill with a pneumonia treatable with tetracycline.

Now Dr. McQueen is quoting from the Upjohn Co.'s report of its own investigator:

Results of our investigation and laboratory studies unequivocally prove to us that there is no difference between—

And this is the code number—

58M and 57M clinically and laboratory-wise. There were no toxic reactions in either group, and reactions as well as therapeutic results were practically the same in both studies.

So as to this study, I take it they are concluding that there was no difference between the combination and its therapeutic effect and tetracycline administered alone, is that correct?

Dr. LEY. That is exactly correct.

Senator NELSON. Quoting again from Dr. McQueen's report:

This report concerns a crossover study of some subjects given two capsules containing 200 million grams each of tetracycline phosphate and novobiocin the first dose, and five days later the subjects were crossed over and given four capsules containing 5 million grams each of the two drugs. Comment: Both tetracycline and novobiocin serum levels are depressed.

What does that mean?

Dr. LEY. That means that neither the tetracycline nor the novobiocin absorb or produce as high blood levels when given in combination as when given individually.

Senator NELSON. Then I would just read from the conclusion of Dr. McQueen:

For approximately 10 years it has been observed from blood serum level studies that Panalba, novobiocin and tetracycline combination results in markedly lower and occasionally serioblood serum levels of novobiocin, and the tetracycline serum level is slightly lower. This would serve to defeat any purposeful effectiveness the two drugs may have had in combination, and certainly leave a great doubt whether this combination has ever been more or even as effective as tetracycline alone in the spectrum in which tetracycline is expected to be effective.

Now, did the Upjohn Co. ever at any time voluntarily advise the FDA that within its files, through its own studies, they had these findings?

Dr. LEY. No, sir. The Upjohn Co. did not so advise the FDA.

I would, however, caution, in all fairness, that this type of negative result is not necessarily the final word in drug evaluation. The basic problem of drug evaluation following the 1962 amendments was that now the firm had the responsibility to present substantial evidence of effectiveness for a drug or a combination.

These negative results can be influenced by a variety of factors. These negative results, in the absence of any positive results, means that this particular product has no place in today's maretplace. But there could be a disease condition—there is no data in our file to support it—where this combination might be shown to have positive and highly beneficial results to the patient. If such data are ever developed for this product or a comparable product, and meet the requirements of "substantial evidence," of efficacy, then those data should be recognized, and such a product, permitted in the marketplace.

But on the data available today on Panalba, this product has no place in today's market.

Senator NELSON. The issue that concerns me is—what is the obligation of the drug company to the physician and to the public?

I am sure that it would present a different kind of a case if they had several more studies, whether or not they were controlled, but with very positive results. But they didn't even have that. And yet they promoted this to the medical profession. My guess would be that—maybe you don't want to answer this—but if you picked up a Panalba promotion ad in which they cited their own studies saying this is what our studies show, would you prescribe it?

Dr. LEY. If these are the studies, Senator, no.

Senator NELSON. I think that this raises a very serious moral question. Seven years after the fact, and during which period all of these studies have been in the files, and the medical profession wasn't notified, the public wasn't notified, the FDA wasn't notified, and the drug was widely promoted, selling as high as $20 million worth in a year. And to me that raises some serious questions respecting the promotion of drugs by the drug industry.

Now, I would ask you this question—and I think it speaks for itself more eloquently than I can comment on it. And that is why I put this in the record. But I would suggest that if the truth were known about this fixed combination—and it would apply to all the rest of those drugs that the NAS has recommended be removed from the market—if the medical profession were aware of the company's own studies as

well as the promotional literature, there wouldn't be a rational doctor in America who would prescribe it. That strikes me as a shocking situation in the practice of medicine, and the promotion of drugs. It isn't the doctor's fault. He believes that this drug has been proven. But the fact is that it not only has not been proven, but there would appear to be no doubt in where a combination of studies indicated that the blood level dropped to zero, where a doctor is prescribing for a patient with the expectation that this drug will do even more than tetracycline and novobiocin in combination, there would appear to be no doubt that he is not giving his patient the best medical care; isn't that correct?

Dr. LEY. One could draw that conclusion.

Senator NELSON. There has been testimony before the committee that because of this product, because of the way the investigations of this kind are done for drug companies, that the companies ought to be required to have the investigator, who did their study, send a copy of his study to the FDA. Do you think that would serve a useful purpose?

Dr. LEY. At this time, Mr. Chairman, I do not believe that this type of loophole exists to any significant degree. It may remain for certain products which have been marketed prior to the 1962 amendments. I do not believe it is present now.

We investigated as well as we could the reason why these data had not been formally provided to the agency before hand. In 1964, as I recall, the firms were requested, as Mr. Goodrich indicated earlier, to summarize all existing material on the older products marketed before 1962, and provide a summary to the agency for review.

Now, as nearly as we can determine, these studies conducted in 1959 and 1960 by Upjohn were not summarized in the material they provided us in 1964. So that we are faced with the fact that these studies should have been provided to us in 1964. They were not, as nearly as we can determine. I believe they should have been at that time.

Senator NELSON. What makes you so confident, then, that it isn't still occurring?

Dr. LEY. I believe that firms doing investigational studies on drugs after 1962 have been far more careful and trustworthy in providing data to us. The 1962 law makes this compulsory for all firms developing new drug products. Since I have been commissioner I have yet to find an example where a firm has not been most proper in providing investigational data to us.

I think the Senator should recognize that we are speaking about a class of drugs marketed between 1938 and 1962 where FDA and industry have had strong differences of opinion. The matter was finally taken to court. Industry questioned the Agency's right to require efficacy data for this group of drug products. Mr. Goodrich can provide the background information on the various legal cases that were raised in the early days of implementating the Kefauver-Harris amendment. This particular group of drugs marketed between 1938 and 1962 has been the subject of very serious discussion and argument, concerning the extent of our authority.

Senator NELSON. Well, as I understood your testimony, you requested the companies to summarize the data that had on all their drugs that came under the purview of the law. What was the status of that request?

Mr. GOODRICH. That was a record and reporting requirement that they were to report to us an initial report certifying that the clinical claims as they appeared at that time, 1964, in the promotional material were supported by the clinical information known to the company, and that if the company had any clinical reports that did not support the claim, they were to submit the report together with a revision of their label.

And an initial report was made on this drug which certified that the claims were supported.

There were no reports of this negative finding as we look at the files today. We only received these reports through an inspection conducted earlier—just a short time ago.

Senator NELSON. And do I understand it to be your interpretation of the law that concerning the requests that the FDA made of the companies to supply them with the summary—or whatever they had—that the FDA had authority under the law to require them to do so.

Mr. GOODRICH. Yes, sir. And the failure to make a report is both a ground for suspending the product from the market and for regulatory action of a criminal nature if the report was not made as required.

Now, as Dr. Ley pointed out, with many drugs, but not with the antibiotics—there was a contention that about a thousand drugs were exempt from the recordkeeping and reporting requirements, because they had become old drugs prior to the enactment of the 1962 amendments, and that the 1962 amendments only required records and reports for those products that remained new drugs as of 1962. We contested that issue. The PMA sued us in Delaware. And the case is still pending there. And PMA has notified the court that it does not wish to press on with the case until it can learn more about the NAS–NRC study which is now underway.

Senator DOLE. Mr. Chairman.

Senator NELSON. Senator Dole.

Senator DOLE. I am still learning about all the drugs and terms, as a freshman member of this committee. But I am wondering, what is the role of FDA in determining the relative efficacy with reference to fixed combinations, with specfic reference to the letter, the report by Dr. McQueen? Is this responsibility you have in fixed combinations to determine the relative efficacy or not? Is this the matter in question.

Dr. LEY. Let Mr. Goodrich, if he will, speak to the legal aspects and then let me speak to the medical aspects.

Mr. GOODRICH. The issue no doubt that you are addressing yourself to, Senator, is the testimony of Senator Ribicoff when he was Secretary of Health, Education, and Welfare supporting the Kefauver bill when he said that we did not seek control over relative efficacy. However, where promotional material makes a relative efficacy claim, then that claim has to be supported by substantial evidence. In this case Upjohn has claimed that Panalba, the combination

of tetracycline and novobiocin, is more effective than either of the two; that it broadens the spectrum of effectiveness, that in some way these drugs are synergistic to one another, that the combination is uniquely better than tetracycline. And where that type of promotional claim is made, the company has been held to the requirement to have substantial evidence to support the claim. So it was not we that opened up the issue of relative efficacy, it was the companies' promotional materials that did so.

Senator DOLE. Is there a requirement on that issue now?

Mr. GOODRICH. I think so. I don't believe there is any dispute about that. We have had this issue confront us many times in the advertising regulation. Advertising is to sell drugs. Advertising is largely competitive. And so competitive, comparative, relative efficacy claims come into that type promotion just as they do in all advertising. What the FDA is requiring the companies to do is support those claims with the adequate back up. And I believe this is different from the pure, relative efficacy point that you raise, that the agency was not given the authority to keep a drug off the market because there was maybe a better drug on the market, so long as this company didn't claim that its drug was better than the existing product.

Dr. LEY. Mr. Dole, I would like to speak to the medical aspects of your question. In controlled studies it is customary in most testing procedures to compare a proposed new drug formulation either with an inert material, a placebo, or with another active material.

Now, the choice of whether you use an inert material or another active material depends upon the disease condition involved. It is medically unethical to test an antibiotic in a seriously ill patient with pneumonia that would kill the patient against an inert placebo. Upjohn itself manufactures a tetracyline. The promotional efforts for Panalba are that it is better than a tetracycline. Medical ethics then would dictate that Upjohn should compare its combination of tetracycline plus novobiocin against tetracyline alone to see whether the combination was significantly better than the single ingredient. One such study is reported in this memorandum which the chairman has referred to earlier today. The choice of a comparative framework for drug evaluation today must be made with due recognition of the seriousness of the patient's illness and the ethical problems involved in withholding treatment. It cannot be justified if withholding the active material from a patient would result in an increased possibility of death.

Do I make my point clear.

Senator DOLE. I think to most people you would, but I am not certain—it is my fault and not yours.

But the combination of drugs is the basic question to me. You have reviewed all these, and you have had this argument since 1966 in the National Academy of Sciences. Have there been any instances where the combination drug was superior, the fixed combination, or in every case have they been inferior and not effective?

Dr. LEY. Mr. Dole, I do not believe that in the area of systemic antibiotics—that is, drugs which would be taken by mouth or by injection for effect all over the body—that the Academy has recommended for efficacy in any one of these products in terms of a fixed

combination. Now, I am aware that in certain other areas which do not involve systemic use of an antibiotic the recommendation of the Academy will be more favorable, and for very good reasons. And that is an issue aside from the topic we are discussing here. To the best of my knowledge, the systemic antibiotics as fixed combinations have been considered inappropriate in every case that has been received and reviewed by our agency.

Senator NELSON. We will take a 5-minute recess.

(Short recess.)

Senator NELSON. We will resume the hearings.

Dr. Ley, as I recall, you were on page 8.

Dr. LEY. Yes, sir. I was going into the details of the organization of the study, Mr. Chairman.

The study was carried out under the direction of the division of medical sciences of the NAS–NRC. This Division's Drug Research Board, with additional representatives to cover all appropriate medical specialties, made up the Policy Advisory Committee (PAC), which we will refer to subsequently, that established guidelines for the review.

In the development of guidelines for the study, the Academy and the PAC made an effort to involve the pharmaceutical and medical communities to the greatest possible extent.

Senator NELSON. May I interrupt for a moment there?

Dr. LEY. Certainly.

Senator NELSON. At the time Dr. Goddard established this procedure for evaluating the efficacy of these drugs, did the industry itself approve or disapprove of this method?

Dr. LEY. We met subsequently with the members of industry, the members of the Policy Advisory Committee, and the panel chairman. Industry did actively participate in the discussion that established the categories of evaluation which were selected for reporting effectiveness. In general I saw and heard of no serious disagreement on the part of industry with the procedures as they evolved. Industry was largely represented by PMA in many of these policy discussions that established the guidelines for the efficacy review.

Mr. Goodrich was here at that time. I was not. He may wish to add a few additional comments on this matter.

Mr. GOODRICH. Only to say that, as Dr. Ley has, I have heard no objection from the pharmaceutical industry or any of its members to this method of review. And indeed Mr. Stetler did attend and participate in meetings before the Policy Advisory Committee. And there are two people from the drug industry—one with Hoffman La Roche, and the other with Merck and Co.—who serve on the policy advisory board of the NAS–NRC.

Senator NELSON. So the procedure for evaluation was participated in by the industry, and you are not aware of any criticism of the procedure?

Mr. GOODRICH. That is right. The opposition comes when an economically important drug is involved, and is coming in the legal contest to the removal of such a drug from the market.

Senator NELSON. You may continue.

Dr. LEY. A broadly representative forum was held on the guidelines prior to their adoption by the PAC. Among the other matters covered, the guidelines provided that—and these are the three points that I mentioned earlier:

The judgments of the panels will be based on the following criteria: (1) Factual information that is freely available in the scientific literature, (2) factual information that is available from the FDA, from the manufacturer or other sources, or (3) on the experience and informed judgment of the members of the panels.

Operating with in these criteria, the panels were asked originally to classify claims for drugs into one of four categories:

(a) Effective.—For the presented indication, the drug is effective on the basis of the criteria which the panel has established for its review.

(b) Probably Effective.—For the indication presented, effectiveness is probable on the basis of the operative criteria, but additional evidence is required before it can be assigned to category (a).

(c) Possibly Effective.—In relation to the indication in question, there is little evidence of effectiveness under any of the operative criteria to support claim effectiveness.

(d) Ineffective.—In relation to the indication in question, the panel concludes that there is no acceptable evidence under any of the operative criteria to support a claim of effectiveness.

Mr. DUFFY. Doctor, if I may interrupt you for a minute, I would be very interested to hear Mr. Goodrich's interpretation of the first three categories. It would seem to me that among the first three we have a question of relative effectiveness, is that not correct?

Mr. GOODRICH. No, I don't think so. The first of course is that the claims are fully supported. The second is "probably effective," that there is some evidence to support the claim, but more research is required before there can be a conclusion of the type required by law that there is adequate well-controlled evidence to support the claim.

The third, "possibily effective," is that there is little evidence of effectiveness. Now, these second and third categories were adopted by the agency to give the companies even additional time after receiving the NAS–NRC report within which to produce the kind of evidence called for by the law. It was pointed out in the hearing recently before the Fountain committee that if we found the product either effective or ineffective, under the law we should proceed immediately to take the drug off the market or leave it on. We as an agency adopted these middle two categories, "probably effective" and "possibly effective," to allow a period of 1 year for the "probably effectives," and 6 months for the "possible effectives, for the development of evidence that would keep the drugs on the market or show in a definitive way whether they were ineffective.

Mr. DUFFY. Is it necessary to develop new evidence, or would it merely be necessary, let's say, to limit the claims? Would either of those two have the result of making the drug "effective."

Mr. GOODRICH. The company can do either. If it wants to abandon the claim we cheer them and encourage that.

Dr. LEY. May I respond to this question too? I have already responded to a similar question in many public statements.

A drug is not a simple matter of effective or ineffective. A drug has claims. And it is the claims we are judging effective or ineffective. Drugs may have a half dozen claims included in the labeling that was current at the time the Kefauver-Harris amendments were passed. Where a drug has half a dozen claims, the Academy finds three claims effective, one claim probably effective, and let's say two claims ineffective, I have pleaded with the firms in public speeches that they simplify the matter by reducing their claims to only those that the Academy finds effective without question and delete the others for the time being.

Certainly the "ineffectives" must be deleted. But it is not a simple matter. This is something that is very difficult to convey to the general public. A drug by itself is neither effective nor ineffective. A drug is effective or ineffective only in terms of the indication for which the physician uses it, and the manufacturer promotes it.

Mr. DUFFY. Mr. Goodrich, can you tell us as a matter of law, when you say a drug is "probably effective," you are not saying that to some degree this drug is "effective."

Now, where do we transcend this question of effective versus probably effective, and what is the legal standard we use in judging this?

Mr. GOODRICH. The legal standard was provided by the Congress in a quite careful definition of what was substantial evidence, that is, evidence obtained from adequate, well controlled studies, including clinical studies, on the basis of which it can reasonably and responsibly be concluded that the drug will have the effectiveness claimed. Now, literally, if we apply that standard today to any of these drugs classified "probably effective" or "possibly effective," they would fail to meet the defined standard, and the department would be authorized to remove them from the market as of now. Because we are getting back judgments from the expert panels of "probably effective" and "possibly effective," we decided as an administrative matter to allow the 12 months and the 6 months additional for the accumulation of scientific evidence. We did that in the expectation that most drugs should either stand or fall, die, or survive on their scientific merit, and that rather than going ahead with initiating a large number of administrative proceedings to withdraw the drugs from the market, we should encourage, as much as we could, the development of evidence that would prove effectiveness.

But if it was not available, if it was not developed within 12 months for the probably effective or within 6 months for the possibly effective, we have let the industry know that we intend to move resolutely ahead to apply the standard that Congress wrote for us.

This, I say, is a legal situation. But we were given the discretion of how quickly to proceed with the implementation of the efficacy requirement. And it was an administrative judgment made by Dr. Goddard, Dr. Ley as a medical director, and by me as the legal counsel, that this was a proper and permissible way to move ahead with the effectiveness review.

Mr. DUFFY. I don't want to belabor this point, but what troubles me is that perhaps we are saying here that these drugs are effective, but they are not effective enough. And the moment we say that, then, query, whether or not we are introducing an element of relative efficacy here.

Perhaps it is just my lack of knowledge of the medical profession that prompts me to ask these questions, but I think it is a fair question to ask on the basis of these presentations.

Mr. GOODRICH. What the panels are saying to us is not that it is somewhat effective or slightly effective, what they are saying is that the scientific evidence available to support the claims is not of the type required by law, but there is some evidence that the drugs are probably effective, or that there is a little bit of evidence that the product is effective in the case of the possibly effective drugs. And rather than move at once to suspend the drugs from the market because there is not the type of evidence required by law to support the claims, they have been allowed 12 and 6 months for the development of that initial evidence. But there has been no compromise with the standard of effectiveness.

Mr. DUFFY. Did I understand you to say that the panel was making legal judgments?

Mr. GOODRICH. No; they were making judgment on the adequacy of the medical evidence.

Mr. DUFFY. They were saying these were not in keeping with the standards required by law?

Mr. GOODRICH. The panels were measuring the medical evidence by the standards required by law. And they found that the evidence did not meet the standards, but nonetheless there was evidence to show that the drug was either probably effective or possibly effective, and recommended that the companies be allowed 12 or 6 months additional to supplement the medical evidence.

Mr. DUFFY. Thank you.

Dr. LEY. As if these four categories were not sufficient, during the course of the study it proved necessary to add two additional categories. One of these, "effective, but," was added to accommodate those drugs which presented special problems such as products which were found effective for the indications listed, but which included ingredients, represented as active, which were concluded to be ineffective, and for products that were effective but required labeling revisions of a major sort. The second category added was "ineffective as a fixed combination," a classification I will discuss in greater detail a little bit later.

In support of each category assignment, panels were expected to present a justification citing the scope of the evidence evaluated and, where appropriate, how this evidence supported the decision. It was evident that these justifications would be of great value to FDA in effecting by regulatory action the recommendations of NAS/NRC. It should be noted that NAS/NRC committees were not charged with the review of safety of the products.

To enable NAS/NRC to proceed with its task, it was necessary to provide the panels with the basic informational material on each drug to be evaluated. On July 9, 1966, the FDA published an order in the Federal Register calling for each holder of a New Drug Application approved between 1938 and 1962 to submit specified information on each drug, preferably on forms prepared by NAS/NRC. The information requested included an identification of the product, copies of the labeling to be reviewed, and a list of literature references most perti-

nent to an evaluation of the effectiveness of the drug. The submission of unpublished articles or other data appropriate for the same purpose was also invited from the firms. This procedure gave the sponsors the opportunity to identify the evidence which they believed supported claims made for the drugs. In October 1966, the same procedure was initiated to include in the drug efficacy study antibiotics which had been accepted for certification prior to 1962.

A small staff at FDA was responsible for the recording and transmission of these reports from the manufacturers to the Academy. This included the assignment of each drug to one or more therapeutic categories. These categories had been previously designated by an ad hoc committee appointed by NAS/NRC.

The staff at NAS/NRC and the PAC did a superb organizational job in preparation for the study. Twenty-seven panels, comprised of experts in medical centers throughout the country, were appointed to cover 21 therapeutic categories of drugs. In the course of the study it became necessary to increase the number of panels to 30 and the drug categories to 22.

Obviously, as already noted in the testimony here, many therapeutic categories were covered by more than one panel.

With the antibiotics, for example, it was five. With the chairman and five other members on each panel, plus consultants obtained for special problems, a body of approximately 200 experts conducted the reviews. FDA assigned 10 and later 11. Public Health Service medical officers to serve as executive secretaries for the 30 panels.

The magniture of this study and the complexity of the decisions involved can hardly be overestimated. Since October 1967, the panels have submitted to FDA 2,824 reports covering approximately 3,700 drug formulations manufactured by 237 companies. About two-thirds of the products could be handled by a single panel, but the remainder, because of the multiplicity of therapeutic indications or claims, had to be reviewed separately by two to 15 panels. The Academy has estimated that considering each claim made for the drug, 10,000 or more therapeutic judgments were required. Panelists spent about 10,000 man-hours in meetings, in addition to the time required for preparatory work.

The responsibility for evaluating and carrying out the Academy recommendations is, of course, FDA's. In January 1968, we established a special task force in the Bureau of Medicine to handle this difficult assignment. The procedures we had decided upon for implementing the recommendations were explained at a public meeting that same month.

We have encountered many complex and time-consuming problems in the process of translating Academy recommendations into agency actions. First, there is the sheer volume of handling more than 10,000 therapeutic judgments. Different panels that reviewed the same drug did not always use the same terms in describing its effects, and consultation with the various panel chairmen frequently was necessary.

The Academy panels considered only the medical aspects of the drugs reviewed, but FDA must consider regulatory responsibilities as well. For many products, this involved translating panel recommendations into completely new or revised labeling, frequently covering a

number of indications. In this process, we must also be sure that the new language is consistent with other labeling for the same product or closely related products that have been developed since 1962.

Despite these problems and others, we have developed procedures for implementing Academy reports which I believe are orderly, rational, and logical. These procedures have evolved from our experience in handling the reports and they are by no means static. Procedures will be changed as necessary to deal with any problems that may arise.

At the present time, our task force makes a preliminary screening of panel reports to determine the Division within the Bureau of Medicine which can best handle the drugs involved.

Parenthetically I would add that the divisional structure within the Bureau of Medicine is ordinarily by major categories of drug effect. For instance, cardiovascular renal is one, and endocrine metabolic is another one. The task force sets a deadline for completion of the evaluation and the preparation of labeling by the appropriate division. Priorities as to the order of evaluation are based upon—

1. Safety, direct or indirect.
2. Therapeutic significance of the drug (or class of drugs).
3. Volume of use of the product.

After we have determined the action necessary to carry out NAS recommendatinos, public notice is given in the Federal Register of FDA's conclusions and subsequent steps to be taken.

If a drug is found "effective," of course, no subsequent steps may be necessary.

For those drugs found "probably effective," we give the manufacturers 12 additional months to provide data to support their claims.

For those drugs found "possibly effective," and I might add that this was originally entitled "probably ineffective"—and then revised to the positive approach—we allow 6 months for the submission of such data (since there is a greater doubt as to efficacy).

For drugs ruled "ineffective," we allow 30 days for the submission of any evidence that may have been overlooked to support efficacy claims.

Senator NELSON. Would it not be correct to say, then, that in the standards established; that is, the probably effective and possibly effective, that you used what would be called a liberal interpretation of the statute in favor of companies rather than a strict interpretation of the statute against the companies; would that be correct?

Dr. LEY. I believe that is an appropriate way to summarize it, Mr. Chairman.

Mr. GORDON. May I ask a question here? On the probably effective and possibly effective drugs, after the time period is up and you find that you receive no evidence, will these drugs be taken off the market after a 30-day period?

Dr. LEY. We will get into great detail in this matter as we go through the statement. We initiate action if (after review of the evidence submitted), we find that there is not substantial evidence. We then initiate action to remove the product from the marketplace after the appropriate time period. The form of action we would take will vary depending upon the circumstances. We believe, for example, with the Panalba mixture, that there is a safety matter involved with the com-

bination product. For this reason we are proposing a more vigorous type of action than we would in the case of a product where no safety question is involved. But the intention is the same, it is just a question of time.

The manufacturer of a drug falling into the "effective, but," category is told what labeling or formulation change is required to meet the recommendations of the NAS panel. Depending upon the action the firm elects to take, the drug will fall into one of the other four categories, that I have mentioned above and the appropriate time limit would apply.

If the companies do not provide the required evidence of efficacy, FDA then initiates action to withdraw approval of the New Drug Application or, in the case of antibiotics, to repeal the applicable regulations which permit the products to be marketed. Companies have the opportunity to request and show reasonable grounds for a public hearing, but whether the drug will be permitted to remain on the market during the course of a hearing depends upon the degree of hazard which its continued distribution may present to patients.

In the summer of 1968, we began to receive the NAS/NRC reports on the antibiotic combination drugs. The conclusions of the Academy panels were in line with what experts in the antibiotic field, and pharmacology textbooks, such as The Pharmacological Basis of Therapeutics by Goodman and Gilman, had been saying for years.

The Academy found the antibiotic combinations "ineffective as fixed dose combinations." Although individual active ingredients were concluded to be useful in treating specific disease entities, no greater effectiveness was shown for the combinations.

Mr. DUFFY. Doctor, if I may interrupt at this point, it is a statement such as the one you just made that gives me considerable trouble, "no greater effectiveness was shown for the combinations." Somehow I read some sort of a test of relativeness in there. And although you tell me this is not the case, perhaps you could explain to me how this is not a relative evaluation. I assume these are your words and that you are not still quoting the panel?

Dr. LEY. These are our words.

Mr. DUFFY. You are not quoting the panel?

Dr. LEY. I will be pleased to answer that. The judgment, in the case of a new drug entering the marketplace, is a question of whether a product should or should not be marketed, always involves the weighing of a benefit to be achieved from the drug versus the risks associated with the drug.

This is always true. And it is not a comparative evaluation. There are instances when we will accept drugs for marketing where the drug may have various serious side reactions in 25 to 40 percent of the patients receiving it, some of them even lethal. But if there is evidence that a drug may possibly cure cancer in 50 percent of the patients receiving it, then we feel that the benefit far outweighs the risk. In this particular case in our opinion, in the opinion of outside experts, and in the opinion of the Academy panel there is no benefit accruing to the patient from the combination of antibiotics as compared to the single preparation. The patients only effect is at least doubling of side effects. So that within this product, combination antibiotics,

the risk-to-benefit ratio is less than—or the benefit-to-risk ratio, putting it the other way around—is less than the ratio for the single ingredient of the combination.

Does that answer your question?

Mr. DUFFY. If I understand you correctly, then, we are really concerned here about the safety features of fixed combination drugs.

Dr. LEY. One must always bear in the back of one's mind, when considering drug actions of any sort, certain aspects of safety. It is impossible to totally disassociate safety and efficacy. Although we may say that prior to 1962 we did not consider efficacy—we didn't as a formal requirement—there were still situations in which efficacy was a feature even in the safety consideration of the drugs administration. I think it is legally proper perhaps to say that you cannot disassociate these two features of drug evaluation. Medically and pharmacologically, there is always a little bit of one along with the other.

Mr. DUFFY. Did I understand you correctly a moment ago—to say that in an NAS/NRC study did not touch on the issue of safety.

Dr. LEY. They were asked not to approach safety, but to approach efficacy. Now, even in that case, although their charge was efficacy, there were in many recommendations comments on safety. Again, it is totally impossible to disassociate these two factors totally from the other. The majority, 95 to 99 percent of the Academy recommendations, are concerned with efficacy. But where the panels have felt it appropriate to call our attention to certain safety hazards, there are comments on safety.

It is appropriate that it be so.

Mr. DUFFY. The action that you are taking with respect to fixed combination drugs is directed more toward their safety?

Dr. LEY. It is directed to both. There is no substantial evidence that there is any benefit from such combinations in a fixed ratio, none whatsoever.

I will be pleased to consider such evidence when it is submitted. But as of this time there is nothing that meets the definition of substantial evidence.

Mr. DUFFY. Mr. Goodrich, do you understand perhaps what I am driving at now? I am trying to understand the legal considerations that are going to obtain when and if these matters get to that stage?

Mr. GOODRICH. These matters have already reached that stage.

Mr. DUFFY. They may have reached that stage. And I just query the advisability of us debating them if they are in fact before the courts. Maybe there is another tribunal that should be deciding.

Mr. GOODRICH. Perhaps so. I understand that the Upjohn Co. will be filing suit today. And if you don't want to discuss it, it is perfectly OK with me.

But to address myself to your issues, as I said a few minutes ago, the claim for Panalba is that it is better than tetracycline, that it broadens the spectrum, that it is useful for unique type of mixed infections in which neither drug separately works as well as the combination. These claims are false, unsupported by substantial evidence. And this is the basis on which—one basis on which the Academy found the drug ineffective as a fixed combination.

It went further to point out that the novobiocin in the combination product was there at a half a dosage, and that this was an irrational part of the mixture.

It made a further finding that there were no unique circumstances in which patients suffered from a combination infection bugs that would be uniquely susceptible to tetracycline and novobiocin. A claim that the combination was uniquely effective was the basic rationale of the company for promoting the drug.

And so the scientific evidence to support the claims was found to be inadequate.

Now, that is the basis on which we took action. As to the basis on which the company takes legal action, we will have to wait and see in the paper.

Senator NELSON. As I understand it, at least from those findings that I have read—I haven't read them all—and correct me, Doctor, if I am wrong—in the fixed combination antibiotics, I understand it to be a health question in every single one of them, because even though the combination may effectively treat the disease, you have exposed the patient to an extra antibiotic to which he may be sensitive, and this is an unnecessary health hazard, is that correct?

Dr. LEY. In general, Mr. Chairman, that is a correct summary of the situation. We believe—and our medical consultants believe—that unnecessary exposure of a patient to an antibiotic which he does not need to cure his infection exposes that patient to the potential and sometimes very serious risk of making that person allergic to the second antibiotic which he does not need. Thus, at some future time the patient, given the second antibiotic, may, instead of getting well, experience a very severe allergic reaction, possibly even a fatal one.

There are several levels of safety questions involved with the combination antibiotics, Mr. Chairman. We have not accentuated the one you have raised in pointing out that we feel that there are different time frames for our action in this area.

For example, the case that we have mentioned several times today, Panalba. Approximately one out of every five patients who receives the novobiocin component of Panalba is expected, on the basis of literature, to react with a hypersensitivity or an allergic type reaction. Most of these are merely irritating. There is a smaller proportion of the patients who experience temporary but very severe liver damage as a result of the novobiocin component.

There is a still smaller number that experience the type of blood reaction one sees with chloramphenicol. We believe that a patient who needs only tetracycline should not be exposed to these additional hazards which are attributable to the novobiocin component. We have no substantial evidence to support that novobiocin produces any benefit.

Mr. DUFFY. Doctor, could you provide for the record the number of cases that might result from some of these side effects, is it thousands or hundreds of thousands or what?

Dr. LEY. In terms of the allergic reactions, there must be literally hundreds of thousands. We will have to get some marketing estimates and extrapolate on the basis of the accepted 20-percent estimate. But I must again, in all fairness, say that many of these reactions are rela-

tively mild. In other words, you may itch so severely you can't sleep for several nights or a week, or you may break out in a very unpleasant, uncomfortable rash. But we can give you some estimate of the number of patients with this type of reaction, the allergy. There must be hundreds of thousands.

Mr. GORDON. Dr. Ley, on novobiocin you have three elements:

1. The high frequency of adverse reactions, principally urticaria and maculopapular dermatitis. Hepatic dysfunction and blood dyscrasias have occurred less frequently.

2. The rapid and frequent emergence of resistant strains, especially staphylococci; and then the fact that novobiocin's spectrum of antibacterial activity is covered by several other safer and more effective drugs.

Dr. LEY. These three elements have been changed slightly since that draft has been written, in that they have separated off the relatively rare blood dyscrasis from the other reactions, such as hypersensitivity, and the liver malfunction. But essentially, this is a very complete summary of the type of problems involved in a patient receiving novobiocin when this is not needed.

(The subsequent information was received and follows:)

FOOD AND DRUG ADMINISTRATION/BUREAU OF MEDICINE REPORT ON NUMBER OF PATIENTS ADVERSELY AFFECTED BY THE USE OF PANALBA

1. Adverse reactions to a combination drug may represent the sum of those expected with each component, or an increased incidence due to drug interaction, or even a lowered incidence of dose-related reactions if the absorption of one or both components is decreased as in this combination.

2. Adverse reactions are under-reported due to multiple reasons.

3. It is impossible to predict the number of patients who will have reactions.

4. Estimates herein are based on percentage obtained in studies of varying quality.

A. Reactions to Tetracyclines

1. Dental staining—in infants and young children, yellow-brown tooth staining—both in children born to mothers given tetracycline during pregnancy and infants and children treated with tetracycline up to age 8 yrs.

References: Lancet (1962,1) and (1962,2) 721

The percentage of children affected may range from 10% to 80% depending on the duration of therapy and age at which treated.

2. *Gastrointestinal tract.*—Nausea, vomiting, diarrhea, stomatitis, glossitis and suppression of normal intestinal bacterial flora with resistant bacterial overgrowth, including staphylococcal enterocolitis.

References: Goodman and Gilman: The Pharmacological Basis of Therapeutics, 3rd Edition, Macmillan, New York, 1965 page 1249.

British Med. Bulletin, 16:67–72, 1960.

Antibiotics Annual 1955–56 pages 867–874.

Gastrointestinal tract reactions occur in over 25% of individuals taking the oral forms of tetracyclines. Cases of very severe staphylococcal enterocolitis have been reported in limited numbers.

3. *Hypersensitivity reactions.*—Skin rashes have been reported but are rare—less than 1% of individuals exhibit minor skin rashes, however a few cases of exaggerated sunburn or photosensitivity have been reported. Rarely a case of exfoliative dermatitis is reported. Anaphylactic shock has been reported.

References: Antibiotic Medicine 4:800–813, 1957.

Diseases of Medical Progress, 2nd Edition, Thomas, 1964 page 25.

4. *Hepatotoxicity.*—Combined parenteral and oral tetracycline has been implicated in liver toxicity and a few cases of liver necrosis in patients with renal impairment.

References: Proc. Staff Meetings, Mayo Clinic 35:593–608, 1960. Goodman and Gilman: The Pharmacological Basis of Therapeutics, 3rd Edition, Macmillan, New York, 1965, page 1249.

5. Other Adverse Reactions that have been reported include: bulging fontanelles in infants under one year of age, anaphylactoid purpura, granulocytopenia and exfoliative dermatitis.

Reference: Diseases of Medical Progress, 2nd Edition, Thomas, 1962 pages 25–26.

B. Reactions to Novobiocin

1. *Hypersensitivity reactions.*—Cutaneous eruptions of varying severity have been reported as occurring in from 7–20% of individuals in series reported in the United States. One foreign report cites 53% of cases treated with novobiocin developed a typical maculopapular exanthema. In many cases drug fever accompanied the rash.

Other reactions including angio-edema, serum sickness. Stevens-Johnson syndrome, are rare reactions that have been reported.

References: Diseases of Medical Progress, 2nd Edition, Thomas, 1964, pages 31–32. Side Effects of Drugs, Fourth Edition, Exerpta Medica Foundation, 1964, pages 193–194.

2. *Blood Dyscrasias.*—Eosinophilia and leucopenia (approximately 1%) are fairly frequent reactions, usually associated with skin reactions. Thrombocytopenia, agranulocytosis and pancytopenia have been reported rarely.

3. *Hepatotoxicity.*—Novobiocin-induced jaundice due to hyperbilirubinemia in infants was reported soon after the drug was first marketed.

One report indicates that hepatomegaly with jaundice occurred in 22% of cases treated.

References: Diseases of Medical Progress, 2nd Edition, Thomas, 1964, pages 31–32. Side Effects of Drugs, Fourth Edition, Exerpta Medica Foundation, 1964, pages 193–194.

C. Adverse Reactions to "Panalba"

Submitted by The Upjohn Company to FDA and include the following:

Blood Dyscrasias, 27 (6 fatal). Including thrombocytopenia, leucopenia, eosinophilia, hemolytic anemia, aplastic anemia (pancytopenia).

Hypersensitivity Reactions, 39 (2 fatal). Including minor skin rashes, urticaria, serum sickness exfoliative dermatitis, Stevens-Johnson syndrome and anaphylaxis.

Gastrointestinal Reactions. 44 (none fatal). These include glossitis, stomatitis, nausea, vomiting, diarrhea, anal pruritis. One physician states that approximately 20% of cases treated developed glossitis and another stated that many infants developed thrush (oral moniliasis).

Liver, 7 (1 fatal). These include jaundice and hepatic necrosis.

Central Nervous System, 22 (none reported as fatal). These include hyperexcitability in children, headaches (severe), drowsiness, and bulging of the anterior fontanelle in infants.

Dental, 4 cases of tooth staining in children. Based on the estimate submitted by The Upjohn Company that approximately 47,500,000 individuals have received treatment with "Panalba" the following incidence of reactions would be expected based on literature reports of reactions due to either tetracycline and/or novobiocin.

Blood Dyscrasias, 1 percent (leucopenia), 475,000.

Hypersensitivity Reactions, 20 percent (one investigator reported 53 percent), 9,250,000.

Gastrointestinal Reactions, 20 percent (one investigator reports 20 percent of infants develop glossitis), 9,250,000.

Liver, 1 percent, 475,000.

Other miscellaneous adverse reactions—including dental staining in children, headaches, hyperexcitability, bulging of anterior fontanelles—estimated at 2 percent, 950,000.

JOHN J. JENNINGS, M.D.,
Acting Director, Bureau of Medicine.

Senator NELSON. Go ahead, Doctor.

Dr. LEY. It was the judgment of the five anti-infective drug panels that the use of these fixed combinations should be discontinued and that the physician should use individual components according to his best clinical and laboratory information. Citing the increased

risk to the patient from the unnecessary exposure to multiple drugs, the panels concluded that the disadvantages of the fixed combinations far outweigh any small advantage of convenience such combinations may seem to offer.

I'd like to quote, if I may, some of the comments of the Academy panels with respect to some of the antibiotics evaluated.

In the interest of time, unless you wish me to read in the record all of these, I might limit my comments to the first two out of the five, and ask that the others be put into the record.

Senator NELSON. That is fine.

Dr. LEY. The first comment is in regard to the drug Panalba.

* * * it would appear hazardous, in the opinion of the panel, to subject persons already hypersensitive to one or more antibiotics to possible sensitization to other antibiotics unless of demonstrated value in therapy of their disease. For this group of patients, there is particular advantage in providing specific therapy with a single drug whenever possible.

2. Mysteclin-F.

The panel is not aware of evidence of proved efficacy of this combination in the prevention of disease due to monilial organisms, although suppression of growth of monilia may be accomplished. It should be noted that the apparent reduction of organisms in the feces may be an artifact due to residual antibiotic activity and thus may not reflect the true state in the patient. It is preferable, in the panel's opinion, to prescribe antifungal drugs when clinically indicated rather than to use them indiscriminately as 'prophylaxis' against an uncommon clinical entity seen during therapy with tetracyclines and other antibiotics.

I would then move to the bottom of page 17.

On December 24, 1968, FDA announced in the Federal Register its concurrence with the Academy's conclusions that Mysteclin-F, Albamycin-T (G.U.), Panalba, and Achromycin Nasal Spray were ineffective as fixed combinations. Early in January both E. R. Squibb & Sons, Inc., which markets Mysteclin-F, and the Upjohn Co., which markets the Panalba and Albamycin combinations, requested additional time to assemble and to submit additional evidence of efficacy. I granted both firms an additional 120 days to collate and submit new clinical data.

I subsequently notified both firms that we were considering cancellation of the time extensions granted in January, and directed them to immediately submit any substantial medical evidence they had that would be relevant to the efficacy of the drugs. Additional data were provided, but these were not adequate to demonstrate the effectiveness of the fixed combinations. Upjohn presented a proposed protocol to develop the type of evidence required by law, but explained that it would be quite costly and would require about 2 years for completion.

Another significant antibiotic action was coming to a head about this same time. Our final review of the Academy's reports on novobiocin, and for the sake of clarity I might indicate that novobiocin, is the established name of the product for which the trade name is Albamycin—our final review of the Academy's reports on novobiocin indicated that marked revisions in the labeling were imperative, not only from the standpoint of efficacy, but on grounds of safety. On May 2, 1969, we published in the Federal Register the new labeling to be required for this antibiotic, including a prominent "warning

box" citing the frequency of adverse reactions—liver malfunctions, and rashes, and the occurrence of a more serious type of reaction, blood dyscrasias.

Which we have already mentioned this morning. I submit a copy of this Federal Register announcement for the record.

Senator NELSON. It will be printed in the record.

(The document follows:)

[From the Federal Register, vol. 34, No. 84, pp. 7252–7253, May 2, 1969]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

FOOD AND DRUG ADMINISTRATION

Ayerst Laboratories

NOTICE OF FILING OF PETITION FOR FOOD ADDITIVE NEQUINATE

Pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 409(b)(5), 72 Stat. 1786; 21 U.S.C 348(b)(5)), notice is given that a petition (41–646) has been filed by Ayerst Laboratories, 685 Third Avenue, New York, N.Y. 10017, proposing the issuance of a food additive regulation (21 CFR Part 121) to provide for the safe use of nequinate (methyl 7–[benzyloxy]–6–butyl–1,4–dihydro–4–oxo–3–quinolinecarboxylate) in the feed of broiler chickens as an aid in the prevention of coccidiosis caused by *E. tennella*, *E. necatrix*, *E. acervulina*, *E. maxima*, *E. brunetti*, and *E. mivati*.

Dated: April 25, 1969.

R. E. DUGGAN,
Acting Associate Commissioner for Compliance.

[F.R. Doc. 69–5256; Filed, May 1, 1969; 8:46 a.m.]

2,4-Dichlorophenyl *p*-Nitrophenyl Ether

NOTICE OF EXTENSION OF TEMPORARY TOLERANCES

The Rohm and Haas Co., Independence Mall West, Philadelphia, Pa. 10105, was granted temporary tolerances for residues of the herbicide 2,4-dichlorophenyl *p*-nitrophenly ether in or on rice straw at 0.5 part per million and in or on rice at 0.1 part per million on May 20, 1968 (notice was published in the Federal Register of May 28, 1968; 33 F.R. 7775), which will expire May 20, 1969.

The firm has requested a 1-year extension of the temporary tolerances to obtain additional experimental data. The Commissioner of Food and Drugs has determined that such an extension of the temporary tolerances will protect the public health. A condition under which these temporary tolerances are extended is that the herbicide will be used in accordance with the temporary permits issued by the U.S. Department of Agriculture. Distribution will be under the Rohm and Haas Co. name. These extended temporary tolerances expire on May 20, 1970.

This action is taken pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 408(j), 68 Stat. 516; 21 U.S.C. 346a(j)) and under authority delegated to the Commissioner (21 CFR 2.120).

Dated: April 28, 1969.

J. K. KIRK,
Associate Commissioner for Compliance.

[F.R. Doc. 69–5246; Filed, May 1, 1969; 8:46 a.m.]

Novobiocin Preparations For Oral and Parenteral Use

DRUGS FOR HUMAN USE—DRUG EFFICACY STUDY IMPLEMENTATION

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences—National Research Council, Drug Efficacy Study Group, on the following oral and parenteral forms of novobiocin:

1a. Albamycin Mix-O-Vial, Power for Injection; 500 milligrams of novobiocin, as sodium novobiocin, per vial;

b. Albamycin Capsules; 250 milligrams of novobiocin, as sodium novobiocin, per capsule;

c. Albamycin Syrup; 125 milligrams of novobiocin, as calcium novobiocin, per 5 cubic centimeters; all marketed by the Upjohn Co., 301 Henrietta Street, Kalamazoo, Mich. 49001.

2. Cathomycin Sodium Capsules; 250 milligrams of novobiocin, as novobiocin sodium, per capsule; marketed by Merck & Co., Inc., Rahway, N.J. 07065.

The Food and Drug Administration has concluded that novobiocin is effective for certain indications and is appropriate for use under the qualifications stated herein.

Preparations containing novobiocin are subject to certification pursuant to section 507 of the Federal Food, Drug, and Cosmetic Act. Batches of the drug for oral or parenteral use for which certification is requested should provide for labeling information in accord with labeling guidelines developed on the basis of this reevaluation of the drug and published in this announcement. The holders of antibiotic forms 5 or 6 approved for a drug of the kind described above are requested to submit, within 30 days after publication hereof in the Federal Register, supplements to their antibiotic form 5 or 6 applications to provide for revised labeling. Those parts of the labeling indicated below should be substantially as follows (optional additional information, applicable to the drug, may be proposed under other appropriate paragraph headings and should follow the information set forth below):

"NOVOBIOCIN

"WARNING

"Novobiocin Should be Used Only for Those Serious Infections Where Other Less Toxic Drugs Are Ineffective or Contraindicated, Because of the Following:

"1. The High Frequency of Adverse Reactions, Including Hepatic Dysfunction, Blood Dyschrasias, and Rashes.

"2. The Rapid and Frequent Emergence of Resistant Strains, Especially Staphylococci.

"3. Its Spectrum of Antibacterial Activity Is Covered by Several Other Safer and More Effective Drugs.

"DESCRIPTION

"(Descriptive information to be included by the manufacturer or distributor should be confined to an appropriate description of the physical and chemical properties of the drug and the formulation.)

"ACTIONS

"In vitro novobiocin shows activity against *Staphylococcus aureaus* and against some strains of *Proteus vulgaris*. It shows no cross-resistance with penicillin against resistant strains of *M. pyogenes* var. *aureus* (*Staphylococcus aureus*); however, in vitro studies indicate that *M. pyogenes* var. *aureus* very rapidly develops resistance to novobiocin.

"INDICATIONS

"Novobiocin is indicated only for the treatment of serious infections due to susceptible strains of *Staphylococcus aureus* when the patient is sensitive or there is other contraindication to other effective antibiotics, such as the penicillins, cephalosporins, vancomycin, lincomycin, erythromycin, and the tetracyclines.

"Add for the oral forms: Novobiocin may be useful in the few urinary tract infections caused by Proteus species sensitive to novobiocin but resistant to other therapy.

"CONTRAINDICATIONS

"This drug should not be administered to persons with known sensitivity to novobiocin.

"WARNING

"Because novobiocin has been shown to affect bilirubin metabolism adversely, its use should be avoided in newborn and premature infants.

"PRECAUTIONS

"Novobiocin possesses a high index of sensitization and appropriate precautions should be taken. If allergic reactions develop during treatment and are not readily controlled by the usual measures, the product should be discontinued.

"Hepatic and hematologic studies should be made routinely during treatment. In the case of development of liver dysfunction, the drug should be stopped. If hematologic studies show evidence of the development of leukopenia or other blood dyscrasias, the drug should be stopped.

"If new infections appear during therapy, appropriate measures should be taken and consideration given to discontinuance of novobiocin.

"ADVERSE REACTIONS

"A high incidence of adverse reactions has been reported with the use of this drug.

"Leukopenia and other blood dyscrasias, including anemia, pancytopenia, eosinopenia, agranulocytosis, and thrombocytopenia, have been reported.

"Reversible liver dysfunction has been reported.

"Skin eruption may take the form of urticarial, erythematous, maculopapular, or a erythema multiforme (Stevens-Johnson Syndrome).

"Pain at the site of injection as well as nausea and vomiting, loose stools, and diarrhea when the drug is taken orally may occur.

"Alopecia as well as intestinal hemorrhage have been reported.

"DOSAGE AND ADMINISTRATION

"1. *Parenteral.* This method of administration should be used only as a temporary measure in severe infections for those unable to take the preparation orally.

"Adults: 500 milligrams intramuscularly or intravenously every 12 hours.

"Children: Moderately acute infections—15 milligrams per kilogram per day in two divided doses at 12-hour intervals; severe infections—up to 30 milligrams per kilogram per day in two divided doses at 12-hour intervals.

"2. *Oral.* Adults: Usually 250 milligrams every 6 hours or 500 milligrams every 12 hours. In severe cases, 500 milligrams every 6 hours or 1.0 gram every 12 hours.

"Children: Moderately acute infections—15 milligrams per kilogram per day in divided doses: severe infections—30–45 milligrams per kilogram per day in divided doses."

The firms listed above have been mailed a copy of the NAS–NRC reports. Any manufacturer, packer, or distributor of a drug of composition and labeling similar to the subject drugs or any other interested person may also obtain a copy from the office named below.

Communications forwarded in response to this announcement should be directed to the attention of the appropriate office listed below and addressed to the Food and Drug Administration, 200 C Street SW., Washington, D.C. 20204.

Requests for NAS–NRC report: Press Relations Office (CE–300).

Supplements: Division of Anti-infective Drugs (MD–140), Office of New Drugs, Bureau of Medicine.

Comments on this announcement: Special Assistant for Drug Efficacy Study Implementation (MD–16), Bureau of Medicine.

This notice is issued pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 507; 52 Stat. 1050–51, as amended, 59 Stat. 463, as amended; 21 U.S.C. 352, 357) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: April 25, 1969.

HERBERT L. LEY, JR.,
Commissioner of Food and Drugs.

[F.R. Doc. 69–5247; Filed, May 1, 1969; 8:46 a.m.]

Dr. LEY. On May 1, 1969, the day this announcement was made public, representatives of the Upjohn Co. came in at my request to discuss the steps to be taken in regard to novobiocin. Upjohn markets this antibiotic as Albamycin. In addition, both Panalba and Albamycin–T, which we had ruled ineffective as fixed combination, contain novobiocin as an ingredient.

At this meeting, we advised the firm that we had stopped certification of new lots and we proposed the following steps with regard to Albamycin:

1. That the company issue a letter to all physicians within 10 days describing the new warning and restrictions on use.
2. Prompt printing of the new labeling.
3. Recall to the user level of all outstanding stocks of novobiocin, both oral and parenteral, with replacement to be made by May 31, 1969, with stocks carrying the new labeling.

With respect to the combinations containing novobiocin, we advised the firm that we had stopped the certification for new lots and we proposed:

1. Decertification of all outstanding stocks of the drugs.
2. Prompt recall to the user level of these outstanding stocks.
3. A report on the status of the combination products in the "Dear Doctor" letter on novobiocin.

We discussed with the Upjohn representatives the company's inability even now to produce or to point to any medical support for their efficacy claims that would satisfy the legal requirements.

I regret to say that the firm, up to now, has taken only one of the steps outlined—it has agreed to the submission of labeling for novobiocin.

We were, therefore, obliged to proceed in other ways to carry out the decisions which I strongly believe are necessary to protect the public health. I submit a copy of the new labeling for the record.

Senator NELSON. It will be printed in the record.

(The document follows:)

NOVOBIOCIN

WARNING

Novobiocin should be used only for those serious infections where other less toxic drugs are ineffective or contraindicated, because of the following:

1. The high frequency of adverse reactions, principally urticaria and maculopapular dermatitis. Hepatic dysfunction and blood dyscrasias have occurred less frefrequently.
2. The rapid and frequent emergence of resistant strains, especially staphylococci.

DESCRIPTION

Albamycin (novobiocin), in the crystalline state, has a light yellow to white color depending upon the state of subdivision. It is odorless or practically odorless. The sodium salt is freely soluble in water, alcohol, glycerine and propylene glycol. One grain of the calcium salt dissolves in about 250 cc. of water, in about 30 ml. of alcohol, in about 450 ml. of ether and in about 1100 ml. of chloroform. In contrast to most antibiotics produced by actinomycetes, novobiocin, like penicillin, is acidic in nature and is stable to the degree of acidity or alkalinity present in the gastrointestinal tract.

ACTIONS

In vitro novobiocin shows activity against *Staphylococcus aureus* and against some strains of *Proteus vulgaris*. It shows no cross-resistance with penicillin against resistant strains of *M. pyogenes* var. *aureus* (*Staphylococcus aureus*); however, in vitro studies indicate that *M. pyogenes* var. *aureus* rapidly develops resistance to novobiocin.

INDICATIONS

Novobiocin is indicated in the treatment of serious infections due to susceptible strains of *Staphylococcus aureus* when the patient is sensitive to other effective antibiotics, such as the penicillins, cephalosporins, vancomycin, lincomycin, erythromycin, and tetracyclines, or when there are other contraindications to these antibiotics.

Add for the oral forms: Novobiocin may be useful in the few urinary tract infections caused by Proteus species sensitive to novobiocin but resistant to other therapy.

CONTRAINDICATIONS

This drug should not be administered to persons with known sensitivity to novobiocin.

WARNING (SEE "BOX WARNING")

Because novobiocin has been shown to affect bilirubin metabolism adversely, its use should be avoided in newborn and premature infants.

PRECAUTIONS

Novobiocin possesses a high index of sensitization and appropriate precautions should be taken. If allergic reactions develop during treatment and are not readily controlled by the usual measures, the product should be discontinued.

Hepatic and hematologic studies should be made routinely during treatment. In the case of development of liver dysfunction, the drug should be stopped. If hematologic studies show evidence of the development of leukopenia or other blood dyscrasias, the drug should be stopped.

If new infections appear during therapy, appropriate measures should be taken and consideration given to discontinuance of novobiocin.

ADVERSE REACTIONS

A relatively high incidence of hypersensitivity reactions, consisting most commonly of skin eruptions, has occurred. Skin eruptions may take the form of uriticarial, erythematous, maculopapular or scarlatiniform rash Erythema multiforme (Stevens-Johnson Syndrome) has occurred but is rare.

Leukopenia, eosinophilia and/or fever have occurred occasionally in patients receiving Albamycin (novobiocin). Rarely, other blood dyscrasias, including anemia, pancyctopenia, agranulocytosis and thrombocytopenia have occurred.

Liver dysfunction including jaundice, elevation of serum bilirubin concentration, and impaired bromsulphalein excretion, have occurred.

Other adverse reactions include nausea and vomiting, loose stools and diarrhea and intestinal hemorrhage. Alopecia has been reported, but relationship to novobiocin has not been established.

DOSAGE AND ADMINISTRATION

Parenteral

This method of administration should be used only as a temporary measure in severe infections for those unable to take the preparation orally.

Adults: 500 mg. intramuscularly or intravenously every 12 hours.
Children: Moderately acute infections: 15 mg./kg./day in two divided doses at 12 hour intervals.
Severe infections: up to 30 mg./kg./day in two divided doses at 12 hour intervals.

Oral

Adults: Ususally 250 mg. every 6 hours or 500 mg. every 12 hours. In severe cases, 500 mg. every 6 hours or 1.0 Gm. every 12 hours.
Children. Moderately acute infections: 15 mg./kg./day in divided doses.
Severe infections: 30–45 mg./kg./day in divided doses.

Dr. LEY. We are prepare to certify batches of novobiocin with this labeling; this does not, however, alter our position that previously certified stocks of novobiocin distributed with the old labeling must be taken off the market.

On May 15, 1969, we published an order in the Federal Register repealing the antibiotic regulations for Panalba and Albamycin-T and decertifying outstanding stocks. These preparations will be subject to seizure when the order becomes effective on June 14, 1969. We set the effective date 30 days after publication to allow the firm to make objections, to show reasonable grounds for a hearing, if it has such grounds, and to give the firm time enough to recall stocks of these products. Upjohn has not initiated these recalls to date.

The firm's position is that these products should not be removed from the market without a public hearing. If reasonable grounds are presented, we would be required to grant a hearing on the efficacy of the preparations—but we do not believe they should remain on the market during the course of a hearing and any subsequent litigation that might ensue. In the light of the hazards involved and the NAS/NRC finding that the products are ineffective as fixed combinations, continued marketing cannot be justified.

I have described in some detail the Agency's actions affecting novobiocin, and combinations including novobiocin, because we intend to follow the same pattern in dealing with other antibiotic preparations received by NAS/NRC.

The committee should understand that reports on other antibiotic combinations were coming to my office from the Bureau of Medicine task force headed by Dr. Bryan during this same period of time. And on April 2, 1969, we announced in the Federal Register our intention to start action to end the marketing of 78 additional antibiotic-contained combination drugs which academy panels had found ineffective as fixed combinations. We included this large number of drugs in one "package" quite deliberately; we wanted to give the medical profession, the industry, and the public a clear signal of the academy's thinking, and FDA's thinking, on these combination preparations. The products involved included antibiotic-sulfa combinations, penicillin-streptomycin preparations, and other combinations including erythromycin, neomycin, tetracycline, chortetracycline, nystatin, oxytetracycline, oleandomycin, and triacetyloleandomycin. Some of the formulations also included analgesics, vitamins, or other ingredients.

Two groups of these products, the pencillin-sulfa and the penicillin-streptomycin combinations, present the same kind of problem as Panalba. They pose a hazard to the patient, which is not offset by any therapeutic benefit that cannot be achieved by using these drugs singly.

The April 2, 1969, announcement gave interested parties 30 days to submit any data relevant to the efficacy of the products listed. It is significant, Mr. Chairman, that only three of the 23 firms listed as marketing penicillin-sulfa and penicillin-streptomycin combinations responded to that invitation.

Wyeth and Pfizer submitted material on the pen-strep combinations, but no new clinical data were included. Squibb proposed labeling changes on its pen-sulfa preparations and also submitted data from a controlled study of this combination in pediatric use. After review of the study, we concluded that it did not provide substantial evidence of the effectiveness and safety of the penicillin-sulfa combination.

I have signed orders to end the marketing of both the penicillin-streptomycin and penicillin-sulfa preparations. Regulations under which these combinations were certified will be repealed. Outstanding stocks will be decertified. These orders will be published in the Federal Register later this week, or very early next week, if the holiday interferes, and will become effective 40 days later.

This will allow 30 days for the companies to file objections and to seek a hearing, 10 days for our review of the objections, and time for recalls to be completed.

Anyone who may be adversely affected by these actions may file objections within 30 days after publication and request a hearing. Such requests must state reasonable grounds for a hearing, identifying any claimed errors in the NAS/NRC evaluation or any adequate, well controlled investigations which may be offered as evidence of safety and effectiveness. As in the case of Panabla, however, we do not intend to permit the continued marketing of the pen-sulfa and pen-strep combinations during any hearing proceedings that may take place.

I also have signed an order to repeal the regulation and revoke certificates for Mysteclin–F, Squibb's combination of tetracycline and amphotericin–B. Since our announcement in December 1968 that this fixed combination is ineffective, we have received and reviewed additional data and have concluded that substantial evidence still is lacking to support claims in the labeling. The order regarding Mysteclin–F will take effect 40 days after publication in the Federal Register unless stayed by proper objections.

I can also report to the committee, Mr. Chairman, that we will be publishing shortly the academy's findings and FDA's proposals regarding sulfonamides, another widely used class of anti-infective drugs. Labeling revisions will be necessary to restrict markedly the indications for use, although the sulfonamides have been found effective for uncomplicated urinary tract infections and for prophylaxis in rheumatic fever. The industry, and any other interested parties, will be given an opportunity, of course, to react to these findings.

I hope that these examples have given the committee some indication of how we are proceeding with the challenging task of carrying out the NAS/NRC recommendations. Let me turn now, Mr. Chairman, to another challenge I believe is involved; namely, that of disseminating the information from the academy as widely as possible within the medical profession. We are using a variety of approaches to achieve this end.

When safety is not an issue, we do not plan to remove a drug from distribution while a hearing is in progress. But in those cases we will insist that all promotional material for such products state the academy's finding, and FDA's concurrence, regarding the drug's lack of efficacy. The physician is entitled to this information and we intend to see that he gets it.

When new labeling is required as a result of academy recommendations, we will require the firms involved to publicize the changes in their advertising and other promotional material. Their detail men also will be required to provide this information to physicians and to others with whom they deal.

Mr. DUFFY. Doctor, it seems to me, having listened to Dr. Kunin's testimony and Dr. Wise's testimony and Dr. Hewitt's testimony and other testimony before this committee, that many of this Nation's physicians are at least circumstantially aware of this information. Most of it was generated back in 1957.

Dr. LEY. You wouldn't believe it from reading the letters that come to my office.

Mr. DUFFY. We have heard opinions as to those letters, and as to why they are written but it still doesn't really answer my question as to the fact that this information has been widely disseminated in the medical press, if I understand the previous testimony correctly.

Dr. LEY. The information in regard to the academy's recommendation on a particular drug product is not readily available to the physicians using that product.

If the physician remembers, for example, in prescribing drugs that somewhere 5 or 6 months ago he read in the AMA News or the Washington Post a statement to the effect that this drug was found to be ineffective, he will put these two pieces of information together. But I do not believe that this is adequate.

Senator NELSON. I have read the complete text of your statement, and it is going to be printed in the record.

I have a luncheon that I must go to. I wonder if you could summarize it—and we will see whether the minority counsel has any further questions—so that I can leave.

Will that be satisfactory?

Dr. LEY. It will be perfectly satisfactory, Mr. Chairman.

Mr. DUFFY. I have no further questions.

Mr. GORDON. Can you summarize briefly the letters that you have received on Panalba and Mysteclin-F—especially Panalba—from doctors as a result of the efforts of the Upjohn and Squibb Cos.?

Dr. LEY. I have some material because, we have looked at this internally. We received approximately 3,500 responses, of which 11 were favorable to our position and the remainder opposed to it. Of the 3,500, approximately a third were letters objecting to our action on Panalba. The other two-thirds were letters objecting to our position on Mysteclin-F. There was a minor difference in the reaction among the medical community. Most of the letters in regard to Panalba took the form: I have been using this product for 10 years, and it does a good job for my patients.

Mr. GORDON. These are testimonials?

Dr. LEY. These are testimonials. There was nothing in the way of a considered judgment, or substantial evidence, or even a summary of the clinical trial in the letters on Panalba. From our point of view, they are not substantial evidence as required by law.

Mr. GORDON. Was there any similarity in wording among the letters?

Dr. LEY. Yes, there was. We noted in both the Panalba and the Mysteclin situation that many letters followed roughly the same wording. Even paragraphs were identical in letters coming from institutions that were not necessarily close together. There appeared to be something that made the letters very similar.

Finally, we received a handwritten note on a letter which a physician had received from the firm requesting that the physician write to FDA. It then became apparent that the firms had been active in stimulating the response.

Mr. GORDON. Would you supply for the record a rather large random sample of the letters?

Dr. LEY. Yes, we can. The staff has analyzed these geographically, and we have some samples of both positive and negative reactions that can be made available for the record.

(The complete prepared statement and supplemental information submitted by Dr. Ley follow:)

STATEMENT OF HERBERT L. LEY, JR., M.D.

Mr. Chairman, we welcome this opportunity to join in the discussion, which was started before this Committee three weeks ago, about combination antibiotic drugs, the review of their effectiveness by the National Academy of Sciences-National Research Council Drug Efficacy Study Group, and the follow-up steps that FDA is required to take to remove these products from the prescription drug market.

Let me begin with two general observations: First, we are most fortunate to have had the assistance in the effectiveness review of medical scientists of the stature of the witnesses who appeared before this Committee earlier. These five panel chairmen, as I'm sure the Committee noted, are not cloistered academicians aloof from the realities of treating infectious diseases. To the contrary, they have been and are now working at the frontiers of the treatment of the most complicated of infectious diseases. Their contributions, which led to their selection as panel chairmen by the NAS/NRC, clearly establish their excellent qualifications to make efficacy judgments for this class of drugs.

Second, we cannot overemphasize the importance of the drug efficacy review in terms of better patient care. The implementation of the panel recommendations with respect to the combination antibiotic drugs will not only eliminate some unnecessary risks in therapy, but will help to return antibiotic treatment to the realm of rational therapeutics.

Specfic treatment for bacterial infections was not available to the physicians until the late 1930s, when the sulfonamides were first introduced. Before that, only bed rest, cold compresses, and similar palliatives were available to deal with even infectious diseases.

The sulfonamide drugs of the 30's were the first effective chemotherapeutic agents employed systematically for the prevention and cure of a variety of bacterial infections in man.

Numerous derivatives of sulfonamides were synthesized and tested for their clinical value in various bacterial, protozoal, and viral diseases. Sulfapyridine produced dramatic results in pneumococcal pneumonia and, for a brief period, it was the agent of choice in this disease. In 1938, sulfathiazole replaced sulfapyridine as the preferred sulfonamide because of its higher therapeutic index. Sulfadiazine soon replaced sulfathiazole and has retained a prominent position among the sulfonamides ever since. Two methylated derivatives of sulfadiazine were soon introduced into therapy.

In 1941, English scientists discovered that penicilin was effective against staphylococcus and streptococcal infections. A vast research program was initiated in the United States to produce this antibiotic and, by the spring of 1943, penicillin was available for the Armed Forces.

Although numerous antibiotic agents have been produced since penicillin was discovered, this drug is still the most widely used for the treatment of infections. In the years since the first crude product was obtained from fermentation vats, chemical manipulation of the penicillin molecule has produced a large number of natural and semisynthetic congeners, and several new penicillins have become important therapeutic agents.

Penicillin itself, however, is generally ineffective in the treatment of infections due to gram-negative organisms. This fact stimulated research for antimicrobial agents effective against such bacteria. In 1947, streptomycin became available after it was shown to inhibit the growth of the tubercle bacillus and a number of gram-positive and gram-negative organisms *in vitro* and *in vivo*.

Dihydrostreptomycin was produced the same year. It had about the same degree of antibacterial activity as streptomycin, but its use is fraught with a high risk of producing irreversible deafness.

The development of the tetracyclines followed penicillin and streptomycin. The discovery of these agents was the result of a systematic screening for antibiotic-producing organisms of soil specimens collected from many parts of the world. The first of these compounds, chlortetracycline, was introduced in 1948. Two years later, oxytetracycline became available and, in 1952, tetracycline came into use. In 1959, demethylchlortetracycline became available for general use.

The tetrecyclines are effective against rickettsia, a number of gram-negative and gram-positive bacteria, and the agents responsible for lymphogranuloma venereum, inclusion conjunctivitis and psittacosis. The tetracyclines therefore became known as "broad-spectrum" antibiotics. Although claims have been made for the superiority of some tetracyclines over others, their chemical, antimicrobial, pharmacological, and therapeutic properties are, with some exceptions, very much alike.

Other antibiotics also became available in this period of post-war discovery—chloramphenicol, erythromycin, the cephalosporin, oleandomycin, triacetyloleandomycin, neomycin, paromomycin, kanamycin, polymixin-B, colistin, bacitracin, lincomycin, and many others.

Combination therapy with antibiotics began almost as soon as two such agents became available.

As new antibiotic entities were developed, their use in combination preparations was quick to follow. Shortly after streptomycin was developed, it was mixed with penicillin and recommended for use in situations in which the cause of the infection was not readily apparent. This was followed in 1950 by the use of penicillin-sulfonamide combinations for the enhancement of the antibacterial action.

In the same year, penicillin was combined with dihydrostreptomycin for use—

"* * * in the treatment of peritonitis, mediastinitis, brain abscess or conditions in which the causative organisms cannot be identified.

"* * * mixed infections, common in the respiratory or urogenital tract.

"* * * [and] for prophylaxis in surgery * * *."

(This combination has been off the market for several years.)

In 1952, penicillin was marketed in combination with APC and antihistamines. This combination was recommended for the relief of symptoms and the prevention of complications of the common cold and other acute upper respiratory infections.

In 1955, tetracycline was combined with vitamins.

In 1956, tetracycline appeared in combination with APC and the antihistamine, chlorothen citrate. The original labeling for the product reads: "* * * for the palliation and treatment of the common cold and for the relief of the symptoms such as headache, muscular aches and pains, prevention of secondary bacterial infections, and relief of mucus and nasal discharge accompanying such a cold." Later that year, a competitor combined tetracycline with glucosamine, APC, and the antihistamine, buclizine hydrochloride.

In 1956, a combination of tetracycline and oleandomycin was marketed in capsule form under the trade name Signemycin.

In 1958, a combination of tetracycline and novobiocin was introduced to the medical profession under the trade name Panalba.

In 1960, tetracycline and amphotericin-B were combined and marketed under the trade name Mystecline-F. This drug was represented to provide simultaneous antimicrobial therapy and antifungal prophylaxis.

The immediate commercial success of many of these antibiotic combinations was remarkable. Mysteclin-F and Panalba have been among the 200 most prescribed drugs since 1961. Signemycin was on this list in 1961, 1963, and 1964. Other antibiotic combinations that I haven't previously mentioned also made this "best seller" list of drugs with some frequency. For example, Pentide-Sulfa made the list six times. Ilosone-Sulfa and Tetrastatin five times each, and Declostatin four times.

The efficacy of these antibiotic combinations in practically every case was supported almost solely by *in vitro* studies—that is, "test-tube type" evaluations comparing combination preparations and single entities. These tests generally showed that the combinations produced increased antibacterial activity, with organisms exposed to the combination building up resistance at a slower rate. But, in general, there was a striking lack of data from carefully controlled, critically evaluated clinical studies to test these drugs in the treatment of disease. In short, the evidence of effectiveness was inadequate in terms of today's legal requirements.

The type of "substantial evidence" now required to support efficacy claims was defined in the Kefauver-Harris Drug Amendments of 1962. These Amendments not only provided that new drugs marketed thereafter must be proven effective, as well as safe, but also authorized a review of the efficacy of all drugs, including antibiotics, introduced from 1938 to 1962.

Even while this legislation was being considered by the Congress, concern was expressed by some medical leaders about the use of combination antibiotics. As a result, the FDA convened a panel of experts in 1963 to evaluate the prophylactic use of antimicrobial agents in combination with analgesics, antihistamines, and other drugs.

This panel concluded there was no acceptable evidence that any antimicrobial agent is of value in the treatment of either the common cold or any viral infections except those caused by certain large viruses. The panelists also concluded that antimicrobial agents are of no value—and should not be used—for the prevention of bacterial complications in patients with common colds who are otherwise healthy. When prophylactic therapy of respiratory infection is justified, the panel said that only antimicrobial agents relatively free of inherent toxicity should be used. This recommendation precluded the use of chloramphenicol, triacetyloleandomycin, and sulfonamide products.

The panel generally did not favor fixed combination products containing antimicrobials. With regard to combinations of antimicrobials with antifungal agents to suppress monilial overgrowth, the panel considered it acceptable to permit a statement to the effect that such combinations may effect a diminution in the fungal population, if it was also stated that the combinations had no proved therapeutic value against fungal infections.

As a result of the proposal and the comments received, significant labeling changes were made. The recommended dose of the antibiotic was increased to therapeutic level and a labeling statement was added recommending that the patient be switched from the combination drug to the antibiotic alone after fever and other symptoms had subsided.

The action on these medications for colds, however, was just a small step in dealing with antibiotic combinations. Many other combinations remained to be considered as part of the overall review of the efficacy of pre-1962 drugs. Moving forward with this gigantic task was one of the first problems that confronted Dr. Goddard when he became Commissioner of Food and Drugs in January 1966.

Dr. Goddard concluded that this review should be conducted by outside experts of the highest distinction whose evaluations would more likely be accepted by both the medical profession and the pharmaceutical industry.

In the spring of 1966, he asked the help of the National Academy of Sciences-National Research Council to undertake the review. After successful negotiations, a contract was signed with the Academy in July 1966. I cannot overemphasize the importance of this agreement. The Academy had the capability of bringing to this work some of the best medical and scientific minds in the country. No other organization could have brought greater objectivity, expertise, or authority to this landmark study. Paramount in the decision of the Academy to do the job was its realization of the importance of the project for the advancement of drug therapy and consequent benefit to the public.

The study was carried out under the direction of the Division of Medical Sciences of the NAS/NRC. This Division's Drug Research Board, with additional representatives to cover all appropriate medical specialties, made up the Policy Advisory Committee (PAC) that established guidelines for the review.

In the development of guidelines for the study, the Academy and the PAC made an effort to involve the pharmaceutical and medical communities to the greatest possible extent. A broadly representative forum was held on the guidelines prior to their adoption by the PAC. Among the other matters covered, the guidelines provided that:

"The judgments of the Panels will be based on the following criteria: (1) factual information that is freely available in the scientific literature, (2) factual information that is available from the FDA, from the manufacturer or other sources, or (3) on the experience and informed judgment of the members of the Panels."

Operating within these criteria, the panels were asked originally to classify claims for drugs into one of four categories:

(a) *Effective.*—For the presented indication, the drug is effective on the basis of the criteria which the panel has established for its review.

(b) *Probably Effective.*—For the indication presented, effectiveness is probable on the basis of the operative criteria, but additional evidence is required before it can be assigned to category (a).

(c) *Possibly Effective.*—In relation to the indication in question, there is little evidence of effectiveness under any of the operative criteria.

(d) *Ineffective.*—In relation to the indication in question, the panel concludes that there is no acceptable evidence under any of the operative criteria to support a claim of effectiveness.

During the course of the study, it proved necessary to add two additional categories. One of these, "effective, but," was added to accommodate those drugs which presented special problems such as products which were found effective for the indications listed, but which included ingredients, represented as active, which were concluded to be ineffective, and for products that were effective but required labeling revisions. The second category added was "ineffective as a fixed combination," a classification I will discuss in greater detail a little bit later.

In support of each category assignment, panels were expected to present a justification citing the scope of the evidence evaluated and, where appropriate, how this evidence supported the decision. It was evident that these justifications would be of great value to FDA in effecting by regulatory action the recommendations of NAS/NRC. It should be noted that NAS/NRC committees were not charged with the review of safety of the products.

To enable NAS/NRC to proceed with its task, it was necessary to provide the panels with the basic information material on each drug to be evaluated. On July 9, 1966, the FDA published an order in the *Federal Register* calling for each holder of a new drug application approved between 1938 and 1962 to submit specified information on each drug, preferably on forms prepared by NAS/NRC. The information requested included an identification of the product, copies of the labeling to be reviewed, and a list of literature references most pertinent to an evaluation of the effectiveness of the drug. The submission of unpublished articles or other data appropriate for the same purpose was also invited. This procedure gave the sponsors the opportunity to identify the evidence which they believed supported claims made for the drugs. In October 1966, the same procedure was initiated to include in the Drug Efficacy Study antibiotics which had been accepted for certification prior to 1962. A small staff at FDA was responsible for the recording and transmission of these reports to the Academy. This included the assignment of each drug to one or more therapeutic categories. These categories had been previously designated by an ad hoc committee appointed by NAS–NRC.

The staff at NAS–NRC and the PAC did a superb organizational job in preparation for the study. Twenty-seven panels, comprised of experts in medical centers throughout the country, were appointed to cover 21 therapeutic categories of drugs. In the course of the study it became necessary to increase the number of panels to 30 and the drug categories to 22. With a chairman and five other members on each panel, plus consultants obtained for special problems, a body of approximately 200 experts conducted the reviews. FDA assigned 10, and later 11, Public Health Service medical officers to serve as executive secretaries for the 30 panels.

The magnitude of this study and the complexity of the decisions involved can hardly be overestimated. Since October 1967, the panels have submitted to FDA 2,824 reports covering approximately 3,700 drug formulations manufactured by 237 companies. About two-thirds of the products could be handled by a single panel, but the remainder, because of the multiplicity of therapeutic indications, had to be reviewed separately by 2 to 15 panels. The Academy has estimated that 10,000 or more therapeutic judgments were required. Panelists spent about 10,000 man hours in meetings, in addition to the time required for preparatory work.

The responsibility for evaluating and carrying out the Academy recommendations is, of course, FDA's. In January 1968, we established a special Task Force in the Bureau of Medicine to handle this difficult assignment. The procedures we had decided upon for implementing the recommendations were explained at a public meeting that same month.

We encountered many complex and time-consuming problems in the process of translating Academy recommendations into Agency actions. First, there is the sheer volume of handling more than 10,000 therapeutic judgments. Different panels that reviewed the same drug did not always use the same terms in describing its effects and consultation with the various panel chairmen frequently was necessary.

The Academy panels considered only the medical aspects of the drugs reviewed, but FDA must consider regulatory responsibilities as well. For many products, this involved translating panel recommendations into completely new or revised labeling, frequently covering a large number of indications. In this process, we must also be sure that the new language is consistent with other labeling.

Despite these problems and others, we have developed procedures for implementing Academy reports which I believe are orderly, rational, and logical. These procedures have evolved from our experience in handling the reports and they are by no means static. Procedures will be changed as necessary to deal with any problems that may arise.

At the present time, our Task Force makes a preliminary screening of panel reports to determine the Division within the Bureau of Medicine which can best handle the drugs involved. The Task Force sets a deadline for completion of the evaluation and the preparation of labeling by the appropriate Division. Priorities as to the order of evaluation are based upon—

1. Safety, direct or indirect.
2. Therapeutic significance of the drug (or class of drugs).
3. Volume of use of the product.

After we have determined the action necessary to carry out NAS recommendations, public notice is given in the *Federal Register* of FDA's conclusions and the subsequent steps to be taken.

If a drug is found "effective," of course, no subsequent steps may be necessary.

For those drugs found "probably effective," we give the manufacturers 12 additional months to provide data to support their claims.

For those drugs found "possibly effective," we allow six months for the submission of such data.

For drugs ruled "ineffective," we allow 30 days for the submission of any evidence that may have been overlooked to support efficacy claims.

The manufacturer of a drug falling in the "effective, but," category is told what labeling or formulation change is required to meet the recommendations of the NAS panel. Depending upon the action the firm elects to take, the drug will fall into one of the other four categories, and the appropriate time limit would apply.

If the companies do not provide the required evidence of efficacy, FDA then initiates action to withdraw approval of the new drug application or, in the case of antibiotics, to repeal the applicable regulations which permit the products to be marketed. Companies have the opportunity to reqeust and show reasonable grounds for a public hearing, but whether the drug will be permitted to remain on the market during the course of a hearing depends on the degree of hazard which its continued distribution may present to patients.

In the summer of 1968, we began to receive the NAS/NRC reports on the antibiotic combination drugs. The conclusions of the Academy panels were in line with what experts in the antibiotic field, and pharmacology textbooks, such as *The Pharmacological Basis of Therapeutics* by Goodman Gilman, had been saying for years.

The Academy found the antibiotic combinations "ineffective as fixed dose combinations." Although individual active ingredients were concluded to be useful in treating specific disease entities, no greater effectiveness was shown for the combinations. It was the judgment of the five anti-infective drug panels that the use of these fixed combination should be discontinued and that the physician should use individual components according to his best clinical and laboratory information. Citing the increased risk to the patient from the unnecessary exposure to multiple drugs, the panels concluded that the disadvantages of the fixed combinations far outweigh any small advantage of convenience such combinations may seem to offer.

I'd like to quote, if I may, some of the comments of the Academy panels with respect to some of the antibiotics evaluated:

1. Panalba

". . . it would appear hazardous, in the opinion of the panel, to subject persons already hypersensitive to one or more antibiotics to possible sensitization to other antibiotics unless of demonstrated value in therapy of their disease. For this group of patients, there is particular advantage in providing specific therapy with a single drug whenever possible."

2. Mysteclin-F

"The panel is not aware of evidence of proved efficacy of this combination in the prevention of disease due to monilial organisms, although suppression of growth of monilia may be accomplished. It should be noted that the apparent reduction of organisms in the feces may be an artifact due to residual antibiotic activity and thus may not reflect the true state in the patient. It is preferable, in the panel's opinion, to prescribe antifungal drugs when clinically indicated, rather than to use them indiscriminately as 'prophylaxis' against an uncommon clincial entity seen during therapy with tetracyclines and other antibiotics."

3. Streptomycin and Penicillin

"The availability of fixed combinations of streptomycin and penicillin has:

"a. Led to inappropriate use of these drugs for treatment of disease states in which the combination is no more effective than one of the components or on which the fixed combination is not the treatment of choice;

"b. Exposed the patient to the increased toxicity inherent in a combination without increasing the benefit;

"c. Denied flexibility of the dosage of the components;

"d. Ignored the marked changes in the pattern of bacterial susceptibility in recent years and the development of new and better antimicrobial agents;

"e. Ignored the availability of penicillin and streptomycin individually for combined use at the discretion of the physician.

These combinations and the limited indications for these combinations have rendered fixed-dosage forms of penicillin and streptomycin of little value in thereapeutics. Accordingly, the panels seriously question whether they still belong in the therapeutic armamentarium. It is the judgment of these two panels that the use of these fixed combinations should no longer be recommended and that the physician should continue to use the individual components according to his best clinical and laboratory information."

4. Penicillin and Sulfa

"* * * the contraindications for the use of any sulfonamide-penicillin combination by the oral route far outweigh any indications for such use. These data from the more recent literature are amply supported by editorial comments from the literature of the early 1950's * * * With all these at hand, it is strongly recommended that use of these fixed combinations should no longer be recommended."

On December 24, 1968, FDA announced in the *Federal Register* its concurrence with the Academy's conclusion that Mysteclin-F, Albamycin-T (G.U.), Panalba, and Achromycin Nasal Spray were ineffective as fixed combinations. Early in January, both E. R. Squibb and Sons, Inc., which markets Mysteclin-F, and The Upjohn Company, which markets the Panalba and Albamycin combinations, requested additional time to assemble and to submit additional evidence of efficacy. I granted both firms an additional 120 days to collate and submit new clinical data.

I subsequently notified both firms that we were considering cancellation of the time extensions granted in January, and directed them to immediately submit any substantial medical evidence they had that would be relevant to the efficacy of the drugs. Additional data were provided, but these were not adequate to demonstrate the effectiveness of the fixed combinations. Upjohn presented a proposed protocol to develop the type of evidence required by law, but explained that it would be quite costly and would require about two years for completion.

Another significant antibiotic action was coming to a head about this same time. Our final review of the Academy's reports on novobiocin indicated that marked revisions in the labeling were imperative, not only from the standpoint of efficacy, but on grounds of safety. On May 2, 1969, we published in the *Federal Register* the new labeling to be required for this antibiotic, including a prominent "warning box" citing the frequency of adverse reactions—liver malfunctions, and rashes, and the occurrence of a more serious type of reaction, blood dyscrasias. I submit a copy of this *Federal Register* announcement for the record.

On May 1, 1969, the day this announcement was made public, representatives of the Upjohn Company came in at my request to discuss the steps to be taken in regard to novobiocin. Upjohn markets this antibiotic as Albamycin. In addition, both Panalba and Albamycin-T, which we had ruled ineffective as fixed combinations, contain novobiocin as an ingredient.

At this meeting, we advised the firm that we had stopped certification of new lots and we proposed the following steps with regard to Albamycin:

1. That the company issue a letter to all physicians within 10 days describing the new warnings and restrictions on use.
2. Prompt printing of the new labeling.
3. Recall to the user level of all outstanding stocks of novobiocin, both oral and parenteral, with replacement to be made by May 31, 1969, with stocks carrying the new labeling.

With respect to the combinations containing novobiocin, we advised the firm that we had stopped the certification for new lots and we proposed:

1. Decertification of all outstanding stocks of the drugs.
2. Prompt recall to the user level of these outstanding stocks.
3. A report on the status of the combination products in the "Dear Doctor" letter on novobiocin.

We discussed with the Upjohn representatives the company's inability even now to produce or to point to any medical support for their efficacy claims that would satisfy the legal requirements.

I regret to say that the firm, up to now, has taken only one of the steps outlined—it has agreed to the submission of labeling for Novobiocin. We were, therefore, obliged to proceed in other ways to carry out the decisions which I strongly believe are necessary to protect the public health. I submit a copy of the new labeling for the record. We are prepared to certify batches of Novobiocin with this labeling; this does not, however, alter our position that previously certified stocks of Novobiocin distributed with the old labeling must be taken off the market.

On May 15, 1969, we published an order in the *Federal Register* repealing the antibiotic regulations for Panalba and Albamycin-T and decertifying outstanding stocks. These preparations will be subject to seizure when the order becomes effective on June 14, 1969. We set the effective date 30 days after publication to allow the firm to make objections, to show reasonable grounds for a hearing, if it has such grounds, and to give the firm time enough to recall stocks of these products. Upjohn has not initiated these recalls, however.

The firm's position is that these products should not be removed from the market without a public hearing. If reasonable grounds are presented, we would be required to grant a hearing on the efficacy of the preparations—but we do not believe they should remain on the market during the course of a hearing and any subsequent litigation that might ensue. In the light of the hazards involved and the NAS–NRC finding that the products are ineffective as fixed combinations, continued marketing cannot be justified.

I have described in some detail the Agency's actions affecting Novobiocin, and combinations including Novobiocin, because we intend to follow the same pattern in dealing with other antibiotic preparations reviewed by NAS–NRC.

The Committee should understand that reports on other antibiotic combinations were coming to my office from the Bureau of Medicine Task Force during this same period of time. On April 2, 1969, we announced in the *Federal Register*

our intention to start action to end the marketing of 78 additional antibiotic-containing combination drugs which Academy panels had found ineffective as fixed combinations. We included this large number of drugs in one "package" quite deliberately; we wanted to give the medical profession, the industry, and the public a clear signal of the Academy's thinking, and FDA's thinking, on these combination preparations. The products involved included antibiotic-sulfa combinations, penicillin-streptomycin preparations, and other combinations including Erythromycin, Neomycin, Tetracycline, Chortetracycline, Nystatin, Oxytetracycline, Oleoandomycin, and Triacetyloleandomycin. Some of the formulations also included analgesics, vitamins, or other ingredients.

Two groups of these products, the penicillin-sulfa and the penicillin-streptomycin combinations, present the same kind of of problem as Panalba. They pose a hazard to the patient, which is not offset by any therapeutic benefit that cannot be achieved by using these drugs singly.

The April 2, 1969, announcement gave interested parties 30 days to submit any data relevant to the efficacy of the products listed. It is significant, Mr. Chairman, that only three of the 23 firms listed as marketing penicillin-sulfa and penicillin-streptomycin combinations responded to that invitation.

Wyeth and Pfizer submitted material on the pen-strep combinations, but no new clinical data were included. Squibb proposed labeling changes on its pen-sulfa preparations and also submitted data from a controlled study of this combination in pediatric use. After review of the study, we concluded that it did not provide substantial evidence of the effectiveness and safety of the penicillin-sulfa combination.

I have signed orders to end the marketing of both the penicillin-streptomycin and the penicillin-sulfa preparations. Regulations under which these combinations were certified will be repealed. Outstanding stocks will be decertified. These orders will be published in the *Federal Register* later this week and will become effective 40 days later. This will allow 30 days for the companies to file objections and to seek a hearing, ten days for our review of the objections, and time for recalls to be completed.

Anyone who may be adversely affected by these actions may file objections within 30 days after publication and request a hearing. Such requests must state reasonable grounds for a hearing, identifying any claimed errors in the NAS–NRC evaluation or any adequate, well-controlled investigations which may be offered as evidence of safety and effectiveness. As in the case of Panalba, however, we do not intend to permit the continued marketing of the pen-sulfa and pen-strep combinations during any hearing proceedings that may take place.

I also have signed an order to repeal the regulation and revoke certificates for Mysteclin-F, Squibb's combination of tetracycline and amphotericin-B. Since our announcement in December 1968 that this fixed combination is ineffective, we have received and reviewed additional data and have concluded that substantial evidence still is lacking to support claims in the labeling. The order regarding Mysteclin-F will take effect 40 days after publication in the *Federal Register* unless stayed by proper objections.

I can also report to the Committee, Mr. Chairman, that we will be publishing shortly the Academy's findings and FDA's proposals regarding sulfonamides, another widely-used class of anti-infective drugs. Labeling revisions will be necessary to restrict markedly the indications for use, although the sulfonamides have been found effective for uncomplicated urinary tract infections and for prophylaxis in rheumatic fever. The industry, and any other interested parties, will be given an opportunity, of course, to react to these findings.

I hope that these examples have given the Committee some indication of how we are proceeding with the chalenging task of carrying out the NAS–NRC recommendations. Let me turn now, Mr. Chairman, to another challenge I believe is involved; namely, that of disseminating the information from the Academy as widely as possible within the medical profession. We are using a variety of approaches to achieve this end.

When safety is not an issue, we do not plan to remove a drug from distribution while a hearing is in progress. But in those cases, we will insist that all promotional material for such products state the Academy's finding, and FDA's concurrence, regarding the drug's lack of efficacy. The physician is entitled to this information and we intend to see that he gets it.

When new labeling is required as a result of Academy recommendations, we will require the firms involved to publicize the changes in their advertising and other promotional material. Their detail men also will be required to provide this information to physicians and to others with whom they deal. FDA itself

also will be communicating with physicians, both directly and through their journals. We are now preparing a "Dear Doctor" letter describing our position on the combination antibiotics, using Novobiocin and Panalba as specific examples. We are providing major medical journals with copies of NAS–NRC efficacy reports and have asked their cooperation in getting this information to physicians.

We are exploring the possibility of developing an FDA publication specifically designed to alert the profession of significant new drug information. We may also utilize "white papers" to explain the scientific rationale for new prescribing information.

Before closing, Mr. Chairman, I would like to touch upon some of the broader implications of the drug efficacy requirements now set forth in law. After enactment of the 1962 Amendments, FDA at first attempted to accommodate its greatly expanded drug review functions within the same system employed to carry out the much simpler job of clearing drugs for safety. In short, these responsibilities were to be carried out wholly within the Bureau of Medicine.

The first departure from this pattern was the decision by Dr. Goddard to utilize the NAS–NRC in the efficacy review of pre-1962 new drugs. This contract opened up to a broad segment of the medical community the whole question of drug efficacy.

I am convinced that we must move farther in this direction. The FDA must be able to tap the resources of the outside medical community to properly carry out its own responsibilities.

During the time I served as Director of the Bureau of Medicine, I initiated the establishment of approximately 10 new advisory committees oriented principally toward classes of drug products. A number of these committees began functioning this past year. In time, I believe all of these committees will assume a role within the Bureau of Medicine as valuable as that carried out in regard to contraceptives by the Advisory Committee on Obstetrics and Gynecology.

Mr. Chairman, you and the other Committee members are undoubtedly aware of the recent proposals to have FDA's drug evaluation function turned over to a group similar to the Dunlop Committee in Great Britain. Presumably, these proposals rest on the assumption that the system in Britain is superior to ours. The British, however, indicated they were not satisfied with their system by enacting a new "Medicines Act." This legislation, not yet implemented, establishes new drug review requirements markedly similar to those of FDA. The chief difference between the projected British operation and our own, as I understand it, is a greater reliance in Britain on advisory committees whose members will serve on a part-time basis as consultants to the permanent staff. But even this difference will diminish in time as FDA makes greater use of outside medical experts.

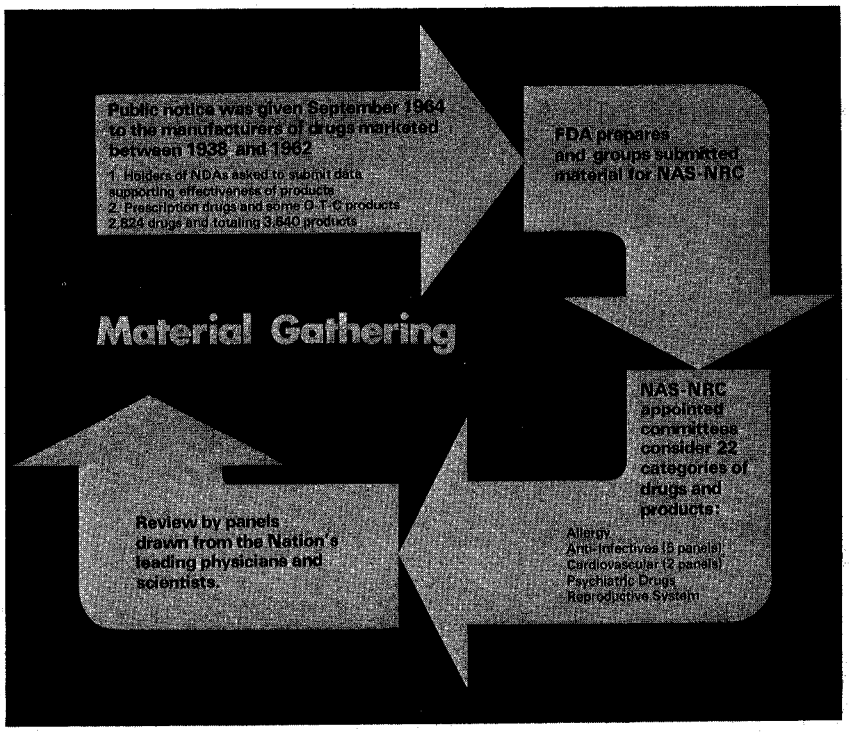
FDA's determination to draw upon the best available scientific and medical expertise can be of only limited value, however, unless the drug industry shows a similar concern. The major problem in industry submissions to FDA is still the poor quality of both basic data and summaries. The most important single step that industry can take to speed up the processing of new drug applications by FDA is to ensure that data presented in support of efficacy are derived, as the law requires, from well-controlled studies. A single, well-designed study involving 200 patients can be far more convincing than masses of data on 2,000 patients studied by 100 different physicians, each of them using different criteria for patient selection and different protocols for drug administration. This fact is so obvious that it shouldn't bear repeating. But I am repeating it because of the equally obvious fact that the drug industry is not practicing the sound research it preaches so well in the READER'S DIGEST and elsewhere.

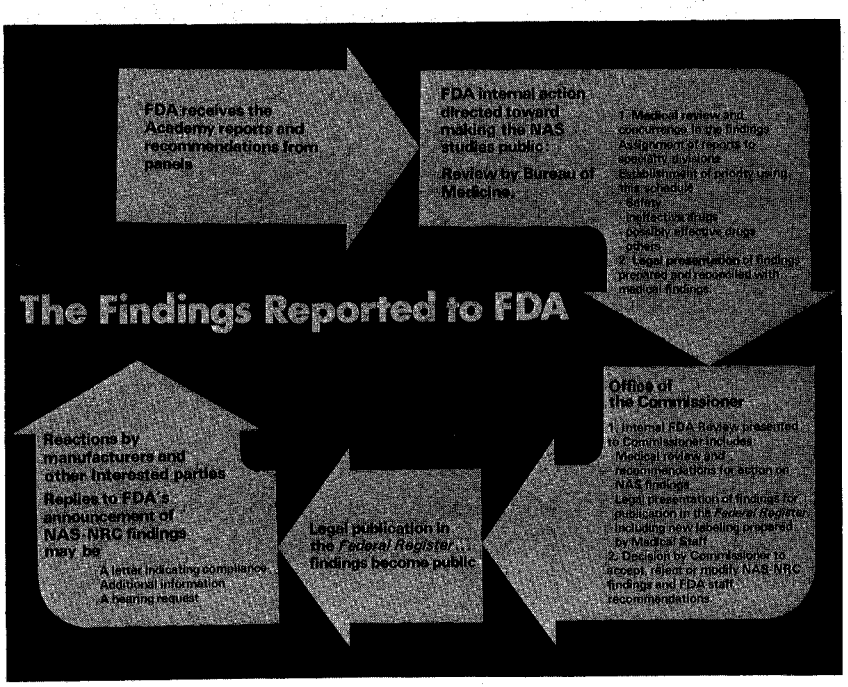
The conflict between commercial and therapeutic goals, a conflict as real as it is regrettable, stands as the major impediment to the prompt implementation of the NAS-NRC efficacy recommendations. It is now apparent that the resistance of industry is going to be both intense and prolonged when the effectiveness of a profitable product is challenged. We anticipate protracted legal confrontation between industry and FDA as the Agency takes the regulatory action necessary to carry out efficacy findings.

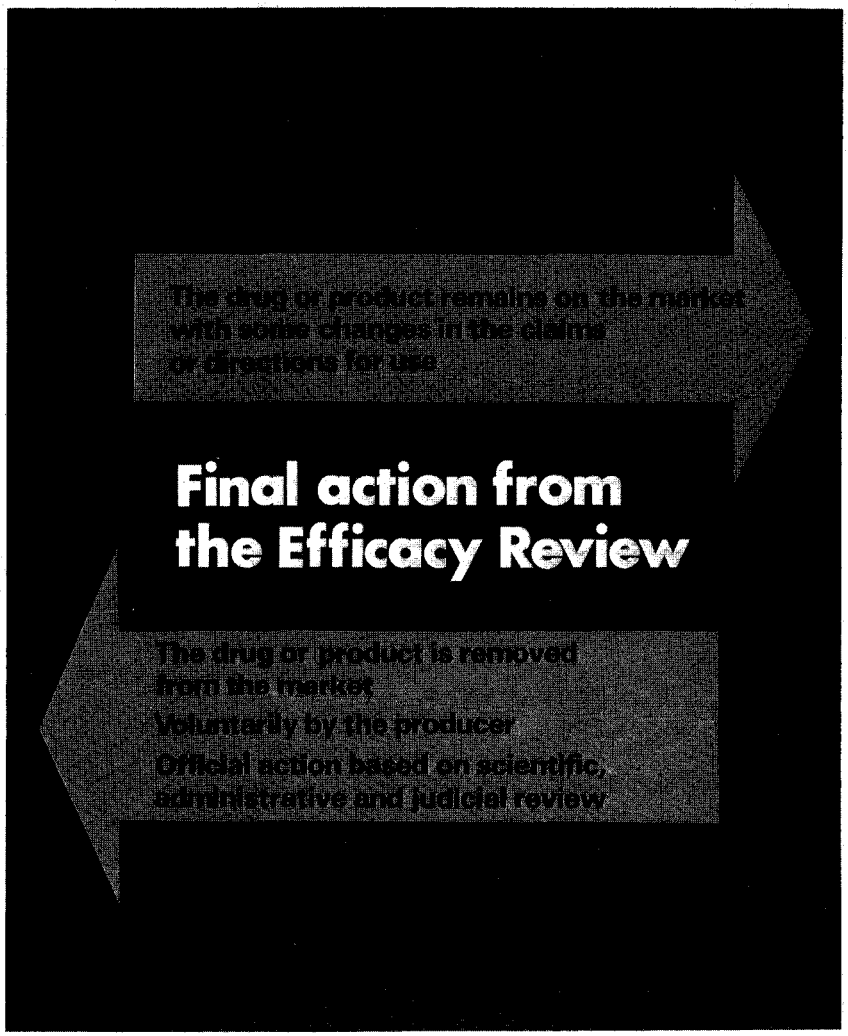
We now estimate that the Bureau of Medicine's work of evaluating and recommending appropriate follow-up action on NAS-NRC reports will be largely completed by the end of 1971. But the full implementation of these decisions in the face of industry opposition, will require a massive effort on the part of the Agency's regulatory and legal staff extending well beyond 1971.

Thank you. My staff and I will be happy to respond to your questions.

FDA Drug Efficacy Study and Implementation


Public notice was given September 1964 to the manufacturers of drugs marketed between 1938 and 1962
1. Holders of NDAs asked to submit data supporting effectiveness of products
2. Prescription drugs and some O.T.C products
2,824 drugs and totaling 3,840 products
FDA prepares and groups submitted material for NAS-NRC
Material Gathering
NAS-NRC appointed committees consider 22 categories of drugs and products:
Allergy
Anti-Infectives (5 panels)
Cardiovascular (2 panels)
Psychiatric Drugs
Reproductive System
Review by panels drawn from the Nation's leading physicians and scientists.


FDA receives the Academy reports and recommendations from panels
FDA internal action directed toward making the NAS studies public:
Review by Bureau of Medicine.
1. Medical review and concurrence in the findings
Assignment of drugs to appropriate evaluation panel
Establishment of priority use of this schedule
Safety
Ineffective drugs
possibly effective drugs
others
2. Legal presentation of findings, prepared and reconciled with medical findings
The Findings Reported to FDA
Office of the Commissioner
1. Internal FDA Review presented to Commissioner includes:
Medical review and recommendations for action on NAS findings
Legal presentation of findings for publication in the Federal Register, including new labeling prepared by Medical Staff
2. Decision by Commissioner to accept, reject or modify NAS-NRC findings and FDA staff recommendations
Reactions by manufacturers and other interested parties
Replies to FDA's announcement of NAS-NRC findings may be:
A letter indicating compliance
Additional information
A hearing request
Legal publication in the Federal Register... findings become public


The drug or product remains on the market with some changes in the claims or directions for use
Final action from the Efficacy Review
The drug or product is removed from the market
Voluntarily by the producer
Official action based on scientific, administrative and judicial review

5/14/59

CHLORAMPHENICOL & METHODS OF PHYSICIANS' PURCHASE TO CHLORAMPHENICOL BASE OF PANALBA & MYSTECLIN-F

STATE	PHYSICIANS	STATE	PHYSICIANS	STATE	PHYSICIANS
Alabama	60	Kansas	69	New York	194
Alaska	3	Kentucky	32	North Carolina	58
Arizona	13	Louisiana	85	North Dakota	2
Arkansas	46	Maine	51	Ohio	220
California	162	Maryland	20	Oklahoma	85
Colorado	35	Massachusetts	156	Oregon	30
Connecticut	73	Michigan	119	Pennsylvania	260
Delaware	11	Minnesota	19	Rhode Island	25
District of Columbia	3	Mississippi	12	South Carolina	48
Florida	82	Missouri	75	South Dakota	8
Georgia	26	Montana	1	Tennessee	37
Hawaii	22	Nebraska	11	Texas	210
Idaho	5	Nevada	20	Utah	4
Illinois	122	New Hampshire	20	Vermont	2
Indiana	61	New Jersey	185	Virginia	46
Iowa	20	New Mexico	7	Washington	30
				West Virginia	14
				Wisconsin	27
				Wyoming	2

CLINICS & HOSPITALS 151

GRAND TOTAL 3,036



MEMORIAL CLINIC
529 WEST FOURTH AVENUE 357-0323
OLYMPIA, WASHINGTON
98501

Herbert L. Ley, M. D.
Commissioner of Food & Drugs
Dept. of Health, Education & Welfare
Washington, D. C.

Dear Dr. Ley:

I have used Mysteclin F for a number of years in my practice. I find it very useful when instituting broad spectrum antibiotic therapy where monilia overgrowths are a factor, as in O. B.'s, diabetics, etc.

I sincerely believe it should remain in our armentarium of antibiotic formulations.

Sincerely yours,

E. S. Vandeman, M.D.



MEMORIAL CLINIC
820 WEST FOURTH AVENUE 357-9323
OLYMPIA, WASHINGTON
98501

Herbert L. Ley, M. D.
Commissioner of Food & Drugs
Dept. of Health, Education & Welfare
Washington, D.C.

Dear Dr. Ley:

I have used Mysteclin F for a number of years in my practice. I find it very useful when instituting broad spectrum antibiotic therapy where monilia overgrowths are a factor, as in O. B. 's, diabetics, etc.

I sincerely believe it should remain in our armentarium of antibiotic formulations.

Sincerely yours,

T. R. Hazelrigg MD



MEMORIAL CLINIC
829 WEST FOURTH AVENUE 357-3323
OLYMPIA, WASHINGTON
98501

Herbert L. Ley, M. D.
Commissioner of Food & Drugs
Dept. of Health, Education & Welfare
Washington, D. C.

Dear Dr. Ley:

I have used Mysteclin F for a number of years in my practice. I find it very useful when instituting broad spectrum antibiotic therapy where monilia overgrowths are a factor, as in O. B. 's, diabetics, etc.

I sincerely believe it should remain in our armentarium of antibiotic formulations.

Sincerely yours,

Roger L Barnett MD



MEMORIAL CLINIC
329 WEST FOURTH AVENUE 357-9223
OLYMPIA, WASHINGTON
98501

Herbert L. Ley, M. D.
Commissioner of Food & Drugs
Dept. of Health, Education & Welfare
Washington, D. C.

Dear Dr. Ley:

I have used Mysteclin F for a number of years in my practice. I find it very useful when instituting broad spectrum antibiotic therapy where monilia overgrowths are a factor, as in O. B. 's, diabetics, etc.

I sincerely believe it should remain in our armentarium of antibiotic formulations.

Sincerely yours,

P.O. Box 2807
Nashville, Tenn. 37219
January 14, 1969

Food & Drug Administration
Washington
D.C.

Dear Sirs:

In regard to your investigation of the drug Mysteclin F, I was a user of this drug, and unfortunately, had a side-effect which affected me more than the illness.

In other words, I question Squibb's contention that the drug is safe.

If you are continuing your investigation and would like more information, by all means let me know.

Sincerely,

Howard B. Olson

Howard B. Olson

RECEIVED
JAN 21 1969
REGULATIONS AND POLICY OFFICE
BUREAU OF MEDICINE
FOOD AND DRUG ADMINISTRATION, DHEW

DATE: 1-15-69

Edward B. Lay, Jr., M.D.
Commissioner of Food and Drugs
Dept. of Health, Education, & Welfare
Washington, D.C. 20204

Dear Doctor Lay;

Kysteclin-F has had a definite useful place among the antibiotics prescribed in my practice, particularly for those types of patients prone to candidal infections(women with a history of candidiasis, elderly patients, diabetics, patients on corticosteroids, etc.)

The FDA order to withdraw Kysteclin-F from availability for prescription use would create an unnecessary and inconvienient restriction on my prescribing freedom to the detriment of my patients.

Sincerely yours,

L. D. Clark M.D.

I have not had any reactions
to Bicillin injections while using
Kysteclin F.

L. D. Clark M.D.