COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

HEARINGS

BEFORE THE

SUBCOMMITTEE ON MONOPOLY

OF THE

SELECT COMMITTEE ON SMALL BUSINESS

UNITED STATES SENATE

NINETIETH CONGRESS

FIRST SESSION

ON

PRESENT STATUS OF COMPETITION IN THE PHARMACEUTICAL INDUSTRY

PART 2

JUNE 27, 28, 29, JULY 24, AND AUGUST 8, 10, 1967

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CONTENTS

HEARING DATES

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

TUESDAY, JUNE 27, 1967

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

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

Present: Senators Nelson, Scott, and Hatfield.

Also present: Benjamin Gordon, staff economist; Daniel T. Coughlin, minority counsel; Susan H. Hewman, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. We will open the hearings of the Senate Subcommittee on Monopoly. I want to read a brief statement prior to hearing the first witness.

In the interest of proceeding in a fair, judicious and orderly manner, I would like to comment at this time on an effort which has been made by Mr. Joseph Stetler, president of the Pharmaceutical Manufacturers Association, to prejudice the work of this subcommittee in the eyes of the general public.

Mr. Stetler has been writing letters to newspaper editors, in my State at least, charging that the hearings on prescription drug prices held so far by this subcommittee have distorted the facts, and that drug manufacturers have been denied an opportunity to testify.

This charge is, of course, completely false, as Mr. Stetler himself knows. However, the newspapers to which he has been writing have no way of knowing for certain that his statements are false, and some have published his statements and editorials in my State, critical of me, based upon his false statements.

On May 10, 5 days before these hearings began, Mr. Stetler and Attorney Roy Ingoldsby came to my office to discuss the hearings. I assured them that ample opportunity would be given the drug industry to be heard. I suggested that he listen to the testimony for a few days and when he decided on the appropriate time for industry to be heard he should come to see me and we would set a time for their appearance. To this date he has not come to me with any request to appear either in behalf of his association or any company he represents.

I wrote this statement last night. Ten minutes before I came down here a letter was written to my office from Mr. Stetler for the first time requesting an opportunity to appear. That letter was based

upon a response to a letter I wrote to him last week, because I thought he ought to have the courtesy of knowing what I was going to say today before I said it.

So I outlined the statements that had been made to Mr. Stetler by me in my office, and then he in response to that delivered a letter, and about 10 minutes to 10 it came to my desk.

I repeated this invitation, that is the invitation I made in my office to him and Mr. Ingoldsby. I repeated this invitation during hearings on May 16, the second day of the hearings. At those hearings I stated that Mr. Stetler had been invited and that the industry was invited to come and would be heard. I said it again on June 8, the fifth day of the hearings, publicly from the chair. During a discussion with Senator Javits, I stated:

We want the companies in here to speak for themselves, and I understand that to be the Senator's position.

Senator Javits agreed with that, said it was his position.

In fact, if the subcommittee should possibly run into difficulty obtaining testimony from the drug companies, Senator Javits suggested that they might be subpenaed. I mention this simply to show the determination on the part of the subcommittee to hear drug industry witnesses. There never has been any question about that point from the very start, and Mr. Stetler knows it.

Yet Mr. Stetler has tried to make that the issue. Even though he has not accepted my invitation after hearing it in my office, and after it was twice repeated at a public hearing, he has repeatedly charged that we will not let him testify.

He made this false charge in a letter released to the press on June 6. He made it again in a letter to newspapers in my State dated June 14.

In this letter of June 14, Mr. Stetler stated:

We have yet no idea when Senator Nelson will give the American public an opportunity to hear from the industry.

This, despite the fact that I had told him twice publicly and once in my office to let me know when they wanted to be heard.

It is interesting to note that on the same day that Mr. Stetler was writing Wisconsin newspapers stating that we were refusing to hear drug industry witnesses, he wrote another letter to the drug industry stating the exact opposite.

In this second letter, also sent on June 14, Mr. Stetler quoted me as having "encouraged all interested persons to participate," and Mr. Stetler went on and urged the drug industry spokesmen to accept my invitation, so we had two contradictory letters going out on the same day.

Meanwhile, as Mr. Stetler was carrying on this dual correspondence, we were actually making arrangements with major drug manufacturers to testify.

On June 12, I personally wrote to the Schering and Parke-Davis companies and invited them to testify. They agreed to do so, and they will be heard in July. Just yesterday, E. R. Squibb & Sons wrote to me to indicate a desire to testify. A date will be set for their testimony.

These are the first requests that I have received from industry to testify. Two industry representatives came to see me in my office and when asked "When do you want to testify?" told me that they weren't

interested in testifying. So the first request I got was from E. R. Squibb & Sons.

For the fourth time, I repeat the invitation of the subcommittee to Mr. Stetler and the drug manufacturers to advise us when they wish to testify.

So that there will be no question about the subcommittee's willingness to hear him, I will remain at the presiding officer's chair at the close of this set of hearings on June 29, to consider requests to testify from Mr. Stetler or any other representatives of the drug industry. A date will be set to hear them, just as dates will be set to hear the three firms which have already responded to my invitations to them to testify.

I hope that, with that question settled, we can get back to the serious questions which form the subject of this inquiry. The subcommittee has an important task to perform, and we will not be dissuaded by attempts to divert us or to inflame public opinion against us.

From the very first day of the hearings it has been perfectly clear that the Pharmaceutical Manufacturers Association intended to indict the committee rather than supply us with any information about the important questions that exist. I am sure that that does not represent the position of the many very fine companies that the Pharmaceutical Manufacturers Association represents, and two companies have come to me privately to say so.

Senator HATFIELD. Senator Nelson.

Senator NELSON. Yes.

Senator HATFIELD. Senator Nelson, I would like to make a comment. I appreciate the statement that you have just made for the record. I would like to add to that statement that prior to the beginning of these hearings, I had conversations with both representatives of various pharmaceutical houses as well as the chairman of this subcommittee, and I recall that even during the first one or two hearings, the chairman reiterated what he told me prior to the beginning of this hearing—that all parties would have an opportunity to be heard, and there is nothing that the chairman has done or said that would indicate contrariwise.

I assured these representatives of the pharmaceutical houses that they would have this kind of opportunity, and if they did not find it convenient or they did not find it possible to testify at certain times, I would like to be informed and I would certainly take it up with the chairman.

I have not been informed to the contrary, so from everything I know from my contacts with the pharmaceutical houses, with my contact with the chairman as a member of this subcommittee, I want to assure the chairman that I can certainly second his comments here as to the procedures that have been followed and are being followed to give fair and equitable hearing to all parties.

Senator NELSON. I want to thank you, Senator Hatfield.

The fact of the matter is I have had the opportunity over a period of some 18 years to serve on legislative committees. I never have intentionally conducted an unfair hearing any time in my life, and I do not intend to now.

This committee wishes to hear the most informed and the best testimony we can get involving various problems in this field. This

is not a hearing to indict anybody. It is not a hearing for the purpose of a running criticism of anybody. Everybody will concede, privately at least, including representatives of the drug industry, that there are problems in the area.

I happen to recognize, as any informed person does, that the drug industry has made a great contribution to medicine. I happen to recognize that the medical profession has made a great contribution, and so has the corner druggist. But that doesn't mean that there aren't problems in existence here that ought to be explored and some sensible solutions to them sought.

We have not, and do not intend to invite people to appear before the committee who are not responsible people. If you look at the list of witnesses you will see that we have had some very, very distinguished witnesses from across the United States, and we will hear distinguished witnesses from the drug industry, and they will be afforded the opportunity to present their position on any issue that has been raised before this committee by any witness, and they will be afforded all the time that they want to do so. And Mr. Stetler has understood that from the very first day of the hearings, though he has misrepresented the position of this committee throughout the United States.

We will hear our first witness this morning, Dr. Harry L. Williams.

Dr. Williams, we appreciate your taking time from your busy schedule to appear here today. You have filed with the committee biographical data. We are all well aware of your very distinguished background and your professional credentials, but if you would for the purposes of the opening of the hearing, just recite briefly your background, we will file in the record your detailed biographical data, and you may present your statement in any fashion that suits you, either by reading it in full, or dealing with it extemporaneously. If you don't mind, I may interrupt you to ask some questions as they occur to me. If you do mind, we can wait until the end.

(The biographical data referred to follows:)

CURRICULUM VITAE: HARRY L. WILLIAMS

Born December 25, 1919, Detroit Michigan.

Degrees

B.S.—University of Chicago, 1949.
M.D.—University of Chicago, 1952.

Education

1939–41—Wayne University, Detroit (night school).
1947–52—University of Chicago.
1952–53—Internship, King County Hospital, Seattle, Washington.

Positions

1938–43—Laboratory technician, Parke, Davis & Company, Detroit, Michigan.
1943–48—Research Assistant in Pharmacology, University of Illinois College of Medicine, Chicago, Illinois.
1951—Research Assistant in Pathology, University of Chicago.
1953–54—Research Associate in Pharmacology, University of Illinois College of Medicine, Chicago, Illinois.
1954–60—Assistant Professor of Pharmacology, Emory University School of Medicine, Atlanta, Georgia.
1960–64—Associate Professor of Pharmacology, Emory University School of Medicine, Atlanta, Georgia.
1963—Professorial Lecturer in Pharmacology, University of Oklahoma School of Medicine, Oklahoma City, Oklahoma.

1964—Professor of Pharmacology, Emory University School of Medicine, Atlanta, Georgia.
1966—Assistant Professor of Medicine, Emory University School of Medicine, Atlanta, Georgia.

Societies

The American Society for Pharmacology and Experimental Therapeutics, Inc.
The New York Academy of Sciences.
National Society for Medical Research.
Alpha Omega Alpha.
American Association for the Advancement of Science.
American College of Neuropsychopharmacology.
Southern Electroencephalographic Society.
Sigma XI; President, Emory Chapter, 1962–63.
American Society of University Professors; President, Emory Chapter, 1963–64.
American Association for Laboratory Animal Science.

Awards

Harry Ginsburg Memorial Prize for research in Physiology (University of Chicago, 1951).
Markle Scholar in Medical Education, 1955–60.
Best Basic Science Professor by Emory Senior Medical Class, 1965–66.
Outstanding Faculty Award for Medicine by Pi Delta Epsilon and the 1967 Emory "Campus".

Emory University activities

Chairman of Animal Care Committee and Director of Central Animal Facility.
Member of Formulary Committees of Grady Memorial and Emory University Hospitals.
Advisory Committee of Division of Basic Health Sciences.
Adult Education Committee.
Premedical Curriculum Committee.
Medical School Curriculum Committee.
Committee on Educational Policy.
Patent Committee.
University Senate; President, 1965–66.
Standing Committee on Promotions and Appointments, Division of Basic Health Sciences.
Interdivisional Student Affairs Committee.
Admissions Committee, School of Medicine, 1954.
Therapeutic Trials Committee, School of Medicine.

Nonuniversity activities

Consultant to Southeast Regional Committee, American Social Health Association.
Medical Consultant, Epilepsy Foundation of Atlanta.
Board of Directors, Planned Parenthood of Atlanta.
Pharmacy and Chemistry Committee, National Institute of Mental Health.
Consultant to Georgia State Drug Vendor Program.
Consultant in EEG, Atlanta Veterans Administration Hospital, 1954–66.
Member Joint Committee, FDA–NIMH, on LSD and Drug Abuse.

STATEMENT OF DR. HARRY L. WILLIAMS, PROFESSOR OF PHARMACOLOGY, EMORY UNIVERSITY SCHOOL OF MEDICINE, ATLANTA, GA.

Dr. WILLIAMS. I don't mind at all.
Senator NELSON. Go ahead, Dr. Williams.
Dr. WILLIAMS. Briefly, just relating to my experience with drugs, beginning in 1937 with a year in a retail drugstore, moved from there to Parke-Davis in 1938, where I worked from 1938 to 1943 as a technician. This was after high school training.

I went in the Navy and was stationed at the pharmacology research part of the Naval Medical Research Institute in Bethesda for 3 years. Following that, I went to the University of Chicago to get my B.S. and my M.D. I was a little bit older than most of the medical students.

I interned at King County Hospital in Seattle, came back to the University of Illinois in Chicago to teach 1 year in pharmacology and then went to Emory University in Atlanta, Ga., in 1954, where I have been since this time. I am now a professor of pharmacology, and an assistant professor of medicine at Emory University.

I have had a long interest in the relative usefulness and the relative cost of drugs, so when I had a chance in 1960 to be adviser to Grady Memorial Hospital in Atlanta in their drug purchasing practices, I was, I might say, happy to take the job. I have advised them since this time, and advised the State on the drugs to be listed in the State drug vendor program.

My special areas of interest are drugs which act on the nervous system. I belong to the usual societies. I am on two national committees, one a joint committee of the Food and Drug Administration and the National Institutes of Mental Health on LSD, and another a committee of the Psychopharmacolog Service Center at National Institutes of Mental Health. I think that is probably sufficient.

Senator NELSON. Thank you, doctor. Go ahead.

Dr. WILLIAMS. As I had indicated, in 1960 Grady Memorial Hospital in Atlanta, Ga., faced with a rapidly increasing expenditure for drugs year by year despite a somewhat limited formulary, decided to appoint a new formulary committee and seek outside help for their drug cost problem. Actually, at this time they hired me as an adviser to a formulary committee.

Grady Hospital is a large charity hospital supported largely by the two metropolitan Georgia counties, Fulton and DeKalb, and operated by the Fulton-DeKalb Hospital Authority. The medical services in the hospital are the responsibility of the Emory University School of Medicine plus a large staff of volunteer physicians from the community. In 1965 the hospital provided for 293,258 days of inpatient care and 486,214 outpatient clinic visits. In addition to a resident and intern staff numbering 210 the hospital provides the major training area for the medical students of Emory University. I say this to point out that this is a very large operation.

Most important to our discussion today is the fact that Grady Hospital pharmacy fills over 600,000 inpatient and outpatient prescriptions yearly. In 1965 the yearly total was 600,542. On a 5-day week basis this amounts to 2,300 prescriptions daily, of which about 1,900 are outpatient prescriptions comparable to those filled in a local pharmacy.

Senator NELSON. These outpatient prescriptions are filled by yourselves?

Dr. WILLIAMS. At Grady, they are filled by ourselves. There are only a few operations as large as this in the country, I believe Los Angeles and a couple of others.

Prior to 1960 as I said, the hospital administration had watched its drug bill rise fairly steadily from $183,901 in 1953 to $470,000 in 1959. This rise could not be accounted for by an increase in prescriptions or patient care. In surveying drug purchase policies and prescribing habits at the hospital, the new formulary committee found that, except

for a very few old drugs such as aspirin, drugs were being ordered by trade names rather than generic names; there were confusing duplications of drugs that had the same therapeutic action and that the pharmacy was in chaos attempting to keep multiple trade name equivalents of the same drug in stock. In addition, the hospital was spending as much as $50,000 yearly for drugs which had no proved useful therapeutic action.

A few examples, many could be cited. The hospital was paying $167 per 1,000—these are wholesale costs—for a trade name cortisone-type drug when a comparable generic product could be bought for $6 per 1,000.

Senator NELSON. May I interrupt a moment here?

Dr. WILLIAMS. Yes.

Senator NELSON. Then you did change in your formulary to the comparable $6 per 1,000 generic drug; is that correct?

Dr. WILLIAMS. Yes, we did.

Senator NELSON. And have the physicians in the hospitals observed any difference in the therapeutic effect of the $6 per 1,000 versus $167 per 1,000 drug?

Dr. WILLIAMS. None whatsoever.

Senator NELSON. So you are satisfied that the generic name was as good as the trade name you had been using.

Dr. WILLIAMS. As a matter of fact, there were later assays on these drugs published by the Medical Letter, who actually assayed them, and the drug we were using was as good.

Senator NELSON. Thank you.

Dr. WILLIAMS. They were paying $22.50 per 1,000 for trade name Dexedrine when equivalent generic dextroamphetamine could be purchased for 71 cents per 1,000.

Senator NELSON. Wasn't Fulton County still purchasing dextroamphetamine as of the time of the hearings a month ago?

Dr. WILLIAMS. That is right. This is sort of a confusing error. The people in New York sent a questionnaire to the Fulton County purchasing agent, and they buy just a few drugs for the county jail, and they don't have any major drug usage. If the letter had gone to Grady Hospital, where most of the drugs are purchased, it would have been different. It caused a local stir in our papers, but it was a little unfair, because they were comparing a generic price in New York with a trade name price in Atlanta.

Senator NELSON. But Grady had already switched over to purchasing generic dextroamphetamine.

Dr. WILLIAMS. We switched from trade name Dexedrine to generic dextroamphetamine.

Senator NELSON. Did you find any difference in the therapeutic value of your generic dextroaphetamine versus Dexedrine?

Dr. WILLIAMS. None whatsoever. We were buying expensive antibiotics such as tetracyclines on a trade name basis. Now there were at the moment no generic tetracyclines available, but I want to make this point, because I would like to show during my testimony that it is possible to get the major drug firms to compete, if one goes about this properly.

But at the time we took over, they would just order one trade name tetracycline or another, and the prices were always the same, right

at $22.50, which was not too different from the price paid by a local pharmacy.

Those of us who had been vaguely aware that trade named items were more expensive than non-trade-named items were nonetheless appalled when trade named items were found, as shown by the examples above, to be in many cases 20 to 30 times as expensive as their generic equivalents. Not 2, 5, or 10 percent more as might be expected in other areas of commerce, but 2,000 to 3,000 percent more.

One of the members of the Fulton-DeKalb Hospital Board that sits on the bid openings for the pharmacy orders, a businessman, was quite shocked. He is used to 1 percent for cash and 2 percent for faster delivery, and he couldn't believe his eyes when he saw these price differentials that came in every month on the drug bids.

The formulary committee of Grady Memorial Hospital was in general agreement on the following procedures for the future operation:

1. Drugs would be prescribed and ordered on a generic rather than a trade name basis and purchased on a low bid basis when possible.
2. Needless duplications of drugs having the same therapeutic action would be deleted from the formulary.
3. Where different trade name drugs had equivalent therapeutic action we would use the drug which was the least expensive. This No. 3 it turned out to give us as much in the way of savings as the use of the generic name.
4. New drugs which were minor molecular modifications of established drugs with no clear-cut therapeutic advantages would not be considered until they had been on the market at least 1 year, where we would have ample time to see if the extravagant claims made for their superiority were really true.
5. Drugs would not be considered that did not have clearly established therapeutic value or therapeutic action clearly superior to older products available under generic names, and which we knew more about in terms of side effects.

The result was a trimmed down hospital formulary of which the committee has copies. Including drugs, nursing items, and diagnostic items, the formulary contains about 800 to 900 items. This compares with as many as 14,000 items in some large pharmacy operations.

It was not easy in the beginning. As you might imagine, the medical profession is conservative. This was a radical departure of performance at Grady Hospital. There were complaints that the committee was trying to dictate the type of medicine practiced at the hospital, that Grady Hospital patients would be poisoned by cheap inferior drugs, that the change from one color of pill to another would upset the Grady Hospital patients in an irremedial manner, that we should buy trade named expensive items to support the research done by the large drug companies, and that the committee was attacking the American free enterprise system.

We persisted, with support from a large part of the faculty, and the total support of the administration of the hospital, who were interested in cutting this enormous drug bill.

We have been fortunate—estimated savings during the first year ran as high as $150,000 on a budget of $480,000 for drug purchases.

Some of this savings was due to the elimination of drugs with no proved therapeutic action; some of it was due to price breaks on trade named items once the major companies were forced to compete on a trade name basis, and this is very important. And some of it was due to the purchase of generic name drugs. Introduction of new useful expensive drugs changing the therapeutic habits of the house staff and some increase in patient load have combined to produce a continuing increase in overall drug costs at Grady Hospital, despite our efforts to hold them down. Reference to page II of the "Grady Formulary" will show that the yearly drug costs at the hospital have increased more or less steadily from $308,000 in 1958 to $738,000 in 1965. Much of this has been due to the introduction of expensive new antibiotics, including the semisynthetic penicillins, the oral antidiabetic agents, and some of the new anti-inflammatory analgesics such as Indomethacin or Indocin. These agents are clearly patented for the next 17 years and Grady Hospital pays essentially the same amount for them that the corner pharmacist pays.

It remains difficult to say exactly how much we save—because of this escalation and change in prescribing habits—by generic prescribing, bid purchasing and the formulary system at the present time, although recently installed computer techniques will give us these figures in future years; we can get an automatic feed-out of just what our savings are.

One way of estimating our savings is to compare the cost of drugs in the outpatient prescriptions at Grady Hospital with the average cost of drugs in the prescripitions of private pharmacies across the country. Between April 28 and June 2 of this year—37 days inclusive—the Grady outpatient pharmacy filled 43,100 prescriptions. The cost of the drugs used was $48,758 for an average drug cost of $1.14 per prescription. Similar figures for community pharmacies can be calculated from the data in Tile & Till (Vol. 53, No. 2, June 1967). Preliminary figures on community pharmacy practice from the Lilly Digest, a report on 1,234 community pharmacies surveyed in 1966, indicate an average prescription charge of $3.56. If we subtract an average markup of 40 percent, the cost of drugs in the average prescription would be $2.14, or nearly double the Grady average outpatient prescription cost of $1.14. It should be noted I think, in fairness, at this time that an operation such as the one at Grady Hospital cannot be equaled by local pharmacies, or even by many very small hospital pharmacies. Grady Hospital gets some discounts for quantity purchases, does some manufacturing, very little, and we prepackage our own drugs—and all of these things are important in reducing the average Grady prescription cost to $1.14. However, since the Grady outpatient prescription is generally for a month's supply of drugs, and the usual private pharmacy prescription is for a shorter period, I think that any minor adjustments in the figures for the drug costs in the two types of prescriptions would not significantly change the ratio. I have a suspicion it might change it in our favor.

The inescapable conclusion is that Grady Hospital, through its formulary and pharmacy practices, is saving a considerable amount of money. In addition to the savings effected, there was a noticeable increase in the quality of pharmacy services and efficiency made possible by the smaller number of items stocked. Several times the watch-

dog action of the formulary committee has prevented the introduction of items such as Mer–29 and some of the long-acting sulfa drugs which were later proved to be toxic, and were withdrawn from the market.

It was some of these things I think that encouraged the hospital staff to support us, the fact that we were doing more than just saving dollars. None of the dire predictions have come to pass. We have poisoned no Grady Hospital patients with "cheap" drugs and have confused neither the patients nor the hospital staff with rare changes in pill color, although we have had one minor instance of poor shelf life and reduced potency in a generic injectable preparation which led us to change suppliers.

Senator NELSON. Did you still get a generic supplier?

Dr. WILLIAMS. No, this happened to be a trade name supplier, but this happened to be in an area where it was an old drug, where trade name costs are not vastly different from generic costs. They may be double, but not 10 or 20 or 30 times.

This drug, incidentally, tested out to be all right by USP methods. It just happens that there are newer, more sophisticated ways of assay which showed it to have reduced potency. So the ordinary USP assay, which would be required on this, showed it to be all right.

We have occasional arguments with the house staff about this or that drug, but in general the administration and the staff of the hospital feel that the formulary committee operation has resulted in improved pharmacy practices, improved patient care and considerable savings in money to the hospital, allowing these funds that might have been spent on more expensive drugs to be diverted to other areas of patient care in the hospital.

We have been fortunate, as I have already stated. We were helped a great deal in the early days by the Medical Letter, whose generally expert opinion on the comparative value of the new and old drugs could be used to reinforce our own stand. We were moving into a new area. We were one of the first major hospitals in the country to do this, and we needed every bit of help we could get.

Senator NELSON. What year?

Dr. WILLIAMS. In 1960. The information presented to the Kefauver hearings helped us a lot, because it helped in subtle ways to change public opinion and the attitude of some of the medical profession toward the generic versus the trade name controversy, and these added ammunition that we could use all the time.

Our experiences over the past 7 years of the formulary committee operation have, however, led me to several conclusions about advertising and pricing policies of the major drug companies and the prescribing habits of physicians, which are just as important:

1. Trade named drugs are arbitrarily priced by manufacturers and the prices bear no relationship to the cost of manufacture, distribution, or research directly relatable to a given drug. New drugs for acute disease states tend to be priced in the $200 to $300 per 1,000 range—antibiotics, et cetera—and new drugs for the treatment of chronic disease in the $30 to $70 per 1,000 range—diuretics, tranquilizers, et cetera. It should be clear all along here that these are wholesale prices to Grady Hospital and that the pharmacy may pay a little bit more, and then the price would be essentially doubled for the patient in the outpatient prescription.

These are arbitrary pricings, with no evidence that the more expensive group of drugs are more expensive to prepare. As a matter of fact, evidence presented at the Kefauver hearings showed clearly that there was no relationship between cost of preparation and sale price of an individual drug item.

2. Good quality generic brands of unpatentable drugs are available at what seem to be ridiculously small fractions of the price of comparable trade named items.

3. If the tyranny of trade name prescribing and ordering of drugs can be avoided, even the large pharmaceutical manufacturers will compete on a price basis.

Let me stop here to expand on this, because some of our greatest savings were in the area of getting pharmaceutical manufacturers to compete. I had indicated that we were buying tetracyclines by trade names and paying roughly $22.50 per 100. This is $225 per 1,000. This is in the upper class of expensive drugs.

We decided, since there was evidence in the literature and in the Medical Letter, that all of the tetracyclines on the market, even though they varied in chemical constitution slightly, were therapeutically equivalent. It didn't make any difference whether you used oxytetracycline or Terramycin by trade name, chloratetracycline, or Aureomycin by trade name or tetracycline. The dose was the same, the effect was the same.

So we said we will use the one for the next 6 months which bids in the cheapest, and after a couple of months of nearly identical bids, the Squibb product tetracycline came down to $19, and then there was some jockeying and there were further reductions.

Mr. GORDON. Excuse me, may I interrupt here?

Dr. WILLIAMS. Yes.

Mr. GORDON. They were sealed bids, were they not?

Dr. WILLIAMS. Our bids were sealed.

Mr. GORDON. But they were still identical.

Dr. WILLIAMS. Yes; not a penny's difference for the most part. No need for it as long as you just order a trade name, because only one company can fill the trade name, so there isn't any point in making a different bid.

It is when you agree that even when they are patented products, three companies' products are therapeutically equivalent that savings can be made. In the absence of monopoly and price-fixing practices, this is when you can use the purchaser's power to force these people to come down in their price.

There were other examples. Our largest savings have come from in the chlorothiazide diuretic group of drugs. Now at the time we took this job in 1960, there were six chlorothiazide diuretics on the market, all patented, all trade named, of five different chemical compounds.

The evidence in the literature indicated that they all had equal side effects, they all were equally therapeutically potent, and that there was no real reason for choosing one or the other. These are not different trade names for the same generic product. These are different drugs that do the same thing.

So we said Grady Hospital for the next 6 months will use the chlorothiazide diuretic with the lowest bid. These by trade name purchase on the market ran right around $50 to $60 a 1,000. In our

first bid we got a break from one company to $40. It successively has broken to $30, $20, $10, and now less than $10.

Senator NELSON. For what you used to pay $56?

Dr. WILLIAMS. For what we used to pay $50 to $60, and as high as $65. This has saved us, under present-day rates, we calculated this out, this saves us alone $40,000 a year, just on chlorothiazide diuretics, because we use just over 2 million of these tablets a year. It is easy to calculate out if you come from $50 down to around $5 that you are saving $45 per 1,000, and on 2 million tablets this is a lot of money.

The tetracycline price, of course, has continued to go down. We got involved with Italian tetracycline, and used it at an enormous saving. If we could have continued to use the Italian tetracycline at the time, we could have saved, our purchasing agent has calculated, over $100,000 yearly.

Senator NELSON. Yearly?

Dr. WILLIAMS. Yearly, on that one drug. Unfortunately, Pfizer brought threat of suit against Grady Hospital if we used Italian tetracycline, and so our legal department felt we had best play it safe at the time, and wait until the suit that Pfizer instituted against New York City was settled. So it was a little while before we could make that saving. At the present time, of course, we have good generic tetracycline made in the United States available, and our savings are enormous over what we would have to pay if we bought the trade named item.

Senator NELSON. Have you found any difference in the therapeutic effect?

Dr. WILLIAMS. There shouldn't be really, since all of the lots are tested by the Government and approved, so in the area of antibiotics there shouldn't be any difference therapeutically and we have found no difference.

To go on to No. 4:

> 4. Detail men, who are the chief source of information about drugs for many physicians, are salesmen. Informed, charming, witty though they may be, I have never heard one of them say that a competing drug was superior to theirs or that their own drug may be dangerous. I would like to quote the chairman of our department, Dr. Neil Moran, who each year reminds the medical students that they who spend from 5 to 12 years in getting a medical education are foolish to let a detail man, who may not even have a college education, tell them what drugs to use for which disease. We tell the students this each year. I think the effect of the lesson wanes as they progress through the clinical years and get out into practice.
>
> 5. The pharmaceutical manufacturers exist to make money for their stockholders, not to render service to humanity or the medical profession, though they may do both excellently in the pursuit of money. I don't question as you did not question the value of their contribution to medicine and to our culture, but they still exist not for this purpose but to make money, and they behave as if they existed to make money.
>
> 6. Arguments about the amount of research done or the amount of profit made by a drug company are not germane to a discussion of generic versus trade name drug prices. You will hear testi-

mony from the drug companies I am sure in the future about the enormous amount of research they do. It should be clear that drug companies do research to find a patentable product which they can sell at an arbitrary price for the 17 years of the patent life or they do it, and they do a great deal of this, for public relations purposes. Were it otherwise their stockholders would not stand for such behavior. To suggest that drug companies do research because they make a lot of money or that they should have a preferential place in the marketplace because they do research violates the canons of economics in a free enterprise society. I should suspect that being able to make a lot of money on old unpatentable products through the ruse of the trade name game deters rather than stimulates research. Other industries do research also and do not ask for a preferred position in the economy.

This preferred position I think has been defined before this committee again and again, and it involves the fact that the doctor who prescribes the drug does not know the price. If he prescribes by trade name, he frequently may not know what the contents of the drug are in terms of chemicals or generic names. The pharmacist who fills a prescription, if the doctor writes a trade name prescription, must use that item, and the patient must pay for it.

This has been said before, but I think it needs emphasizing, that this is not a free market practice, because the man who pays has nothing to say about what he gets, and he is unable to even shop around.

Senator NELSON. In your State of Georgia, if a doctor prescribes a trade name drug, the pharmacist may not substitute?

Dr. WILLIAMS. No, it is one of the States where legally he may not do this.

Senator NELSON. But if a generic named drug is prescribed, he may substitute a trade name?

Dr. WILLIAMS. Yes, if a generic name is prescribed, since a trade name drug has the same generic name, if a generic name is prescribed, he may either use the cheaper generic drug and pass the saving on to the patient, or he may use the more expensive trade name drug, and charge his usual price.

However, I still think, and I will repeat this again at the end of my statement, that if the pharmacist has a choice, and if the patient has a choice, which he does have in this case, he can shop around, and in the end I think in our economy this will pull drug prices down and prevent monopoly and price fixing, and allow a choice. Maybe I am too much ivory tower and have too much faith, but I think if you give them a choice they will pull the prices down.

Senator HATFIELD. Dr. Williams, I want to ask you a question.

Dr. WILLIAMS. Yes.

Senator HATFIELD. I am not quite clear on your conclusion here that this preferential position in the marketplace, because they do research, violates the canons of economics in a free enterprise society.

Dr. WILLIAMS. I maybe got out of my field and should be caught short on that. What I meant was that there is no choice at present when a trade name drug is prescribed, there is no choice for the person who buys it.

Senator HATFIELD. But if I read your language correctly here——

Dr. WILLIAMS. Maybe you don't.

Senator HATFIELD. Are there no patents that are given for other products that are developed out of the laboratories of research in various industries in our free enterprise society, and that enjoy certain preferential treatment in the marketplace?

Dr. WILLIAMS. Yes, but you have the choice of whether you want to buy them or not. You have a choice of whether you want to buy an Oldsmobile with certain patented products on it, or a Ford, or no car at all. In this particular case——

Senator HATFIELD. I think you should delineate though between a research product and the product that comes out of research which may be prescribed by a doctor in the course of a personal relationship between a doctor and a patient.

I think you are getting far afield in the field of economics here about making this as an inducement on the drug industry. I think it is a little unfair, because I think you will find that many industries, in fact, most of our products today come out of research laboratories and upon many of these patents are given. As a result of those patents, you could say they enjoy a preferential treatment in the marketplace.

Dr. WILLIAMS. Right.

Senator HATFIELD. And also I would say that out of this exercise of research and patent acquisition you stimulate further research. To hold the drug industry up here as a special case in point I think is not quite fair.

Dr. WILLIAMS. I think later on in my statement I clear this up, and I think, lay the blame at the door where I think the blame should be laid.

Senator HATFIELD. Good.

Dr. WILLIAMS. And it is always dangerous I suppose for a pharmacologist to get into the area of economics.

7. The enormous pressure of advertising and detailing creates a market sometimes where none exists and unfortunately, for good medical practice, this may lead physicians to the use of unnecessary or even unsafe drugs.

Mr. GORDON. Can you give us some examples?

Dr. WILLIAMS. Yes. I think that you have had examples presented previously. I think the antibiotic field is one of these, and the use of penicillin for the treatment of the common cold, which is demanded from the physician by the patient in this case, the overuse of antibiotics by physicians, in general, lead to serious and even fatal antibiotic reactions. I think in the absence of quite so much advertising pressure, there would be less of this.

In my own area, the present exploitation of the field of tranquilizers has resulted in a great deal of addiction, and the beginnings of drug abuse in our society, in a group of people who previously were not involved in this, and this can be documented again and again.

I look on the above seven statements almost as statements of self-evident fact and except for item 7 I am not sure that there is anything that should not be so in the above statements. For if I believe in a free economy—and I do—then I must agree in a company's right to invent, patent, and sell its product. Here is where I think, Senator Hatfield, I answer your question as to my stand.

In terms of the cost of the drug to the patient rather than the wholesale operation at Grady Hospital, I have no information which would indicate that the local pharmacist makes an exorbitant profit on his operation. As a matter of fact, the prescription markup in today's pharmacies is about what I remember from my own time in a retail pharmacy in 1937. Maybe it is a little less—I am talking about the stated average markup.

The primary responsibility for the problem of drug prices today must in the end be the physicians and only the physician can change the system; for if the physician prescribes a trade name drug, the pharmacist must fill the prescription with that item and the patient must pay accordingly. There is no caveat emptor, the buyer, the patient, has no choice in the matter nor the pharmacist with a trade name prescription, only the physician.

This leads me to some more conclusions:

1. The physician, in general, is unaware of comparative drug prices and is frequently unaware of the price of the drug he prescribes. This is almost a conspiracy of ignorance. From the time he is a freshman medical student to the end of his professional career he is supplied with drugs and even baby foods by the major manufacturers. None of the information that he gets contains prices, as for instance when he uses the Physicians' Desk Reference as a source of information. This book has no prices in it. Unless a patient complains to him, or unless, as sometimes happens, he is caught in the boondocks with no drugs and has to go buy them himself, he has frequently no idea of the cost of drugs.

2. The physician has almost no source of information on the comparative efficacy of drugs of a given class or on their comparative prices and no source of information on generic prices versus trade name prices except possibly the Medical Letter, which unfortunately is used by few physicians. He has the Physicians' Desk Reference—PDR—which is a trade item paid for by those companies whose products are listed, but the PDR does not list any prices and contains no critical comparative information as to relative efficacy of drugs.

A physician faced with the choice of using a trade name tranquilizer chlordiazepoxide or Librium for a patient who is anxious, this sells wholesale for somewhere around $50 a 1,000——

Senator NELSON. Librium?

Dr. WILLIAMS. Librium, somewhere around $50 a 1,000. Faced with a choice between whether to use that drug or to use phenobarbital, which we use at Grady Hospital, and which in many cases is equal to and in some cases superior to Librium, which costs us 9 cents per 1,000, this is 9 cents versus $50, the average physician has nowhere to go to find out whether the statement made by the drug company that Librium is the successor to the tranquilizers is really true. He has no place to go.

Senator NELSON. Did you say that phenobarbital is 9 cents a 1,000 your cost?

Dr. WILLIAMS. Our cost at Grady Hospital.

Senator NELSON. And $50 a 1,000 for Librium?

Dr. WILLIAMS. Somewhere between $40 and $50.

Senator NELSON. And that in many instances phenobarbital performs the satisfactory function which you seek?

Dr. WILLIAMS. Yes, and in many instances it is superior.

Senator NELSON. To Librium?

Dr. WILLIAMS. Yes.

Senator NELSON. Dr. Williams, your indictment here of the medical profession's educational training program concerns me a bit. If I read your statement after listening carefully here, I gain the impression that the inadequacies of the present format of medical education which is being followed is obviously inadequate, and puts the patient in a rather precarious position because of the lack of knowledge of the prescription of drugs.

Is this a question that is being studied by your profession? What do I, as a patient, have as a guarantee that I am going to get the proper drug prescribed, if what you say here is true of the average doctor that he has so little understanding?

Dr. WILLIAMS. You have no guarantee.

Senator NELSON. I am at the mercy of my physician?

Dr. WILLIAMS. Yes, in the end this is, I think, as it should be, because in the end, when properly enforced——

Senator HATFIELD. I don't like to be at the mercy of anyone who is ignorant.

Dr. WILLIAMS. All right.

Senator HATFIELD. What are we doing here in the medical field? As a former educator, I must say I have great concern here and a great interest as a member of this committee. Are our medical education programs so totally inadequate or so unaware of their inadequacies that we are not doing something to correct this terrible situation that you portray here?

Dr. WILLIAMS. Ninety percent is the figure frequently given, it is certainly close to the exact figure; 90 percent of the drugs that are prescribed today were not even on the market 10 years ago. The average physician got out of medical school some time longer than 15 years ago. Unless he is unusual, and many of them are unusual, his source of information about drugs is the detail man or advertising literature in his own journal.

Now, even if he reads the journals carefully, objective comparative information on drugs is not available to him, and I will develop why this is so later.

So the physician is in a difficult position. As I will state in a minute, I am unable to keep up with drugs, and this is all I have to do. I don't have to see patients or do anything except be familiar with drugs.

Senator HATFIELD. What is the relationship, though, to the present medical student between pharmaceutical information and understanding and his medical curriculum in general?

Dr. WILLIAMS. The present medical student gets pharmacology. At Emory University he spends as much time on it as he does in physiology and almost as much time as he does in anatomy. He gets this in his sophomore year.

In addition, we have a large clinical pharmacology group, who work with the students in the junior and senior years at Grady Hospital.

Then he graduates. Depending on where he goes, if he is an intern at Grady Hospital, he would still be getting information from the clinical pharmacology people. If he is not, this about ends his formal training in drugs.

Senator HATFIELD. That is for general practitioners?

Dr. WILLIAMS. This is for a general practitioner.

Senator HATFIELD. What about internists?

Dr. WILLIAMS. Internists in general do not have formal critical training on the use of drugs. As has been said elsewhere, they are trained in the diagnosis of disease, but the use of drugs in the treatment of disease frequently is by custom and habit and precept, and actual critical discussions of the comparative value of drugs is frequently not available to the physician.

Senator HATFIELD. Isn't there commensurable time between diagnosis and therapy or prescription?

Dr. WILLIAMS. I hope so; but in terms of choosing which drug out of a large group of drugs, maybe hundreds of forms of drugs, which may be available to him that would be superior in the treatment of this particular disease, he not only does not have the information, as I will show you, I think, he has no source for the information.

Senator HATFIELD. Then what is the alternative for the physician today whom you criticize for relying on the drug salesman for his information and upon that information making his prescription of drugs to his patients? What is the substitute for that procedure that seems to be, according to your statement, the only course open today to the average practicing physician?

Dr. WILLIAMS. I think I will answer this when I make some recommendations later. The reason I feel it is the only alternative is that, as I have indicated, I think a drug company should have the right to invent, patent, and sell its product.

I think they should have a right, if they don't tell lies to the physician, or in their advertising or through their detailing procedures, I think they should have a right to push their drug. I think these rights are important.

If this is so, then there has to be some source of critical information not put out by the drug companies available to the physician.

Senator HATFIELD. Dr. Williams, it seems to me that this hearing might then be expanded to not include only the drug houses and the manufacturers and the users in terms of your hospitals and other such groups, but perhaps the medical society or the medical profession, and more particularly the deans of medical educational programs, because it seems to me that, without expanding the scope of this hearing, we cannot in this committee get to the real heart of the matter of protecting the American public. I think we ought to protect them more than just against overpricing of drugs. We should be concerned basically about their health and well-being, and if there is this loose practice that is being carried on today in the prescription of drugs, with as little information on the part of the physician as you indicate, it seems to me that this should be even paramount, to take the priority of this committee's attention over just the matter of economics, because I think health and well-being is far more important than mere economics.

Dr. WILLIAMS. I think the committee must have its plans, and I would hate to agree to a red herring, but I would have to agree with you that this is in the end the thing I am most interested in.

Senator HATFIELD. Good.

Dr. WILLIAMS. Because in the end if you can't help the physician, and if he does not change his prescribing habits, once you have prevented monopoly, and where this may occur, once you have done this, and prevented the drug company from actually lying to the physician, I don't see what other avenue is open to you except to help the physician.

Senator NELSON. May I say at this stage to both Dr. Williams and Senator Hatfield that the issue raised by Senator Hatfield is precisely the issue that has been raised by several witnesses before, and I agree with Senator Hatfield that it is a very fundamental question. It is my hope, if this committee accomplished nothing else, we would come up with a solution, some kind of a solution to the very issue you raise here about prescribing.

Two previous distinguished witnesses, both of them medical doctors and pharmacologists, Dr. Modell and Dr. Burack raised exactly the same question, the continuing education of the physician in just about the same way that you have raised it here and made about the same statement about it, so I as a member of the committee consider it a very important issue. It is one of the problems to which we would like to get a solution.

Mr. GORDON. Could you say a few words about overmedication, that is, the prescribing of drugs unnecessarily? Are you going into this subject?

Dr. WILLIAMS. Yes, I have previously mentioned some of this in terms of the fact that advertising pressure from major drug houses leads the physician partly—directly and partly through pressure from the public into use of drugs which the physician might not otherwise use.

Each year I stand up and tell my students that penicillin is not good for the common cold, it is a dangerous drug, and sometimes causes fatal illness.

I had a former graduate who is in practice in Alabama come back to me 3 years ago now, and he said, "Dr. Williams, you were all wrong when you said penicillin shouldn't be used for the common cold." And I said, "What do you mean?"

And he said, "I have to use penicillin for the common cold because if I don't my patients go to another doctor."

And he had been in practice about 3 years at the time, and I asked him, I said, "How much did you make last year?"

He said, "$40,000."

And I said, "Well, that is your answer."

He didn't have to, but he was doing it.

The physician then has no source of comparative information about the relative effectiveness of similar drugs or the relative toxicity frequently of similar drugs, and no source of information about price.

The PDR, as I stated, does not list the prices and does not contain any comparative critical information as to relative efficacy of drugs. The PDR should be considered for what it is, a sometimes useful catalog of drugs, their use and side effects, written really as advertising copy and paid for as such.

It might be said that the physician has available to him the scientific literature and can make his judgment about the relative value of drugs from the literature.

This is just not so—the physician does not have the time.

I am a pharmacologist and my professional role is to keep up with drugs and I am unable to do so. I subclassify myself as a neuropharmacologist, which means I only have to keep up with drugs which act on the brain. In terms of original literature, I wonder if I even accomplish keeping up with this narrowed field.

Time is not the only problem for a high percentage of the clinical and drug studies reported in the literature are paid by the parent drug house and this should be clear, the major pharmaceutical manufacturers do not support comparative studies which might show their product to be inferior. In a sense, they would be foolish if they did so, and their stockholders should correct them, since their object is to sell their drugs.

Mr. GORDON. Have you had any experience along these lines?

Dr. WILLIAMS. We have had a funny experience at Emory, which illustrates this point. Wyeth, one of the major drug firms, was interested in its drug Serax, a chemical congener of Librium being tested in the Emory Dental School for its action in anxiety in patients who were facing serious dental operations, and they agreed to pay for the study, and the people at the dental school came to us for design of a critical experiment, a double blind experiment which would tell them whether Serax was helpful in these patients.

In designing it, we designed the experiment to compare phenobarbital, Serax, and placebo or blank.

Wyeth said they were sorry they could not pay for the study with phenobarbital included, but would be happy to pay for the study comparing Serax and a placebo, and if you look at the literature, this is what happens for most drug studies.

You have to raise the question at the present time. I have some suggestions about this, but you have to raise the question who pays for drug studies?

Universities do not.

Most drug studies which are in the literature, even the good ones, controlled studies, are paid for by manufacturers, and manufacturers are not interested in comparing their drug with a similar drug, unless they have evidence that their drug is clearly superior to the similar drug.

So most studies do not produce critical comparison. They will show, and many of them are excellent, that the drug A is better than a blank.

Senator NELSON. Better than a placebo?

Dr. WILLIAMS. Better than a placebo, but they do not show that drug A is better than drug B. They don't want to get involved in this controversy. So that since they do not support comparative studies, it is difficult for me and for other people in the area of pharmacology, and must be just as difficult for people in the practice of medicine to even find a study which critically compares, say, phenobarbital with Librium. It is hard for us to find this information.

Senator NELSON. Does the FDA do any studies of this kind?

Dr. WILLIAMS. Not as yet, but I will have some suggestions. I think they should get involved. These studies thus far have been done by the Veterans' Administration, which has done some excellent studies.

When the question about the effectiveness of isonicotinic acid hydrazide on multiple sclerosis came out, several good clinics around

the country reported it to be effective, this is INH, and so the Veterans' Administration coded a large double blind study out of Washington, which was excellently designed, and which showed after an appropriate time when the code was broken, that there was no significant difference between those subjects who had gotten the placebo and those who had gotten INH.

This is the sort of study we need.

The Army and Navy do these sort of studies. Many of you will remember that antihistamines were widely touted as a treatment for the common cold some 15 years ago now.

This was not just advertising or anything like that. Several clinics had reported that the antihistamines were effective against the common cold, but the studies were not critical.

Well, the Army did the critical study in large numbers of men, and showed that the course of the common cold was not affected by the administration of antihistamines, and that is the antihistamine couldn't be differentiated from the blank.

These types of studies, however, are rare in our literature. They are very rare.

What are the solutions available?

As I have indicated, beyond preventing price fixing or monopoly practices, beyond making sure that drug companies do not tell lies to physicians through their advertising, it is fruitless to bandy words about profits and research and service to humanity. The one person in the team who can change things is the physician, and he needs help.

The physician must have available critical unbiased information on the relative value and cost of drugs, trade name as well as generic. The physician and the pharmacist must have available lists of approved generic products which they can use with confidence and which will allow them to prescribe and fill generic prescriptions where this is desirable.

Ideally, this information should come from the two professions of medicine and pharmacy. Actually at one time in the past, the American Medical Association assumed this role, but it has abandoned it since the 1930's, and shows no sign of taking it up again.

Senator NELSON. When the American Medical Association did perform that function, did they do a good job?

Dr. WILLIAMS. They did an excellent job. Some of you may remember their work in eliminating quack drugs and quack medicines which extended from the period after 1900 right up through about the 1930's. They were extremely active. They had an AMA seal of approval, sort of like the Good Housekeeping seal of approval, and before they would accept an advertisement for a drug in the AMA Journal, it would have to have the stamp of approval. They had their own laboratories. They assayed these drugs before they approved them. They were crusading and did a tremendous job.

However, about 6 years ago, 6 or 7 years ago, the AMA offered me the job of secretary of their council on pharmacy and chemistry, which then handled the problem of drugs.

I went up to look at the job because I felt there was a real job that needed doing. This job was offered to me by Dr. Turner at the AMA shortly before his untimely death.

I was upset at the time by drug advertising, but found out, when I got to Chicago, that with the reorganization—the previous person in that job had left—and the hiring of myself, the function of control of advertising was removed from under the purview of the council on pharmacy and chemistry. So I would be employed by an organization which was advertising drugs in a manner that I could not agree with, and I had nothing to say about it. So I didn't take the job.

Senator NELSON. Do you know the reason that the AMA ceased to perform this valuable function?

Dr. WILLIAMS. I think the proliferation of drugs got to be so rapid and the problem became so huge that even attempting to do these analyses would have been a serious financial burden to the AMA.

Now, I have heard suggestions that since they accept all these drug ads and make over half of the income necessary to publish their various journals from drug advertisement, that they stopped because of this. I am not sure of that.

I think the problem just got out of hand and they could no longer handle it.

Senator NELSON. I will let you finish your statement. Go ahead.

Dr. WILLIAMS. Anyway, the AMA has abandoned this role, shows no sign of taking it up again.

I am frequently asked by retail pharmacists which generic house can be depended upon to supply good quality drugs. I cannot give them an easy answer. I suggested to pharmacists in a talk last year to the Georgia Pharmaceutical Association that if they really want to know what is a good generic drug, and I get asked this question all the time, which one should they buy, that although they can't do these analyses themselves, they certainly can as an association, do the analyses and put out a list of drugs which meet the standards they set.

I have seen no sign that they are interested as an association in taking out this function either. I think what we are going to have to have is something like a regular FDA newsletter which will go out to all physicians and pharmacists.

Let me back up here in the statement.

It would seem that the role that was formerly handled by the AMA must be assumed by a Federal agency, such as an information service, possibly a regular FDA newsletter to all pharmacists and physicians, utilizing information in FDA, NIH, Army, Navy, and Veterans' Administration files as well as consultation with outside experts.

The Medical Letter does a good job with what it does but its sources are inadequate for the job and the circulation is too small at the present time to seriously affect the prescribing habits of the Nation or of the physicians of the Nation.

Since writing this, I have had some thoughts that possibly this should be handled by contract support of the Medical Letter people and let them do the job as an unbiased group intermediate between Government and industry in the way that the Rand Corp. operates.

I don't know what the final solution will be. But in the end it must get to the physician and the pharmacist, critical, comparative information about the relative value of drugs and their relative prices.

I believe that the average physician is interested in the financial welfare of his patient as well as his patient's health, and I firmly believe that if he had the information available to him, information in

which he could place some credence, he would use it to treat the patient more effectively and save the patient money.

I go out and talk to physicians and small communities around the State and I believe this. They say, "If you can give us proof that this product is as good, we will use it."

At the present time they have faith in the major pharmaceutical manufacturers. They are used to depending on their statements as statements of truth, and you have to bring something equally authoritative, if you will, to show them another side of the story.

I also believe that the average pharmacist is honest, and will pass the savings on to the patient.

In any event, armed with a generic prescription, the patient is back in the marketplace and he can shop around for lower drug prices.

Senator NELSON. Did you say earlier in your testimony that 90 percent of drugs on the market have been created——

Dr. WILLIAMS. In the last 10 to 15 years.

Senator NELSON. Ninety percent in terms of numbers?

Dr. WILLIAMS. Ninety percent that are prescribed.

Senator NELSON. Ninety percent of the prescriptions?

Dr. WILLIAMS. Ninety percent of the prescriptions right, are for drugs which are new drugs within the last 10 to 15 years.

Senator NELSON. Are you saying 90 percent in terms of numbers or 90 percent in terms of the money spent in the field?

Dr. WILLIAMS. As a matter of fact, I can't remember which it was.

Senator NELSON. I don't think there is any doubt but what you raise here a very serious question of great public interest.

Now, your hospital, for example, has its own formulary. You have the benefit of your specialists in all the various fields participating as well as pharmacologists and pharmacists. You have an opportunity for clinical and scientific observation with experts in many aspects of clinical medicine. So with considerable safety and a controlled situation, it is possible then for the doctors there to rely upon your formulary and prescribe from it, and you have an attentive, intelligent group who are continuously evaluating and revising the formulary.

That is the situation, is it not?

Dr. WILLIAMS. That is the situation, and many drugs undergo months of discussion before we introduce them into the formulary, and sometimes even here, even for our group, finding the information to make the choice is difficult under our present system.

Senator NELSON. And many other formularies around the country, hospitals in New York and elsewhere follow this same procedure and the doctors who work with it are able then to be relying upon a formulary that is established by some reliable, distinguished, knowledgeable people in the field. The private practicing physician doesn't have that opportunity.

Dr. WILLIAMS. Unfortunately, no.

Senator NELSON. Even though you have your formulary committee, you aren't able to do double blind tests, for example, on various drugs that you use yourself, so what you do have is the information and experience of a number of doctors in various fields, and that is what you rely upon, plus whatever studies are made around the United States that come to your attention.

Dr. WILLIAMS. That is right.

Senator NELSON. You made a suggestion as to how this question ought to be tackled. Is there any reason why, for example, the FDA might not, through a series of arrangements, contract with your medical school and your hospital to do a certain amount of testing, and contract with half a dozen or whatever it may be, a dozen medical schools with associated teaching hospitals. They could contract in various ways for testing chemically the drugs that are coming out, to see what their potency is, and make double blind studies of various drugs, to see whether they have therapeutic value that is asserted for them? Does that strike you as a problem that is too large for the Government to tackle and successfully meet?

Dr. WILLIAMS. I think it is best to state that it is a problem that is so large that only the Government can tackle it. This is what we wind up with.

I think, in addition to the pathways you have mentioned, that I would like to emphasize that the Government treats an enormous pool of patients in Veterans' Administration and similar organizations, and I think that these studies frequently can be effectively done within this sort of organization, not experiments with new drugs necessarily, but the critical comparison of older drugs with newer drugs.

Senator NELSON. There is at least—I don't know anything about the field—there is at least two things that can be done. One of them is to do a chemical analysis of the various drugs and determine whether they are in the potency range that is established by the pharmacologist. That produces one result.

Then there is the other question of doing your clinical studies to find out the therapeutic comparisons between these drugs and a placebo on these drugs and other drugs.

Dr. WILLIAMS. The first is easy. This can be done in a Government laboratory.

The second is difficult, because it requires the cooperation of the medical profession at large, including as you mentioned, the medical schools and so on.

Senator NELSON. You think it would be relatively easy to test the potency of all prescription drugs on the market, and to run a continuous testing of them?

Dr. WILLIAMS. I think what will probably happen is that——

Senator NELSON. I am talking about the chemical testing.

Dr. WILLIAMS. I am talking about the chemical testing.

I think what will probably happen is that as the Food and Drug Administration continues its present area of functioning, that manufacturers who do not maintain the standards which should guarantee adequate potency in the drugs, their license to manufacture will be taken away from them.

I mean this is an area where if the Food and Drug Administration were actually able to do the policing job that it already had the powers to do, the fly-by-night bucketshop operator that you hear so much about, producing supposedly spurious drugs, simply could not operate.

Senator NELSON. In terms of the size of the problem, I don't know what to compare it to, but every meatpacker in the United States that ships any meat in interstate commerce, which is most of them, have on the job in the plant a Federal meat inspector whose salary is paid for by the packer himself.

I don't know that that would be the solution here, but, it seems to me, if we exercise this amount of care about shipping in interstate commerce meat, which a casual purchaser frequently can tell whether or not it is good, in terms of a matter as serious as prescription drugs, we ought to be concerned enough to have adequate inspection wherever necessary, either in the manufacturing plant or batch sampling to protect the public in the consumption of drugs, and to advise the physician, of course, about the drug.

Dr. WILLIAMS. Actually, an on-the-job inspector is something I had really never considered, and something that I want to start thinking about.

I think that possibly this is an excellent way to bring some operations up to standards. Something needs to be done in this area so that the physician and the pharmacist can have confidence if they use a drug from a generic house that this drug, in most respects, will be as stated by the manufacturer.

Now, all people can make errors, and Dr. Burack in his book pointed out that major drug firms make errors, too, as do small drug firms. This may be a meaningless point, but in terms of the amount of drugs that people get which are in error, if the implications of Dr. Burack's statements are correct, then since the drug trade letter lists that only 5 percent of prescriptions in the country are being written generically today, 95 percent for trade named items, the indication would be that more people are having trouble with trade named items than with generic items, but this is, as I said, sort of circular reasoning.

Senator NELSON. You stated that to do a chemical test of drugs for potency and chemical composition would be at least relatively easy.

It is when you get to the question of testing the clinical effect——

Dr. WILLIAMS. That is correct.

Senator NELSON. That it becomes more difficult.

Is there any doubt in your mind that it is feasible as a practical matter for the Government, using the resources it has—that is, the thousands and hundreds of thousands of people that are treated by the Army—and they make tests now—plus contracting with distinguished medical schools and hospitals for purposes of doing double blind tests and paying for them, do you see that as a feasible approach to this problem?

Dr. WILLIAMS. I think so. I think this is what is going to have to be done, the use of expert opinion plus in some cases where the information is not available, subsidized research which will give the answers that we need to actually say whether one drug is better than another. The drug houses do not do it.

Senator NELSON. What I am seeking to get at here, then, is the end result. In your hospital you do have a formulary committee and your own formulary. Is there any reason why, doing these kinds of chemical testing as well as clinical testing using the resources of the Government and contracting privately, you can't end up with a formulary which lists all the trade name drugs, lists all the generic name drugs that are the same as the trade name, the same compound, listing the side effects, listing the results of double blind tests, listing all the information, in an indexed book form, so that as a practical matter a practicing physician could rely upon this sort of formulary and keep it up to date in an annual or semiannual way?

Is there any reason why that couldn't be done?

Dr. WILLIAMS. Such a pharmacologist's bible would be a wonderful thing to have, for all of us, for those of us in teaching, too. No; I think this could be done. I think this will have to be done.

I might say that in the area of new drugs which will come on the market from now on, the efficacy provisions in the Kefauver drug laws, when they are able to administer them adequately, the Food and Drug Administration can demand of the company that this comparative study be made.

For drugs from here on out, the Food and Drug Administration can actually say to the pharmaceutical manufacturer, "Show us that your product Librium is superior to phenobarbital and in which way is it superior."

So I think the big problem that we face in the next 15 years will be adequately administering that part of the law, and going back over the wealth of useless drugs which clog our literature and our formulary; drugs, many of them which have no therapeutic action at all.

Senator NELSON. Has there ever been an adequate test of all the drugs put on the market to find out whether they have any therapeutic value or not?

Dr. WILLIAMS. No. You see, as the 1938 food and drug law was written, it did not require approval for old drugs that had already been on the market, so you take an agent like strychnine, which is very toxic, self-evidently poisonous, and which has no therapeutic action that we know of is widely sold in this country as an ingredient of some common laxative preparations, to which it adds nothing. An agent like strychnine which has no therapeutic action and is as poisonous as strychnine is, and which actually results in poisoning of children every year, this agent would not be allowed on the market under the 1938 food and drug law, but agents which were in common use prior to the 1938 food and drug law were never tested for efficacy or toxicity, neither one.

Mr. GORDON. You mean the 1962 law, don't you?

Dr. WILLIAMS. No; I mean the 1938 food and drug law.

Now, this moves up to 1962, but I think under the 1962 law they can go back, when they get the time, and eliminate toxic substances from the market.

Senator NELSON. Or any substance that does not have therapeutic value or just toxic substances?

Dr. WILLIAMS. I am not too sure about the law.

Someone else may know better than I, but I am sure under the 1938 law that this could not be done.

Senator HATFIELD. Dr. Williams, I think the quality control factor here in this discussion is very important, but also I want to go back for a moment to the educational part of this problem.

It seems to me that in your portrayal of the average American physician today as a sincere overworked dolt, as he relates to the prescribing and the understanding of drugs is something that must be the concern of this committee and to the profession.

Since you are in a very unique situation as a professor of pharmacology at a very distinguished college of medicine, I would like to know if there is any possibility that in conjunction with your university school of medicine, that this committee could have—Senator Nelson, if it would be appropriate for me to make this request at this time—

an analysis of the curriculums as it relates to both the general practitioner and also to the specialist in internal medicine, an analysis of that curriculum as it relates to the infusion of pharmacology and an understanding, not only in terms of the toxicity, the efficacy, the therapeutic values and all of these other things. Price, I think that is really secondary. I am more concerned about the therapeutic values of the drugs which will be generally in the field of his practice.

Again, I emphasize, as I did before, that I think the protection of people's lives is so important, and that if the physician is doing as you say he is doing here, due to ignorance, due to lack of understanding, it seems to me that we must not only attack it from the point of view of those who are already in the practice, providing them with this added service, or source of reliable information, but we should do a very careful review of the curriculum and the educational programs in which these medical students today are engaged and the premedical students are moving up into.

I don't think we can leave that front unattended and not emphasized to the proper degree, and I am wondering if you could not be very helpful to us in this way, because of your dual professional status, training, and background, and now involved in this great institution of learning, as well as in your knowledge of the hospital.

I am very interested in the educational aspects of it.

Dr. WILLIAMS. So am I. Let me be defensive for a moment.

Senator HATFIELD. I didn't mean to put you on the defensive.

Dr. WILLIAMS. No, I just meant that your use of the term "dolt" is your interpretation of my remarks and not a statement that I made.

Senator HATFIELD. No.

Dr. WILLIAMS. Because some of my best friends are physicians and I wouldn't want to get involved in that.

Senator HATFIELD. But when you make these observations that the average practicing physician today is really making prescriptions with very little knowledge except that which is told him by a salesman of drugs, this is certainly not in terms, I believe, of high professional practice.

You indicated, of course, he is sincere and he is overworked.

Dr. WILLIAMS. That is right.

Senator HATFIELD. But I think it is a matter of prescribing in ignorance as you indicated awhile ago, that in ignorance he does this. So I don't mean to indicate either that all physicians are dolts, but as I read your portrayal in many instances he is ignorant.

Dr. WILLIAMS. He just doesn't know, that is correct, and he has no source of information.

Senator HATFIELD. But he should know.

Dr. WILLIAMS. But he should know for your safety.

Senator HATFIELD. All right. So he is ignorant.

Dr. WILLIAMS. Right.

Senator HATFIELD. Then he is a dolt in that sense?

Dr. WILLIAMS. He is uninformed. Let me use the term uninformed.

Senator HATFIELD. Uninformed, all right.

Dr. WILLIAMS. No; you are completely right, and I think this has crept up on us.

Senator HATFIELD. I am completely right on the dolt, you mean?

Dr. WILLIAMS. No. You are completely right that we need to really look into the problem of education, in the nature and the use of drugs for the physician today.

Look what has happened. In 1900 the most important subject in medicine was anatomy. It occupied an enormous time.

Today anatomy is less important, and other things like physiology and pharmacology are more important.

But today Grady Hospital patients go out of the hospital with four, five, six, and for certain diseases even seven drugs. Even in the practice of medicine at Grady Hospital, where the medical school theoretically has control of the quality of medicine, there is frequent use of drugs or sometime use of drugs which should not be used in combination, and so on and so on, so that even where they are this close to their original medical training, it is a problem, and as they move out into medicine, the problem becomes greater because primarily there is no objective source of critical comparative information in which the doctor can place any faith yet, except the Medical Letter.

Senator HATFIELD. Is there any hope of getting the AMA back onto this job of analyzing and evaluating that they were doing prior to the 1930's?

Dr. WILLIAMS. I don't know. I think that this statement should have to come from them. I doubt it. I think at the present time the situation is such that I don't know whether they could handle it. I would hope that the operation that could be set up would be one that would have the support of the American Medical Association.

Senator HATFIELD. But, again, Dr. Williams, isn't there a question here of professional standards? When you say that the average physician in many instances is uninformed, isn't this more than just a matter of excusable ignorance? Isn't this a question of professional standards?

He is holding himself out as one who is professionally qualified to assist a person in physical need, and if that person goes to him and is to rely upon his counsel, which includes a prescription of a drug, and you say he is prescribing this drug out of ignorance in many instances, and out of being uninformed, isn't that a question then of professional standards, of conduct, that the medical society and AMA should certainly be concerned about, and not just be uninvolved in?

Dr. WILLIAMS. I think it should be clear that where the physician is uninformed is whether drug X be better than drug Y or not. Now in terms of the drug he uses, the average physician is aware of the side effects. He is aware of the dangers. He will be using out of the thousands and thousands of drugs available regularly only a small group of these drugs, and he is informed in general in this area.

When it comes to knowing for this particular condition whether phenobarbital might be better than Librium or not, he not only does not know, he does not have the information available to him to tell whether it is better. I would not like the idea to get across that the physician is using drugs in ignorance. The physician is ignorant of the relative value of the drug compared with another drug, and he is ignorant of the price of the drug compared with the price of another drug.

Senator HATFIELD. But on page 4, where you said under No. 7, "The enormous pressure of advertising and detailing creates a market some-

times where none exists and unfortunately for good medical practice this may lead physicians to the use of unnecessary or even unsafe drugs."

Dr. WILLIAMS. Yes, sir, that is correct. I would repeat that statement.

Senator HATFIELD. When you say "unsafe drugs," then you can't say that physician is acknowledgeable about what he is prescribing. He wouldn't knowingly prescribe unsafe drugs, would he?

Dr. WILLIAMS. No; I think the difference here comes in my statement about lack of knowledge of comparative value of drugs. I said the average physician has no knowledge of the comparative efficacy of a group of drugs in the same class. I think unfortunately detailing pressure has resulted in the use of unnecessary and unsafe drugs, but I don't think by the average physician.

I think by a smaller group of the medical profession. There is no question about what it happens. This has been documented in the misuse of penicillin, and a widely used agent, nicotinic acid, which is given to a great number of old people in this country for dilating their cerebral blood vessels.

The information in the medical literature would indicate that nicotinic acid doesn't dilate cerebral blood vessels, and this information has been there for years. But they have no source of getting this information as opposed to the detailing pressures of the companies that are selling the nicotinic acid.

Senator HATFIELD. And under No. 4 on that same page where you say, "And Dr. Neil Moran"——

Dr. WILLIAMS. Yes.

Senator HATFIELD. Who indicates there that some detail man is telling a physician what drugs to use for which diseases, you are talking there then not about generic drugs but brand name drugs?

Dr. WILLIAMS. Either brand name drugs that do not have another maker, or a brand name drug that may be sold by other companies under another brand name. This problem of generics, all trade name drugs also have a generic name.

Senator HATFIELD. Yes; so I understand.

Dr. WILLIAMS. So detail men only advertise trade name drugs. Some of these may also have generic equivalents under other trade names; yes, this is true.

Senator HATFIELD. But it does seem to me that you have given us at least an impression in certain statements here which would lead one to the conclusion that there are physicians today prescribing drugs, which as you indicate in one place could be unsafe, in another place which have been prescribed on counsel of a salesman. This puts us back to the question of whether or not a physician is truly following the highest standards of practice based upon his information, based upon his understanding. It, therefore, should become a concern for the medical practitioner and the medical profession as well as those of us here on this committee who have been besieged by the economics of all this. I think we need to concern ourselves with the economics, but there is this factor to me that is even more preeminent and takes priority over the economics.

Dr. WILLIAMS. They are inextricably intertwined.

Senator HATFIELD. That is right.

Dr. WILLIAMS. When one uses a drug which is not necessary, the cost to the patient, the unnecessary cost to the patient is the total cost of the drug, whether it be trade name or generic.

Senator HATFIELD. Yes; but there could be dollar cost and also health cost.

Dr. WILLIAMS. Very serious health costs.

Senator HATFIELD. And the health costs can be far more expensive than the dollar costs.

Dr. WILLIAMS. Yes; as expensive as fatal. May I add one word here which is not in my statement. There is another problem. Mostly we have been dealing, as you mentioned, about the private contract between the doctor and the patient, and attempting to extend our studies and our findings at Grady Hospital over into the general area of drug use. But there is a growing amount of money in this country being spent by the Government, tax money, for drugs, drug vendor programs.

Grady Hospital is one example, but the State drug vendor program the Federal Government is pouring millions of dollars into, some $4 million into Georgia alone this year.

Here another problem exists that is a little bit different from the ordinary private contractual relationship between the patient and the doctor and the pharmacist, if you will, the question of whether or not the patient pays for a useless drug, if it is nondangerous, which the doctor may prescribe, and which may do the patient, give the patient excellent benefit in terms of a placebo reaction is really to me not so much of a moral problem.

The question whether the State should pay for a drug which in medical literature has again and again stated is useless in the treatment of patients, I think, is a different problem. I think it has a different level or morality, and I think this is something that this committee should consider in a sense as two separate problems.

There is another area of abuse here, and this is true in our practice at Grady Hospital, when the doctor who I said I believe is concerned about the cost of medication to his patient realizes that the Government is going to pay for the medication, he becomes, since he is fallible, much more prone to prescribe a drug with less consideration than he might otherwise do.

Sometimes this can be good, where he will prescribe a drug which may be good for a disease than he might have withheld for the patient who couldn't pay for it. But sometimes it can lead to a large increase in needless and useless prescribing by the medical profession, and this is something which this country faces in the future as an increasing share of the drug bill is paid for by tax-supported agencies on a local and a Federal basis.

Senator NELSON. Thank you very much, doctor. Excuse me. Senator Scott?

Senator SCOTT. I think the questions I had in mind, Senator Nelson, have been well covered, and I have no questions.

Senator NELSON. Does committee counsel have any questions?

Mr. COUGHLIN. I have none.

Mr. GORDON. You mentioned on page 1 about the cortisone-type drug which cost $167 per 1,000.

Dr. WILLIAMS. Right.

Mr. GORDON. When a comparable generic product would cost $6 a 1,000.

Dr. WILLIAMS. Yes.

Mr. GORDON. Which drug do you have in mind?

Dr. WILLIAMS. I would like to change the word "comparable generic" to comparably therapeutic product here in this particularly instance, although I could have used another product. Actually the $167 per 1,000 was methylprednisolone.

Mr. GORDON. Methylprednisolone?

Dr. WILLIAMS. Or Medrol, and we went over to prednisone, which is therapeutically equivalent but is really not the same generic drug.

Mr. GORDON. Concerning the hospital formulary, do you have any sustained release drugs on it?

Dr. WILLIAMS. We have some sustained release Thorazine or chlorpromazine, because by peculiarities of drug marketing, a sustained release preparation is cheaper to us than the equivalent tablet. This is the only sustained release preparation we have.

Mr. GORDON. How about drug combinations? Do you have any on your formulary?

Dr. WILLIAMS. We have a few drug combinations of the old-fashioned type like elixir of phenobarbital and belladonna, which are in general used for their placebo effect, but none of the newer combinations are available. This is for several reasons.

One, using combinations pushes the price up because the combination even of the generic drugs can be peculiar to a certain trade-named item. This is one reason. But the chief reason as we feel, and the medical department feels very strong on this, that the use of drug combinations is medically unwise, because for each patient with some very rare exceptions the dose of each drug should be adjusted individually according to the patient's tolerance for the drug and the patient's need, so that we do not have combination drugs except these minor things that I have mentioned.

Mr. GORDON. You referred to new drugs which are minor molecular modifications of established drugs with no clear-cut therapeutic advantages. Will you give us some specific drugs which fall into this category?

Dr. WILLIAMS. Oh, some of them are annoying. Schering's patent on chlortrimeton ran out in 10 years instead of 17 years because they had been taken over by the alien property custodian. Chlortrimeton was a big seller. It is an excellent potent antihistamine.

Faced with no patentable product, and with the price of generic chlortrimeton down in the range of a couple of dollars a 1,000, they separated the D and L isomers of chlortrimeton in the chlortrimeton fraction—chlortrimeton is a salt that contains two isomers of the drug, two chemically related forms of the drug. Only one of the chemical forms is active, the D form, so they eliminated the L form, cutting the dose from 4 milligrams to 2 milligrams, came out with an advertising statement which said "Schering eliminates the molecular dross," and attempted to charge many, many times the cost of the original product for this product which didn't even result in a molecular modification.

Roche has for 17 years sold one of the better sulfa drugs, Gantrisin Sulfisoxazole, an excellent drug, and they have been able to charge full price on this drug with no serious competition over a 17-year

period. Faced with the loss of the expiration of their patent and a drop in the cost of the generic product to one-fifth or less of the trade name product, they came out with a minor molecular modification of Gantrisin called Gantinol.

Advertising for this drug indicated that it was unique and new. Actually it is an agent which has exactly the same spectrum as the parent compound, maybe slightly longer acting, but it has been shown to have no qualitative unique action different from Gantrisin. We don't use Gantinol at Grady Hospital. And I could go on and on with the list of drugs where, in an attempt to get a saleable item, one drug firm will make a minor modification in a molecule already introduced by another drug firm, or sometimes in one of their own products as the two instances I have mentioned, in order to get back on the trade name basis.

Mr. GORDON. Does the Grady Hospital employ any inspection or testing procedures to insure that the drug supplies meet proper standards?

Dr. WILLIAMS. No, we do not, and this is why among other things I would be very interested in having this. We purchase from generic houses, we buy the bulk of our purchases, which are by and large established houses. Our antibiotics come from Primo, and so on.

We in the early days of our work arbitrarily set some minimum standards. Actually the then hospital administrator set a minimum Dun & Bradstreet rating which we would accept for a supplier for the drugs. This was a little unfair, but in the absence of other information gave us at least some standard to go on.

In addition, we keep records and watch the recalls noted by the Food and Drug Administration. If we get a drug which we suspect, we turn it over to the local food and drug authorities and have them test it for us, which they do. If a company has drugs recalled for what are serious errors, we stop using that company.

In addition, we do inspection of the generic suppliers, and when a new generic supplier turns up, either Mr. Dorsey, our chief pharmacist, or I, will attempt either by telephone to people locally in the area or by a trip to check on this supplier, but we do not do laboratory testing of anything except the things we make ourselves.

Mr. GORDON. I understand you manufacture some items. What do you manufacture?

Dr. WILLIAMS. Actually minor items, saturated solution of potassium iodide and so on. We manufacture all of our own fluids, and we do check tests on these, and this affects our total drug bill, but not the out-patient costs.

Mr. GORDON. Now, the figures you gave us in your statement show the savings as a result of adopting a formulary system. Could you give us some specific examples as to money saved by buying generically, that is specific drugs?

Dr. WILLIAMS. I have already mentioned some of these in previous testimony. I think one of the most dramatic was in terms of generics, was the savings that we made by switching from methylprednisolone to prednisone, or from trade name prednisone to generic name prednisone, which would have given us essentially at that time the same saving.

Mr. GORDON. How much money did you save on that?

Dr. WILLIAMS. It is not used as widely as the antibiotics of some other drugs, it ran right at $20,000 in 1 year. The two big savings, because these drugs are so much used, were in the area of trade-named items where we forced companies to compete, the chlorothiazide diuretics, the $40,000 saving, and presently today between generic and trade-name tetracycline, where the savings will run as high as $100,000 a year.

Mr. GORDON. In teaching you generally use generic names for drugs. Is that right?

Dr. WILLIAMS. I generally use generic names.

Mr. GORDON. The textbooks use generic names too, don't they?

Dr. WILLIAMS. They do.

Mr. GORDON. Are you acquainted with the Merck Index and the Merck Manual?

Dr. WILLIAMS. Yes.

Mr. GORDON. Isn't it the case that where the Merck Co. itself prepares scientific material it uses generic terms also, does it not?

Dr. WILLIAMS. That is correct. You could have 50 trade names for one generic item. Which trade name would you pick to list it under?

Mr. GORDON. So it is potentially dangerous to use trade names, especially if the physician may not know what the ingredients are?

Dr. WILLIAMS. It is confusing and potentially dangerous.

Mr. GORDON. As well as expensive?

Dr. WILLIAMS. As well as expensive.

Senator NELSON. Dr. Williams, we appreciate very much your testimony. It has been an excellent contribution to the hearings. We appreciate your taking the time to come. We will take a 30-minute break so that we don't get too much lunch. We will recess and reconvene at 12:30. In the meantime I will be at the desk for 5 minutes for any of the drug industry representatives who would like to come up and advise me whether or not their companies would like to be heard, and we will make arrangements for a future date. I will stay here for the next 5 minutes. We will resume in 30 minutes. I will put in the record here at this stage an exchange of correspondence at the request of Senator Sparkman, with additional relevant material.

(The supplemental information submitted by Senator Nelson follows:)

U.S. SENATE,
COMMITTEE ON BANKING AND CURRENCY,
Washington, D.C., June 23, 1967.

Hon. GAYLORD NELSON,
Chairman, Monopoly Subcommittee of the Senate Small Business Committee, Washington, D.C.

DEAR MR. CHAIRMAN: I would appreciate having the enclosed information and exchange of views included in the record of the hearings on drug prices, which I understand are to resume on June 27.

With best wishes, I am,
Sincerely,

JOHN SPARKMAN.

Enclosures.

PHARMACEUTICAL MANUFACTURERS ASSOCIATION,
Washington, D.C., August 22, 1966.

JAMES L. GODDARD, M.D.,
Commissioner of Food and Drugs, Department of Health, Education, and Welfare, Washington, D.C.

DEAR COMMISSIONER GODDARD: Considerable publicity was generated by your comments at the recent annual meeting of the Drug and Allied Products Guild that "We have to conclude that one out of every fourteen drug units manufactured is violative just on potency alone." This conclusion was based, according to your talk, on the results of FDA analyses of 4,200 drug samples representing 20 major therapeutic categories.

As you know from my letters of June 4 and August 18, requesting background data on your statement that one third of the PMA membership is involved in violation of the advertising regulations, we are deeply concerned with reference to statistics of this type without making available to the industry substantiating data. The PMA and our member firms should be in a position to know the source of and more details concerning these generalizations to determine what corrective action, if any, is indicated.

We respectfully request, therefore, that you forward a copy of the tabulation of the 4,200 samples involved, including name of products and manufacturers and the type and degree of deviation from labeled potencies involved. We, of course, are willing either to reimburse the Food and Drug Administration for any expenses involved or provide personnel to prepare the compilation from your analysis records.

In the alternative, we would appreciate a tabulation including only those instances involving members of P.M.A. In your letter of June 30, you stated that you deemed it inadvisable to submit names of companies involved in conduct allegedly violative of the Federal Food, Drug and Cosmetic Act in instances where FDA had determined that no action involving publicity should be taken. While we would prefer that you reconsider that decision, our companies' compliance efforts would be assisted even if you would transmit the types and number of violations involving PMA members without divulging the names of companies involved.

Sincerely,

C. JOSEPH STETLER.

PHARMACEUTICAL MANUFACTURERS ASSOCIATION,
Washington, D.C., August 25, 1966.

Mr. FRED J. DELMORE,
Director, Bureau of Education and Voluntary Compliance, Food and Drug Administration, Department of Health, Education, and Welfare, Washington, D.C.

DEAR GENERAL DELMORE: It was certainly a pleasure for Mr. Stetler and me to talk with you the other day on plans of the Bureau of Education and Voluntary Compliance, and to discuss possible ways in which the pharmaceutical industry could be of assistance to the Bureau in its future program.

During our conversation I mentioned that it would be helpful to have certain information on results of F.D.A. examination of samples of drug products obtained in the field. It was concluded that I should send you a letter discussing some of these points.

The discussion was prompted, of course, by public comments from Commissioner James L. Goddard and others on results of analyses of 4,200 samples recently obtained in an F.D.A. survey. Concerning the specific group of 4,200 samples, Mr. Stetler wrote to Doctor Goddard on August 22, stating in part "We respectfully request, therefore, that you forward a copy of the tabulation of the 4,200 samples involved, including name of products and manufacturers and the type and degree of deviation from labeled potencies involved". Mr. Stetler then said "In the alternative, we would appreciate a tabulation including only those instances involving members of P.M.A." . . . "Our companies' compliance efforts would be assisted even if you would transmit the types and number of violations involving P.M.A. members without divulging the names of companies involved".

I might add that it would also be helpful to know where the drug product pick-up occurred, because different results could be expected if the product sampled was resting in the shipping room of the original manufacturer, or in a warehouse in another part of the country, or in a retail pharmacy.

If it is not possible to disclose the names of companies producing the drug samples tested, it would be helpful to know the names of the drugs, or at least the therapeutic categories of the drugs involved. I am thinking here of nonproprietary drug names such as penicillin, and therapeutic categories such as antihistamine, tranquilizer, etc. To be of maximum usefulness to the industry, any tabulation should also give some idea of the type of manufacturer involved, in the event the name of each manufacturer cannot be disclosed. By type of manufacturer I refer to whether the manufacturer is a member of P.M.A. and some idea of whether the company has its own quality control and research facilities.

It would be most helpful if studies of this kind could furnish some of these necessary details. To summarize, I would suggest the following information:

(*a*) The name of the drug, or at least the therapeutic category.

(*b*) The name of the manufacturer, or the type of manufacturer as defined above.

(*c*) The nature and extent of the alleged defect found in the drug.

(*d*) The source of the drug sample tested (manufacturer, wholesaler, retailer).

Sincerely yours,

KARL BAMBACH.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
Washington, D.C., August 31, 1966.

DR. KARL BAMBACH,
Pharmaceutical Manufacturers Association,
Washington, D.C.

DEAR DR. BAMBACH: I have your letter of August 25 in connection with your request for data on the results of analyses of 4,200 samples recently collected in an FDA survey.

I am forwarding a copy of your letter to the Commissioner's Office since, as you related to me and also indicated in your letter, Mr. Stetler wrote Dr. Goddard on August 22 concerning this same subject. I am sure that you will be hearing from this office on this subject within the near future.

Sincerely yours,

FRED J. DELMORE,
Director, Bureau of Education and Voluntary Compliance.

PHARMACEUTICAL MANUFACTURERS ASSOCIATIONS,
Washington, D.C., October 27, 1966.

JAMES L. GODDARD, M.D.,
Commissioner of Food and Drugs, Department of Health, Education and Welfare,
Washington, D.C.

DEAR COMMISSIONER GODDARD: As you know from past correspondence, reports from officials of the Food and Drug Administration on the alleged low quality of drug products are a matter of increasing concern to the pharmaceutical industry and particularly to the Pharmaceutical Manufacturers Association. In my letter to you of August 22 I referred to your comments at a meeting of the Drug and Allied Products Guild that one out of every fourteen drug units is violative with respect to potency, according to an FDA analysis of 4,200 drug samples. I asked for details of this study, hoping to receive information on the 4,200 samples involved, including the names of products and manufacturers and the types and degree of deviation from labeled potencies. In the event this could not be furnished, we at least expected to receive a tabulation of instances involving members of PMA.

This same study was mentioned by Gen. Fred Delmore at the seminar conducted by the University of Wisconsin at Hershey, Pa., and on August 25 Karl Bambach of our staff wrote to General Delmore requesting similar information.

On September 1 Deputy Commissioner Winton Rankin acknowledged these letters, stating "We are considering your request and will be in touch with you later." No further reply has been received.

We have recently read in the press and in the *Congressional Record* about the speech given by Deputy Commissioner Rankin before the American College of Apothecaries on October 15, 1966, in which he states "We collected almost 4,600 samples of drugs last spring representing the output of about 250 manufacturers. We examined these samples for potency . . . 7.8% of the generic-name drugs were not of acceptable potency. 8.8% of the brand-name drugs were not of acceptable potency." Again we would respectfully request information concerning this study, and we would also like to receive clarification of the findings referred to by Commissioner Rankin.

If possible, we would like to know the names of the products and manufacturers involved, and the results of the examination. If this is not suitable for transmission to us, we would think that at least a tabulation of the classes of drugs and the results of examination, by classes of drugs, could be furnished.

We also have at least one specific question related to Commissioner Rankin's speech. He states that about 2,600 of the drugs were sold by generic name only and about 2,000 by brand name. If the results he summarizes are to have significance, with respect to the generic and brand name controversy, it would be necessary to know the proportion of substandard lots made by firms which produce so-called generic drugs almost exclusively, and compare this with the performance of the companies which make both brand-name and generic-name drugs, but which are commonly regarded as brand-name houses. For example, several of the very large pharmaceutical firms offer a complete line of drugs which includes about as many drugs sold by generic names as those sold under trademarks.

We believe it is most important to obtain meaningful information on the performance of drug manufacturers of various kinds, so that mutual efforts can be put forth by the industry and the Food and Drug Administration to raise the level of quality of the drug supply as high as possible. We believe that a discussion of the figures already available to the Food and Drug Administration would provide a useful start for this project.

Sincerely yours,

C. JOSEPH STETLER.

PHARMACEUTICAL MANUFACTURERS ASSOCIATION,
Washington, D.C., December 1, 1966.

JAMES L. GODDARD, M.D.
Commissioner, Food and Drug Administration,
Washington, D.C.

DEAR COMMISSIONER GODDARD: The purpose of this letter is to again request information on the drug potency study undertaken several months ago by the Food and Drug Administration which has been referred to in several FDA speeches.

You may recall that I wrote to you on two previous occasions, August 22, and again on October 27 requesting the information. In our meeting in your office on November 1, you indicated that the material would be forthcoming.

I am most anxious to submit the data to careful anlysis and at the earliest possible moment because of the serious nature of the conclusions which have been reached by the FDA and the impact which this study is sure to have in connection with prospective hearings by the Senate Finance Committee next year.

It would be most helpful if you would provide us with a complete list of the drugs that were examined. That is, we are interested in obtaining a list of those drugs which were acceptable as well as those which were found to be subpotent or otherwise did not meet labeling requirements.

It would also be helpful if the following information could be provided to assist us in our analysis:

1. The nature of the sampling technique or design.
2. The source of the sample, i.e., retail pharmacy, hospital pharmacy, wholesaler, manufacturer's distribution point or warehouse, reserve samples, etc.
3. The lot or control numbers of the products found to be subpotent.
4. In the case of nonofficial assays, the method of analysis used.
5. The limits of potency for non-U.S.P. or N.F. drugs.

I recognize that some of the above information may be difficult to supply, however, to the extent possible I would appreciate consideration of as many of these items as possible.

Your prompt attention to this request will be very much appreciated.

Sincerely yours,

C. JOSEPH STETLER.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
Washington, D.C., February 1, 1967.

Mr. C. JOSEPH STETLER,
President, Pharmaceutical Manufacturers Association,
Washington, D.C.

DEAR MR. STETLER: This replies to your letter of December 1, 1966, requesting information on the drug potency study that we conducted some months ago.

The enclosed computer printout release and summary give the results of the survey.

It is not possible to retrieve the lot numbers of individual samples from the computer and we have not undertaken the manual task of reviewing each file to obtain the lot numbers.

The printout is filed in our Office of Education and Information where it is available for review by any interest parties.

Sincerely yours,

JAMES L. GODDARD, M.D.,
Commissioner of Food and Drugs.

PHARMACEUTICAL MANUFACTURERS ASSOCIATION,
Washington, D.C., February 24, 1967.

JAMES L. GODDARD, M.D.,
Commissioner of Food and Drugs, Department of Health, Education and Welfare, Washington, D.C.

DEAR DR. GODDARD: This letter is written in further reference to the drug potency study conducted last year by the Food and Drug Administration and will serve to advise you that, to date, the information we requested in previous correspondence on this subject has not been receivd.

Your letter of February 1, the FDA press release of January 31 and the computer print-out report of the study have been carefully reviewed. This data, however, is not adequate to answer the questions we previously raised. Consequently, we are repeating our request for more complete information in order that members of this Association cited in the report are afforded the opportunity to adequately study the data and undertake whatever action may be indicated.

You will recall that the following information was requested in my letter of December 1, 1966:

(1) The nature of the sampling technique or design.

(2) The source of the sample, i.e., retail pharmacy, hospital pharmacy, wholesaler, manufacturers' distribution point or warehouse, reserve samples, etc.

(3) The lot or control numbers of the products found to be subpotent.

(4) In the case of nonofficial assays, the method of anaylsis used.

(5) The limits of potency for non-U.S.P. or non-N.F. drugs.

The information requested on limits of potency for non-U.S.P. and non-N.F. drugs was not supplied but is ascertainable from the speech given by Deputy Commissioner Rankin before the American College of Apothecaries on October 15, 1966. It is also my understanding from our conversation on February 16 that lot and control numbers will be supplied to the firms involved upon request. Information on items 1, 2, and 4 above are prerequisite to a meaningful evaluation of the data thus far provided, however, and I respectively request again, therefore, that it be supplied. More recently questions have arisen as to when the samples in question were obtained by FDA. We would, therefore, also like to have an indication of when the samples identified in the study as violative were acquired by FDA.

The effects of the study in question on the industry and the public are substantial. We are particularly concerned by the publicity given to this material because of the admittedly questionable validity of the study and the improper conclusions drawn from it. We have therefore directed the enclosed letter and questionnaire to PMA firms whose products were found to be violative by the FDA in the study. The replies we receive will be tabulated and analyzed and I shall promptly notify you if additional data from the FDA is needed to confirm or deny the conclusions which have thus far been released.

The ability of PMA member firms to properly evaluate their performance depends in a large measure on the availability of complete information in instances in which their products are allegedly found to be in violation of the statute or regulations. It is for this reason that I most earnestly request your prompt attention to this matter.

Sincerely yours,

C. JOSEPH STETLER.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
Washington, D.C. March 15, 1967.

MR. C. JOSEPH STETLER,
President, Pharmaceutical Manufacturers Association, Washington, D.C.

DEAR MR. STETLER: This will provide additional information concerning the drug potency survey in response to your letter of February 24, 1967.

The FDA District offices were requested to obtain one or more samples of each dosage form of the drugs in the categories listed from each primary manufacturer. Appropriate analytical procedures were used for non-official preparations, and included procedures submitted with New Drug Applications, AOAC procedures and others published in the scientific literature. The survey was initiated in late March 1966, and continued for approximately two months.

You are correct in your understanding that lot or control numbers are being supplied to each manufacturer on request. Information on the method of analysis is included when requested. The criteria used in evaluating the potency findings were arbitrarily set at 90–110% of the declared amount, except where compendia or NDA's were controlling, as announced in our press release.

As indicated in the release, our samples were obtained from lots ready for sale. We do not believe we would be justified in expending the time and funds required to obtain and list the specific source of each sample.

Sincerely yours,

JAMES L. GODDARD, M.D.,
Commissioner of Food and Drugs.

PHARMACEUTICAL MANUFACTURERS ASSOCIATION,
Washington, D.C., May 4, 1967.

JAMES L. GODDARD, M.D.,
Commissioner of Food and Drugs, Department of Health, Education, and Welfare, Washington, D.C.

DEAR DOCTOR GODDARD: As you know from past correspondence and conversations, the Pharmaceutical Manufacturers Association and a number of our member firms are attempting to evaluate the methods and tests employed in and the results of the 1966 FDA drug potency study.

The results of this survey have been given wide publicity by FDA and others, and some of the conclusions reached have frequently been cited in support of generic prescribing and dispensing legislation. On four occasions the study has been referred to in the *Congressional Record* by proponents of such legislation. The most recent reference to the report was made by Senator Gaylord Nelson in his address to the Senate on Wednesday, April 26, 1967. At that time he announced that he will initiate investigative hearings, involving the drug industry in the Monopoly Subcommittee of the Senate Small Business Committee beginning on May 15. Included in Senator Nelson's address was a reference to a newly published book "Handbook of Prescription Drugs" by Dr. Richard Burack, which also contains a reference to the survey. The fact that this survey will no doubt play an important part in the hearings announced by Senator Nelson makes it even more imperative that the information we and individual companies have previously requested be made available as soon as possible.

Many of the PMA member firms involved have still not been informed of the source or sources from which their alleged violative samples were obtained. I respectfully request again, therefore, that this information be made available to them at the earliest possible date. We cannot agree with the conclusion you

previously expressed that the time and funds required to obtain and list the specific source of each sample would not be justified. It is our considered opinion that such information is exceedingly important. Conditions of storage including temperature and humidity can have an important bearing on the potency of many drug products. Information concerning the source of samples can be provided to this office or directly to the firms involved.

Pursuant to the comment in your letter of March 15, I shall again advise our member companies involved, which have not already done so, to request the method of analysis for the specific alleged violative samples in question.

It will be greatly appreciated if prompt attention can be given to any inquiries directed to you or your staff by our member firms with respect to sample sources and methods of analysis. This information will assist us in completing our review of the overall survey which to us is a project of major significance.

Sincerely yours,

C. JOSEPH STETLER.

1966 FDA drug potency study comparative analysis

	P.M.A.	Non-P.M.A
I. Total number of firms in study	84	162
II. Total number of products examined	1,933	2,640
(a) Generic	531	2,050
(b) Brand	1,402	590
III. Number of violative samples	119	257
IV. Average number of products per firm	23.0	16.3
V. Number of firms with generic and brand violations	5	29
Percentage of firms with generic and brand violations	5.9	17.9
VI. Number of firms with violations (generic or brand)	49	78
Percentage of firms with violations (generic or brand)	58.3	48.1
VII. Number of firms without violations	35	48
Percentage of firms without violations	41.6	51.8
VIII. Generic products:		
(a) Number of firms with generic products in study	53	134
(b) Number of generic products in study	531	2,050
(c) Average number of products per firm	10	15.3
(d) Percentage of generic products in total sample $\frac{IIa}{II}$	27.4	77.6
(e) Number of products sampled among violative firms	241	1,706
(f) Percentage violative samples among violative firms studied $\frac{g}{e}$	10.7	10.6
(g) Number of violative samples	25	175
(h) Percentage violative samples of generic products in total sample $\frac{g}{b}$	4.9	8.5
(i) Number of firms with violative samples	13	66
(j) Percentage of violative firms $\frac{i}{a}$	24.5	49.2
(k) Number of firms without violations	40	68
(l) Percentage of firms without violations $\frac{k}{a}$	75.4	50.7
IX. Brand name products:		
(a) Number of firms with brand name products in study	77	106
(b) Number of brand name products in study	1,402	590
(c) Average number of products per firm	17.9	5.5
(d) Percentage of brand products in total sample $\frac{IIb}{II}$	72.4	22.3
(e) Number of products sampled among violative firms	1,120	372
(f) Percentage violative samples among violative firms studied $\frac{g}{e}$	8.3	22.0
(g) Number of violative samples	94	82
(h) Percentage violative samples of brand products in total sample $\frac{g}{b}$	6.7	13.8
(i) Number of firms with violative samples	41	42
(j) Percentage of violative firms $\frac{i}{a}$	53.2	39.6
(k) Number of firms without violations	36	64
(l) Percentage of firms without violations	46.7	60.3

STATEMENT BY FDA OFFICIALS CONCERNING THE POTENCY SURVEY

1. Commissioner James L. Goddard in an address to the Drug and Allied Products Guild, Ellenville, N.Y., June 8, 1966:

"Between March 24 and June 3 of this year, the Food and Drug Administration collected almost 4,200 drug samples in 20 major therapeutic categories—corticosteroids, anticoagulants, antihypertensives, diuretics, nitrates, and so on, 7.6 percent of them deviated to a material extent from declared potency—they failed to meet USP or NF limits, or in the case of non-official drugs their potency fell outside the range of 90–110 percent of declared potency.

"On the average, then, we have to conclude that one out of every 14 drug units manufactured is violative just on potency alone . . .

"* * * These are facts of life—of human life and of economic life. But I must tell you that the Food and Drug Administration is interested first and foremost in the facts that protect human life . . ."

2. Deputy Commissioner Winton B. Rankin, in an address to the American College of Apothecaries, Boston, Mass., October 15, 1966:

"We collected about 4,600 (sic) samples of drugs last spring representing the output of about 250 manufacturers. We examined these samples for potency . . . The quality of a drug was judged by applying the potency limits of the USP or the NF [United States Pharmacopeia or the National Formulary] if it was an official drug. Otherwise, it was considered acceptable if it contained 90 to 110 percent of the active ingredient declared on the labeling. 7.8 percent of the generic-named drugs were not of acceptable potency. 8.8 percent of the brand-named drugs were not of acceptable potency . . . Manufacturers who would like to avoid increasing demands for extension of batch-by-batch Government testing of additional drugs would be well advised to clean their own house rather than waiting for the Government to do it . . . The main issue is: If a drug manufacturer cannot put out good drug, then he will have to get out of the drug business . . ."

3. FDA news release, for A.M.'s January 31, 1967:

"* * * There were 4,537 drug samples collected in the survey. Analysis showed that 376 samples—or 8.2 percent of the total—were above or below acceptable potency levels. The 376 samples came from 127 different firms . . . Follow-up action on violations of potency standards included the collection and examination of additional samples, re-inspection of manufacturing plants, recall or seizure of products, or citation of the manufacturer . . ."

4. Dr. Goddard, in an address to the Philadelphia Chapter, Defense Supply Association, February 9, 1967:

"* * * Altogether there were 4,573 drug samples collected. On just potency levels alone we learned that 8.2 percent of the total survey—that is, 376 drug samples—were above or below acceptable potency levels. As a physician—and, every now and then, as a patient, too—I regard 1 percent as the outside limit."

5. Dr. Goodard, in an interview in the February, 1967 issue of *D.O.*, publication of the American Osteopathic Association:

"* * * Well, you can quibble about minor differences; you can talk about whether this sample was statistically significant—it did have more than 4,500 drugs in it—about half of them were trade names, about half of them generic drugs. But you can't argue away the fact that about one out of twelve (sic) drugs didn't measure up on potency . . . In one out of twelve instances the patient isn't getting what the physician intended . . ."

STATEMENTS FROM SOURCES OTHER THAN FDA ABOUT THE POTENCY SURVEY

Senator Philip A. Hart, Senate Floor Speech, October 21, 1966

Mr. President, last Saturday the Deputy Commissioner of the Food and Drug Administration, Winton B. Rankin, pointed out that if doctors and pharmacists are attempting to supply patients with the best drugs, they might be better advised to use generics over brandname drugs.

A quality check by FDA of 4,600 samples of 20 of the most important groups of drugs—generic and brandnames—Mr. Rankin reported, showed 7.8 percent of the generics not of acceptable potency. But 8.8 percent of the brandname drugs failed to meet standards.

The percentages, admittedly, are still too high in both categories and demonstrated, as Mr. Rankin said:

"That drug manufacturers and the government are going to have to do a better job."

Under the direction of FDA Commissioner Goddard, I am confident that agency—which has been improving rapidly in recent months—will do the better job required.

"The main issue, as the FDA sees it, is:

"If a drug manufacturer cannot put out good drugs, then he will have to get out of the drug business."

"The agency plans to apply that rule firmly, Mr. Rankin assures us. And he outlines how they will reach that goal . . .

"Mr. President, I ask unanimous consent that FDA Deputy Commissioner Rankin's speech of Saturday, October 15, to the American College of Apothecaries at Boston be inserted at this point in the Record."

Midlothian, Tex., Mirror, October 27, 1966

Charges against the effectiveness of generics now should be laid to rest by a recent survey of the Food and Drug Administration. A quality check of 4,600 samples of 20 of the most important groups of drugs—generic and brandname—showed, in fact, that generics had the edge on potency. Of the brandnames, 8.8 percent failed to meet potency standards, compared to 7.8 percent of generics.

Obviously consumers would be well advised to confer with their doctors on the possibility of using generics for their prescriptions.

St. Louis Labor Tribune, February 16, 1967

In a survey of 246 drug manufacturers to determine the potency of their products, more than half of the firms had one or more product samples that did not meet acceptable standards. The results of the survey were released by Food and Drug Administration Commissioner James L. Goddard who said his agency would investigate other drug qualities in a broader survey.

Charles Kuralt, CBS Radio Network, February 28, 1967

The drug inspectors found that more than half of the manufacturers had at least one product sample that did not meet the standards of potency. Some were more potent than they were supposed to be, a few had very little potency at all . . . About eight percent of the total were unacceptable, either too potent or not enough. The unacceptable samples came from 127 different firms . . . The FDA, our watchdog over drug quality has made some conclusions from all this. And what does the agency conclude? . . . The Food and Drug Administration was impressed by its survey of drug potency. Impressed with the need for further surveys to watch and safeguard the quality of thousands of drugs we use today.

Senator Joseph M. Montoya, March 8, 1967, address to the Senate, quoting Science Newsletter for March 4, 1967

There is no doubt that research carried out by wealthy drug houses has led to the discovery of many new drugs. Whether or not a brandname insures a high quality product, however, is a matter of considerable debate. In fact, a recently reported analysis by the Food and Drug Administration revealed that 8.2 percent of 4,573 drug samples did not meet potency standards. Breaking this down into products marketed under brandnames versus those sold under generic names, 8.8 percent of 1,991 brandname samples were deficient compared to 7.7 percent of 2,582 generics. "Nobody came out of this survey looking good," an FDA official commented.

Senator Russell B. Long, letter to the editor, Medical World News, April 21, 1967

In a survey of drug potency recently completed by the Food and Drug Administration, some 4,600 drug samples were tested for conformance with accepted standards of potency. While the FDA found 7.7% of the established-name drugs failing to meet those standards, it also found 8.8% of trade-name products unacceptable. Fourteen of the drug manufacturers who advertised in your February 17 issue produced drugs included in the survey. And nine of the 14 advertisers produced unacceptable products!

Senator Gaylord Nelson, April 26, 1967, address to the Senate

It is correct that problems can arise as to the safety, potency or purity of drugs. But the point is that such problems are not necessarily limited to low-priced drugs sold under generic names . . .

In 1966, the U.S. Food and Drug Administration sampled 4,600 drugs from 250 manufacturers. About 2,600 were drugs sold by their generic names, and about 2,000 were drugs sold by brand names. The FDA found that 7.8% of the generic-named drugs were not of acceptable potency and 8.8% of the brand-named drugs were not of acceptable potency.

The Washington Post, May 7, 1967

One of the determinants of therapeutic response is potency—that is, whether a drug is of a required strength. A drug that is subpotent is a bad drug, even if it meets all the other requirements and is purer than pure. A year ago the Food and Drug Administration checked the potency of drugs from 250 suppliers. The products fell into 20 key categories but did not include antibiotics, whose quality is assured by the FDA's premarketing, batch-by-batch inspection. Of 2,600 samples sold under less expensive generic names 7.8 percent were found subpotent and therefore unacceptable. Of 2,000 brand-name samples 8.8 percent were below strength. (It should be understood that the difference between these percentages is very little, and under no circumstance should one conclude from the FDA findings that the quality of generics is necessarily higher than that of brand-name drugs.).

"The Handbook of Prescription Drugs," by Richard Burack, M.D.

"Not the least of the reasons forcing us to believe that brand-name drugs are not necessarily better than those sold by generic names is a finding made in the spring of 1966 by the United States Food and Drug Administration. At the direction of its new, no-nonsense Commissioner, Dr. James Goddard, the Agency sampled 4,600 drugs from 250 manufacturers. Quoting Mr. Winton B. Rankin, Deputy Commissioner, as he addressed the American College of Apothecaries on October 15, 1966, in Boston, Massachusetts: 'About 2,600 of the drugs were sold by their generic name only and about 2,000 by brand name. They represented 20 of the most important groups of drugs used in medicine—antihypertensives, oral antidiabetics, anti-infectives, digitalis and digitalis-like preparations, for example. Antibiotics were not included because every lot of antibiotics for human used is checked before sale'. Deputy Commissioner Rankin then went on to reveal to a hushed audience of pharmacists that '7.8 percent of the generic-named drugs were not of acceptable potency, 8.8 percent of the brand-named drugs were not of acceptable potency.' Later, in reply to a question from the audience, the speaker made it clear that the difference between the 7.8 and 8.8 percent figures is not large enough to allow one to conclude that genric drugs are necessarily better than those sold by brand name."

SUMMARY OF FDA DISCLOSURES, MAY, 1967

Products of 246 manufacturers were involved in the 1966 FDA survey. Of these, 84 are PMA members. Of the 84, 49 were found to have one or more violative products. (PMA has 138 members).

FDA reported on tests of 4,573 products. Of these, 1,933 were products of PMA members. Of the 1,933, 119 were found by FDA to be violative.

Overall, 8.2 percent of the products in the survey were found to be violative.

For the PMA-member products, the comparable percentage was 6.1.

SUMMARY OF PMA INVESTIGATION

(Please see attached questionnaire).

Responses to Question #12 are the most significant.

Forty-two firms, with 1,467 products in the survey, have undertaken internal reanalyses of their 100 products alleged to be violative. Results from 40 firms show that only 14 of these products were deficient, and that 80 were not. Reports on reanalyses of six products are pending. Two firms have not reported results to date.

Seven firms, with 146 products in the survey, have not reported undertaking reanalyses of their 19 products alleged to be violative.

Eight firms so far have reported that their in-house reanalyses were repeated by outside, independent laboratories. Results so far show that of 14 allegedly violative products among these eight firms, five have been found not violative, two were confirmed to be violative, and reports are pending on seven.

Thus, careful reanalyses of the products of 40 PMA member firms, alleged to be violative, show that only one percent did not meet standard potency limits.

Responses to Questions #2 and #3 are also highly significant.

Only six firms have reported being notified by FDA of alleged violations involving their products in the seven months following completion of the survey in June, 1966. Thirteen companies were suddenly notified in January, 1967, just a few days prior to public release by FDA of the more detailed survey results on January 31.

Responses to other questions reveal that FDA failed to advise 36 firms of the sources of the samples found to be violative. This is important, because it did not afford the firms an opportunity to check whether, for example, unusual storage conditions may have accounted for the potency violations alleged. Similarly, 36 firms were not told when the samples were obtained.

Twenty-three firms state that they have reason to believe there were more samples of their products obtained by FDA during the survey than were accounted for by FDA as either acceptable or violative when the results were finally published. For example, one company received a report on 79 samples (including four alleged violations found baseless on reanalyses), and has had no information on 36 additional samples obtained from the company by FDA at the same time.

FDA SURVEY OF DRUG POTENCY QUESTIONNAIRE 1966

(This is a copy of a questionnaire sent Feb. 10, 1967, by PMA to the presidents of 49 of its member firms alleged by FDA to have one or more violative products on the market. Replies for each question, supplemented with later information received from the firms, are shown.)

To be answered as completely as possible and returned to P.M.A. no later than Friday, February 24, 1967. Address replies to C. Joseph Stetler. Use additional sheets, if necessary.

1. Did your firm receive any information from the F.D.A. or from an F.D.A. inspector that samples of your products cited in the enclosed list (acceptable or violative) were to be the subject of this study?

Yes	8
No	36

2. Did your firm receive any private communication from the F.D.A. or from an F.D.A. inspector concerning the results of their analysis of your products (acceptable or violative)?

	Acceptable	*Violation*
Yes	1	22
No	33	20

3. When was your firm advised of either (1) or (2) above?

1. Date*
   - April 1966–7
   - August 1966–1
2. Date*
   - July 1966–1
   - August 1966–1
   - September 1966–1
   - October 1966–1
   - November 1966–1
   - December 1966–1
   - January 1967–13
   - February 1967–1
   - No date submitted—2

*Violative only.

4. Does your firm have any reason to believe that a larger sample of your product(s) than is cited in the attached list was obtained by F.D.A. for purposes of the study? If your answer is yes, list the product(s) and number of excess samples (by lot or control number, if possible) on a separate sheet. You may wish to use a composite sheet for answers to questions 4, 5, 6, 7, 8, 9, 10, 11.

Yes	23
No	20

5. Did F.D.A. indicate to your firm the source(s) of its sample(s) of your product(s) (acceptable or violative)? If your answer is yes, list the product(s) and their source(s) on a separate sheet.

Yes	8
No	36

6. Did F.D.A. indicate *when* the sample(s) of your product(s) were picked up? If your answer is yes, indicate the date(s) on a product-by-product basis on a separate sheet.

Yes	8
No	36

7. Is your firm able to identify either the source(s) of the sample(s) of your product(s) or the date(s) of sampling? If your answer is yes, indicate source(s) and date(s) on a product-by-product basis on a separate sheet. Do not include information on source(s) or date(s) provided by F.D.A.

Yes	18
No	24

8. Did F.D.A. specifically identify the lot or control number(s) of your product(s) (acceptable or violative)? If your answer is yes, indicate the lot or control number(s) on a product-by-product basis on a separate sheet.

Yes	39
No	7

9. Is your firm able to identify the lot or control number(s) of your product(s) (acceptable or violative) cited in the attached list? If so, please identify by lot or control number on a product-by-product basis on a separate sheet.

10. Please list your products in the attached list which *have not* been identified by lot or control number by either F.D.A. or your firm. Use separate sheet.

11. Does your firm have any reason to question the validity of F.D.A. methods or the statistical analysis of the results as the latter is related to sampling error or limits of variations? If your answer is yes, please qualify.

Yes	36
No	5

12. Has your firm undertaken an analysis of the product(s) (acceptable or violative) cited in the attached list which you have been able to positively identify? If so, indicate results in terms of percent active ingredient as related to potency declaration in labeling or U.S.P. and N.F. standards on a product-by-product basis on a separate sheet.

Yes	42
No	3

13. Does your firm plan to, or will you be willing to, undertake such an analysis of the product(s) which can be positively identified?

Yes	38
No	2

NOTE.—These two firms had done so prior to receipt of the questionnaire.

14. Has F.D.A. initiated any action or follow-up on the violative products of your firm?

	Yes	*No*
Additional samples	20	19
Reinspection of plant	12	24
Recall	2	32
Seizure	1	32
Citation	1	32
Other	4	26

15. Please add any additional comment, suggestion, or explanation which will assist us in the conduct of the project.

Company _____
Signed _____

Please return to Mr. C. Joseph Stetler, Pharmaceutical Manufacturers Association, 1155 Fifteenth Street, N.W., Washington, D.C., 20005, by February 24, 1967.

(Whereupon, at 12 o'clock noon, a recess was taken until 12:30 p.m., the same day.)

AFTERNOON SESSION

Senator NELSON. We will reopen the hearings now with Dr. Donal Magee, chairman of the Department of Physiology and Pharmacology at Creighton University Medical School in Omaha.

Dr. Magee, we appreciate very much your taking the time to come here and testify before the committee. You may proceed to offer your testimony in any way most convenient to you, by reading or extemporizing, and if you don't mind we may interrupt for questions as they occur. I see your opening statement mentions your professional credentials, so you just go ahead and present it in any way you like.

STATEMENT OF DR. DONAL F. MAGEE, CHAIRMAN, DEPARTMENT OF PHYSIOLOGY AND PHARMACOLOGY, CREIGHTON UNIVERSITY MEDICAL SCHOOL, OMAHA, NEBR.

Dr. MAGEE. I might add in addition to the opening statement that I teach. I don't practice medicine, and I don't buy drugs except as a patient.

I am Donal F. Magee, chairman of the department of physiology and pharmacology at Creighton University Medical School, Omaha. I have a degree in medicine from Oxford University earned in 1948 and a Ph. D. in physiology from the University of Illinois earned in 1951. From then until 1965 I was on the staff of the Department of Pharmacology at the University of Washington, Seattle.

In teaching pharmacology to medical students, keeping up to date with new products is a major problem. Every teacher is required to teach branches of the subject in which he has no immediate research interest and must, therefore, have recourse to the published literature and advertising. For new products this is difficult. Every teacher must assess the worth of the product; that is, is it worth mentioning at all, should it be condemned, criticized, or favored. In my opinion, a new product to justify itself must treat an ailment against which no other agent is effective or it must treat an ailment better than any existing therapy. If it meets neither of these criteria it must be less toxic than existing drugs or be easier to administer and, finally, if it is equal in all these respects to existing agents, it must be cheaper. Such comparative information is almost impossible to obtain even for pharmacologists who have the training and time to search for it. It is not obtained from company advertising, despite its improvement over the last few years, and only rarely is it obtained from detail men.

In the past, in response to requests to detail men and companies, I have only once received information which could be used in a lecture. One would imagine that it would be in the interest of drug manufacturers to keep the teaching pharmacologist informed of the therapeutic and pharmacological reasons for the production of a new drug, but this has not been my experience. My judgment of advertising material is that its purpose is to make a name known or to develop in the mind of the reader an enduring relationship between a name and a certain symptom complex or disease.

As an example of this, I cite a piece of literature that I used to get twice every week which mentioned the name of an antibiotic, and told me that this antibiotic was acceptable to children because of its good taste, and this of course for the teacher and for the practitioner is valueless.

Advertising literature is not intended as a basis on which the practicing physician can form an assessment of a product. This is so of all advertising, but in my opinion there has to be an essential difference between the advertising of drugs and the advertising of products like chewing gum, tobacco, and automobiles, because at least with these one has a choice.

Most clinicians are not in a position to evaluate the efficacy of new preparations and their patients have no choice but buy what is prescribed and submit to treatment which may be more costly and less efficacious than existing medications.

An example of this sort of thing is provided by the spate of expensive antibiotics touted a few years ago, all of which were said to deal with penicillin-resistant organisms and most of which have now disappeared.

I ran into this because for many years, up until 1964, I taught the pharmacology of antibiotics. As new ones were advertised I sought literature and information from the companies marketing them, since many were too new to have made an appearance in the usual scientific literature and one had to decide whether they were important or not.

One or two of these I examined rather thoroughly, and was alarmed to find out that as the undesirability of these became more and more obvious, the advertising became more strident and reached a crescendo before the drugs finally disappeared. One can only suspect that the companies concerned anticipated failure and wished to recoup as much of their loss as possible before it occurred, irrespective of the needs of the patient.

The classical example in my opinion of suppression of the critical faculties of the practitioner is in the distribution of multivitamin preparations. The advertising of these needs no description but drug companies employ good scientists who must know that extra vitamins are not needed by the bulk of the population—there is a very small segment, and we should be ashamed it exists which does show deficiencies I am told, but it is usually too poor to buy supplements.

Physicians apparently do not realize that the bulk of the population are in no need at all of vitamin supplements, or if they do, have had their opinions suppressed by advertising since virtually every pediatrician prescribes them. Probably more people in the United States take daily vitamins than have TV sets or cars. I prefer to think the physician is ignorant rather than dishonest. It is impossible to be so lenient with the drug companies. Treatment of imagined and suggested vitamin deficiency can only be seen by them as a lucrative source of income.

I can give you an example of the persuasiveness of this advertising. Many of my colleagues who know that vitamin deficiencies are unknown or virtually unknown nevertheless have wives who give daily vitamin capsules to their children. They are despite their professional knowledge unable to convince their own wives of the futility of this.

Senator NELSON. Are there any simple procedures for determining vitamin deficiency?

Dr. MAGEE. Most vitamin deficiencies are obvious, a child with a vitamin D deficiency, for example, gets rickets, and the early signs of this show up on X-ray, but in our society this is no longer a problem.

It hasn't been a problem for many years, but it has been presented to us as if it were an ever present problem. We are also being told that without added vitamin supplements we become more susceptible to colds and flu, et cetera. There is no shread of evidence at all for this.

Senator NELSON. Do we have any statistics on the percentage of the population that does have a vitamin deficiency?

Dr. MAGEE. I don't know of any offhand. I think perhaps these might be found in the annual publications of the World Health Organization table. Our university has a clinic which ministers to Winnebago Indians, and I am told an occasional Indian child appears with an apparent vitamin deficiency, but it is very, very occasionally.

Senator NELSON. Insofar as other children are concerned, it is rare?

Dr. MAGEE. Yes, it is not seen. I am told that occasionally in the children of migrant farm workers, vitamin deficiencies have been seen also, but today in the middle class, the vitamin buying income group, vitamin deficiency is unknown.

Senator NELSON. What is the basis for the prescription of vitamins? Or are these self-prescribed?

Dr. MAGEE. Well, some are self-prescribed. Many are not. As I said, most pediatricians will prescribe them, and to give you the statement of one pediatrician, the man who attended my children. After the children had been attending him for months my wife finally said, "No, we are not giving them their daily vitamins." He said, "Well, I should have known. Your husband is a physiologist and perhaps he wouldn't believe in these or think that they were necessary," and she replied, "Why do you prescribe them?" He said, "Because the mothers expect that I do."

Senator NELSON. That is the only reason he gave?

Dr. MAGEE. This is the only reason he gave, and I think that this is not an uncommon reason. It is expected that pediatricians and obstetricians too give vitamins.

Senator NELSON. Thank you. I have one more question. You say probably more people take vitamins than have TV sets. Are there any hard statistics on how many people take vitamins? Do we have any knowledge about that?

Dr. MAGEE. No, I don't believe we have a total, but there are figures, and I have them here, giving the annual production of vitamins in terms of dollars. I think it is about $60.6 million worth per annum, and the production of penicillin, which is a life saving drug, is $86 million.

I tell my students in lecturing on the subject, which I do in the pharmacology course, that we have the most nutritious sewage in the world, because of course excess vitamins for the most part are excreted in urine.

A few years ago obstetricians succumbed to the notion that molybdenum added to ferrous salts rendered them more efficacious in the treatment of iron deficiency anemia. There was no evidence and the

preparation was expensive. I looked into this personally also because my wife was prescribed molybdenum with iron. I did not get it, and I was reprimanded by the obstetrician.

Still today iron preparations are touted and prescribed which contain an enormous array of ingredients at enormous cost when only the cheap iron salt is needed.

Iron preparations are on the market which contain all sorts of metals, copper, manganese, ascorbic acid, intrinsic factor, vitamin B–12, a colossal array of stuff. These are expensive. Iron deficiency anemia can be treated with ferrous sulphate, which is very cheap.

Senator NELSON. Do these other substances have any affect at all?

Dr. MAGEE. If an animal is copper deficient it gets anemia; but it it very, very difficult indeed to produce copper deficiency.

There are parts of the world, in South Australia, for example, where sheep grazing on a copper deficient pasture, get copper deficiency, but apart from that, I never have heard of a spontaneous copper deficiency in man or animals.

Vitamin B–12 treats pernicious anemia, for pernicious anemia the quantities present in these tablets when given by mouth are useless.

Mr. GORDON. Are you saying vitamin B–12 cannot be given for anemia?

Dr. MAGEE. No; but it cannot be given orally because the reason people have pernicious anemia is that they can't absorb vitamin B–12.

The vitamin business, in my opinion, is largely fraudulent and based on the gullibility of both the public and the physicians. An added difficulty to me in the assessment of advertising material is the knowledge that in the past this has been shown to be inaccurate and misleading. Since this has occurred one cannot help but be suspicious and therefore be wary of a recurrence.

There are examples of advertising which, as pointed out in the hearings before the Kefauver committee, in which less than a proper account of toxicity, and side effects had been presented to physicians.

In every medical school pharmacology department in the country, that I am aware of, only generic drug names are used, in teaching. It is impossible to teach in any other way. The alternative is confusion. We heard this morning that there may be 50 different trade names for one drug, and this, of course, is true. The relationship between one drug and another is hidden, by trade names, as is the fact that some chemicals have a physiological function. Who would guess, for example, that Levophed is norepinephrine, which is a physiological substance occurring within the body. I have met practicing dentists and physicians who did not know that Levophed was a physiological material.

I am sure that there can be very few pharmacologists anywhere who have not been telephoned at one time or another to explain, for example, that the dose and the side effects of Luminal, a trade name, and phenobarbital are exactly the same because they are the same substance. The only difference is the cost.

In using generic names in teaching we hope, or at least many of us do, that our students will use them in prescribing. They will know more about the science of therapeutics if they do, and they will save their patients money. This is not denied even by companies selling under trade names. The sick have no sales resistance, and the cost of their treatment should be a prime concern, in my opinion, of the physi-

cian. But as we have heard this morning, the physician often doesn't know the cost. The patient puts his trust in his physician. The physician does not respect that trust if he prescribes drugs which are much more costly than they need be. In fact, if he is aware of this, in my opinion, he is dishonest. But I think in general he is not aware of it.

In all that I have read and heard on the subject, I have seen no proof that generic drugs are inferior to trade name drugs. They are bought by many hospital authorities, and I expect our politicians and Presidents, when they are treated, are treated with generic-name drugs, if they go to Walter Reed Hospital.

It is common knowledge that one primary producer often supplies the drug to both the low-cost generic marketer and the high-priced trade name seller. Indeed, in several instances the primary producer is the expensive trade name seller. Some examples of this are prednisone, thiopental, and chloroamphenical, and some of the antihistaminics, tripellenamine, for example. We are asked to believe by the trade name companies, that they pay for the research and development from the high prices charged the individual patient and they sell in bulk at a loss to the low-priced generic purveyor who is underselling them.

I can't believe this. I think the drug companies know enough about business to make sure that in selling drugs in bulk, they cover the cost of their research and development.

Finally there are high-priced trade name sellers who have not done any research and development work on the product they sell and still they sell at high prices, higher even in some instances than the companies which have done the research. An example of this sort of thing are drugs which have been developed in Britain and in France, and are sold here at much higher prices than they are in either Britain or France. Chloropromazine is one of these drugs, and some of the oral antidiabetics, for instance tolbutamide, is another one.

The drug market, in my opinion, is fantastic because I know of no other segment of the economy in which the high price seller has a larger share of the market than the company that sells the same product for less. This happens, in my opinion, because the purchaser is captive, and because the physician lacks the appropriate knowledge or is prejudiced, and because the advertising is effective.

Now by prejudice here I mean that one hears from many physicians that they will prescribe only the medications prepared by reliable companies, and that they are opposed to "fly-by-night" manufacturers. Generic-name companies in general in many instances have been so designated.

The pharmacist in our own medical school uses this designation for many companies which are selling generically. I have constant and frequent arguments with him. I have never been able to convince him just as I have not been able to convince many of my medical colleagues that generic in drugs are in no way inferior.

Hoover was once synonymous with vacuum cleaners. Today a trade name Benadryl ® is synonymous with an antihistaminic which is prepared by a particular company. Just as with Hoover, so today there are many generally available drugs known to physicians only by trade names.

I, for example, can remember only the trade name of the common antihistaminic drugs. They are easier to remember. To lecture I have

to go and look up the generic names of these, because, no doubt, I have succumbed to advertising as have most physicians.

I do not believe that there is any justification for the high trade name prices charged the patient, except for higher profits and bigger advertising. The arguments for higher production costs, greater purity and research and development are at best unconvincing and at worst false. The testimony before the Kefauver committee brought this out.

This country has now, rather belatedly, accepted the principle that good health is a right rather than a luxury, and that all have an equal right to the available treatment. There are many factors militating against this, and one of these is drug cost. Much could be done to reduce drug costs if we had an informed public, informed and altruistic physicians and honest pharmacists. The pharmacist can seemingly set any price he wants for any drug, generic or otherwise. He can and often does, as the AMA has recently found in Chicago—the AMA conducted a survey of druggists in Chicago purchasing drugs under generic names, and found that these are often more expensive than drugs bought under proprietary names. I think all that this proved was that in Chicago there are pharmacists who are taking advantage of the patient who appears with a generic name prescription.

Senator NELSON. I don't know whether this issue was raised or not, I simply saw a news story about it, but isn't one of the problems the fact that there are so many drugs on the market the doctors generally prescribe by trade name? I don't know whether you checked that in this case, but couldn't it have been possible that the pharmacist just didn't have available the generic and that he is allowed under the law to supply the drug under its trade name instead of under its generic name?

Dr. MAGEE. That is possible; yes. I got the impression from the article in the AMA News, that generic names were available, but no cheaper.

It did not specifically say so as far as I remember, but this was my impression. Of course, this again is another factor in the cost of drugs. The druggist has to stock such an enormous number of trade name items, oftentimes the same drug, sometimes slightly different, but with the same action.

For example, I would suspect there are something of the order of 50 different antihistaminic drugs. This number is quite unnecessary. In lecturing on the subject I treat them as one since virtually all have general characteristics in common.

Senator NELSON. All antihistaminics?

Dr. MAGEE. Practically all antihistaminics. They differ slightly in degree. For example, virtually all antihistaminics produce depression. Some of them to a lesser extent than others. Practically all of them have local anesthetic activity, some slightly more than others. There is, therefore, no justification for 50 or even 20 separate and distinct antihistaminic drugs.

Senator NELSON. Do you know how many drugs there are on the market?

Dr. MAGEE. Antihistaminics? I think there must be over 20.

Senator NELSON. I mean in total.

Dr. MAGEE. In total I don't know.

Senator NELSON. Total number of prescription drugs?

Dr. MAGEE. I have no idea. It is probably an astronomical figure. Antihistaminics are an example of molecule manipulation. The bulk of them have got similar structures. Antihistaminics, when they appeared, did look like a breakthrough. They were disappointing, but even so, most major drug companies have their own antihistaminic under a trade name.

Senator NELSON. Is there any substantial therapeutic difference among them?

Dr. MAGEE. Not really. Some of them, for example, produce less depression than others. Obviously, if the physician knows this, he will prescribe the one that produces the least depression, because this is one of the undesirable side effects.

Senator NELSON. How would he find that out?

Dr. MAGEE. Well, the way things are managed at present, this is found out only in the course of time. It is found out if one reads medical journals. In the course of time papers are published giving comparative data. This ultimately gets into the pharmacology textbook.

Let's say I am teaching my course next year. A new antihistaminic has appeared on the market and is being prescribed. I would find it well nigh impossible to assess this for the students.

Senator NELSON. Supposing it is an antihistamine that has been on the market for 4 or 5 years; where would you look?

Dr. MAGEE. If it has been on the market for 4 or 5 years, I can find it probably in the pharmacological journals, and in the clinical literature.

Senator NELSON. How difficult a research job is it to find it?

Dr. MAGEE. For me it wouldn't be very difficult, because we have in our libraries indexes of medical and scientific literature. I could look this up in the index and find the literature. We have publications like the Medical Letter, and I could perhaps find it in that. But for a man practicing, it might be very difficult indeed.

Senator NELSON. There isn't any easy reference place where he could look under antihistamines?

Dr. MAGEE. No.

Senator NELSON. And find out which one was the present or——

Dr. MAGEE. No; not that I know of. If he treats patients with a drug, he might in the course of time arrive at an evaluation, if patients have had antihistaminics before they would probably tell him that they feel drowsier with this particular preparation than with previous ones, but it would be hard for him, in my opinion, to assess a drug's comparative depressant activity just from the literature that is available from the drug company or from the detail man.

Senator NELSON. All right, please proceed.

Dr. MAGEE. Recognizing the right of the sick to treatment and the dismal fact that medicine in this country is not up to par, particularly when the patient is poor, we should have the best medicine in the world. I think the time has come for a reappraisal. The present patent laws and the methods by which drugs are merchandised and advertised are not in my opinion in the best interest of the patient.

Who, for example, is benefited by the present quinine monopoly? The resultant price increase may be good for business, but it is bad

for medicine. Who will develop the invaluable but unprofitable drug? By this I mean a drug which is treatment for a disease that very few people get, and therefore hasn't a big market.

In defense of drug companies, I have to say that some such have been developed by drug companies, and presumably there is no profit in them. There is a penicillin derivative for example which removes copper from the body. A few people have a disease in which they have excess copper.

The needs of private industry, be it the drug industry or the insurance industry, are diametrically opposed to those of medicine. Medicine wishes to treat disease effectively and as economically as possible. If it is not economical it is often not effective. The companies, on the other hand, wish to make profits and to pay for their research and advertising. And of course it is proper that they should.

The patient has no option but to pay when he is sick. Then he can least afford it. It is an unsavory and almost unique fact that medical expenses still reduce people to destitution in the United States, and our large drug companies still make enormous profits.

It is proper that drug companies make reasonable profits, and it is true that they do an enormous amount of research. I don't think there can be any dismissal of this fact.

I would question myself whether it is proper for them to make excessive profits from the sick, and whether it is proper that the sick be required to foot the bill for all medical research. At the moment, the sick pay twice for the medical research, that is they pay both as taxpayers, they support the U.S. Government's medical research, and they pay as purchasers of medicine.

Advertising again is proper, but how much of it and of what sort? It is obviously fraudulent to persuade us that we are on the verge of vitamin deficiency, but free stethoscopes for every sophomore medical student in the country every year sounds wonderful.

Is it, however, when it means that some patient is paying three times as much as he need pay for his digitoxin. Every pharmacologist in the country I would suspect, myself included, benefit financially in one way or another from the big drug companies. I don't mean that anyone benefits personally, but the big drug companies give money to departments of pharmacology. They give money to ours, and they give money to most.

Senator NELSON. For what purpose do they give the money?

Dr. MAGEE. They give money sometimes for people to run basic research and clinical trials on potential drugs. I myself am in receipt of a sum of money to the department simply because I am a new chairman in the department of pharmacology. This can be used for the purchase of books or in any way that I see fit to develop the department.

Senator NELSON. What money did they contribute?

Dr. MAGEE. They gave me $5,000.

Mr. GORDON. Any strings attached?

Dr. MAGEE. No strings at all, and I don't believe for a second that this was given me in order that I lay emphasis on this company's product when I teach.

Senator NELSON. There was testimony this morning by Dr. Williams that his department was requested to do research for a particular company. The company only wanted the research to be done on its

drug vis-a-vis a placebo. The medical department wanted it to be a research of that drug versus the efficacy of another drug versus the placebo, and the company wasn't willing to fund that. Is that normal practice in asking that research be done?

Dr. MAGEE. This happens, and judging by the literature, it happens quite often. I can remember several years ago when I was teaching pharmacology in antibiotics, in answer to a request I sent to a company which produced a new antibiotic, they sent me a reprint of an experiment or a test rather.

There were 20 patients with pneumococci pneumonia, and they were treated with the new drug. Eighteen of them got better. Now I of course wanted to know, to evaluate this, how many of them would have gotten better if they had been given penicillin instead of the new drug. Maybe all 20 of them would have recovered with penicillin.

Mr. GORDON. The study did not demonstrate its effectiveness vis-a-vis another drug?

Dr. MAGEE. No, this is very rare, very rare indeed, and of course this is what the teacher wants. It is also what the practitioner needs.

Mr. GORDON. How do you know if the patients wouldn't have gotten better if they got nothing?

Dr. MAGEE. Well, they might of untreated pneumococcal pneumonia, which is a disease which lasts 7 or 8 days. With antibiotics it can be stopped in 2 or 3 days, which is what they did.

Senator NELSON. Doesn't the fact that the comparative studies you were just referring to as to the effectiveness of one drug verus another drug, and that those studies are rare, an indication that there is a substantial gap in the type of research studies that we are doing in this country on drugs?

Dr. MAGEE. Yes, it does indicate that.

Senator NELSON. Do you have any ideas as to how that deficiency ought to be remedied so that the information can be available for the prescribing physician?

Dr. MAGEE. As was indicated this morning, I think that some organization, be it the FDA or the Pharmaceutical Manufacturers Association or the pharmacists ought to be interested in comparison of the worth of drugs. As I indicated earlier, I don't believe that there is any justification at all for a new drug on the market which is not as efficacious as drugs which already exist.

Senator NELSON. How is that going to be accomplished unless you have some independent organization perform tests? I don't suppose anybody would expect to rely upon any party that had an interest in the outcome.

Dr. MAGEE. No. I think it would be most reliably done if it were carried out by an independent organization, but I think it probably also could be done if let's say the drug companies themselves as a body set up some sort of testing agency, these competing companies as a body might conceivably run their own comparative testing program.

I doubt very much that this would be done, because of course it would mean that the products of some companies would go by the wayside, but I was thinking of something in the nature of a pharmaceutical better business bureau. The usual better business bureau is paid for and sponsored by the businesses in the community. Its pur-

pose is to keep up standards and to maintain business ethics. But, however it is done, I think there is an absolute need for comparative testing, and the information has to be available to the physician.

Senator NELSON. Did you hear Dr. Williams' testimony?

Dr. MAGEE. I did, yes, this morning.

Senator NELSON. He discussed that in some detail. Do you agree with his position that it is a very important matter that ought to be settled, that is, that there ought to be testing chemically, clinically, and comparatively, and that the information ought to be available in some easy form for the physician to refer to?

Dr. MAGEE. I do. You mentioned meat inspection. I think it is at least as important as meat inspection, because we have a past record of death and disablement from the prescription of drugs which were not properly tested. We have an unfortunate backlog of this sort of thing, and we have been saved from a few others recently almost by chance.

Senator NELSON. Even if there weren't any danger to the drug, even if in fact the drug is an efficacious one, isn't it important for the doctor to know which of these drugs are the most efficacious?

Dr. MAGEE. It is important for them to know that, because there is danger that drug may be given which is not particularly efficacious for a condition. The patient may in consequence be denied a more efficacious drug. Again with a multiplicity of drugs, with more or less efficacy, as I said earlier, the cost is kept up.

Senator NELSON. Do you think it is a feasible project for someone, whether it be the Government, as suggested this morning, someone at least who can clinically test all drugs, and to make arrangements via contracts and various other ways to have clinical tests made so that in one place you can collect all the information that told you what you needed to know about the efficacy of the drug, the side effects, and so forth and so on for generic and trade-name drugs. Do you think it is feasible to do that?

Dr. MAGEE. I think it is not only feasible, but essential. I believe now that we have FDA and USP chemical testing of new drugs, but we haven't comparative clinical testing of the same order to the best of my knowledge I think that it is absolutely essential.

Senator NELSON. I used the word feasible. This raises the question whether it is practicable to do it. How big a job is it?

Dr. MAGEE. It would be a very large job. I am certain in the interests of those who are sick, and in view of the fact that illness is a national concern, a concern of every American, whether he is ill or not, that this is something that has to be done. As I say here, our medical record needs improvement.

Senator NELSON. Of course I am reminded of the very large number of drugs, but I would suppose you would take the relatively small group of drugs that is most frequently prescribed, and settle that issue as to their chemical composition and as to their clinical, comparative clinical therapeutic value, wouldn't you?

Dr. MAGEE. Yes, that could be done and I believe is being done now to some extent. There are many older drugs. Those that have proved to be toxic, generally have been dropped in the course of time after illness and death has resulted from their use.

The drug aminopyrine was once a constituent of headache powders. It is now gone. A number of people suffered in gaining this experience, but amongst the old drugs we haven't separated what is efficacious from those that are not. The toxicity of new drugs, however, is a different matter.

Chloramphenicol is an example of a drug that was put on the market before the whole story of its toxicity was known.

Senator NELSON. Do we know of the old drugs, is there enough knowledge among the pharmacologists to know what of those that are on the market have some efficacy and those that do not, or are there those on the market that we don't even know about?

Dr. MAGEE. I think pharamacologists know, but there are drugs that are toxic or useless which are still prescribed. One was mentioned this morning, strychnine. Therapeutically they do nothing. Pharmacologists know this. The prescription of some of these is justified by physicians in terms of psychosomatic effects. The patient believes he is ill. If he feels something has been done, then he doesn't feel ill.

Senator NELSON. Why would one of those drugs make you feel better than just a placebo?

Dr. MAGEE. They don't. But these things are time-honored tonics. Patients are told they are going to be given a tonic that will "buck them up."

Concerning the financial benefit that the pharmacologist gets from the drug company, most pharmacologists appreciate this, I certainly do, but this has become a way of life, and one doesn't often equate grants and scholarships with prices, or with the money that the patient has to pay.

The drug companies, for example, contribute as sponsors to many independent professional scientific societies, and in a way help maintain these.

It is sad and rather frightening in my opinion that organized medicine in the shape of the AMA has set itself against the patient in the drug price controversy. I say frightening because if the physicians' organization is neglectful of the patient's interest in this respect may it not be equally neglectful though less obviously in other respects?

Senator NELSON. Is this a new position for the AMA vis-a-vis the stand they took 20 or 30 years ago?

Dr. MAGEE. This is new, yes, new in a sense. Twenty or thirty years ago they were against quackery, and quackery is not exactly within the bounds of medicine, but since quackery involved nostrums and treatments outside the profession, they were against it. Until comparatively recently they were concerned with drug standards. They had a council on drugs which gave its approval to new preparations.

Senator NELSON. Do you feel that the AMA is not adequately concerned with drug standards today?

Dr. MAGEE. I get the impression myself that the AMA seems to be more interested in safeguarding business and in safeguarding private enterprise, in this instance at least, than in the patient. The impression I get is that the AMA sees a greater danger to private enterprise than it does to the patient.

Senator NELSON. But why particularly should they be concerned in this instance about say drugs or drug prices, drug standards, versus the welfare of the patient they are sworn to uphold?

Dr. MAGEE. What they have said is that the ultimate judge of the efficacy of a drug is the physician, and they have given the impression that any action on the part of the Food and Drug Administration to test the efficacy of drugs will detract from the physician. But I have pointed out I hope, and Dr. Williams pointed out earlier, that most physicians are not in a position to get this information for themselves or to judge efficacy of drugs.

Mr. GORDON. You mean relative efficacy?

Dr. MAGEE. Yes, relative efficacy. Much of the information that they get is from advertising, and much of it, very much of it is from detail men. At lunchtime Dr. Williams gave me an example of the power of the detail man. Apparently his hospital formulary omitted the Smith Kline & French dextroamphetamine, Dexedrine, because Smith Kline & French couldn't compete with another supplier. Following this, the detail man no longer pushed this drug in the hospital. Dr. Williams has told me that the prescriptions for dextroamphetamine went down 50 percent.

Senator NELSON. For Dexedrine or dextroamphetamine?

Dr. MAGEE. For dextroamphetamine.

Senator NELSON. For the generic went down?

Dr. MAGEE. Yes.

Senator NELSON. Or for the drug itself?

Dr. MAGEE. For the drug itself. Evidently 50 percent of the supposed need for this drug was due to the detail man.

Senator NELSON. The AMA certainly must be aware of the problem that confronts the doctor. It has been discussed by several doctors and pharmacologists before this committee, that is the lack of available information to make a quality judgment between various drugs, and if they are aware of that, why wouldn't they wish, as a professional organization, seek some way to see to it that the doctor is informed?

Dr. MAGEE. They must be aware of this, but I think there is a matter of professional pride here. I know among doctors, one doctor wouldn't question the intelligence of another one publicly at least. The doctor does occupy a substantial position in society. This might suffer somewhat if it became known that the doctor wasn't as informed about drugs and therapy as he is thought to be. But other than this, which may not be the true reason, I don't know why. There have been many actions of the American Medical Association which I don't understand at all.

Senator NELSON. Go ahead, or have you finished your statement?

Dr. MAGEE. Yes, I finished all I had to read.

Senator NELSON. Have you any questions, Mr. Coughlin?

Mr. COUGHLIN. No, I have not.

Mr. GORDON. On the first page of your statement you present the criteria which justifies the development and marketing of a new product. You say:

> A new product to justify itself must create an ailment against which no other agent is effective or it must treat an ailment better than any existing therapy. If it meets neither of these criteria it must be less toxic than existing drugs or be easier to administer and finally if it is equal in all of these respects to existing drug agents it must be cheaper.

Dr. Magee, can you tell us the drugs which have been developed by the drug industry in the last 5 years which treat ailments against which no other agent was effective? Do you know of any offhand?

Dr. MAGEE. I have trouble with 5 years. There have been drugs produced recently which have been a boon to medicine and which in some sense have marked a breakthrough. They may be over more than of a 5-year span. The thiazine antidiuretics I put in this class and the oral antidiabetics I would also put in this class.

Mr. GORDON. Developed in Europe?

Dr. MAGEE. In Europe, yes. If you would expand this to 10 or 15 years, there have been a host of preparations produced by the drug industry, antibiotics, derivatives of adrenal steroids and so forth, which have represented real breakthroughs.

Mr. GORDON. But not in the past 5 years for those?

Dr. MAGEE. No, these are over a longer period of time, that is true, but it would be improper I think to pretend that we do not owe a tremendous lot to drug company research. Many of the sick are now in a better position than they were 20 years ago as a result of drug company research and other research aside from drug companies, but the question is whether the cost of the drug is out of line with the cost of research, and I think the Kefauver committee made it plain that it was.

Mr. GORDON. How many drugs can you think of which treat ailments better than any existing therapy? Prostaphlin would be an example, would it not?

Dr. MAGEE. The synthetic penicillins. They were developed originally in England, and may have been developed a little more than 5 years ago, but this is the case, that they treat a type of infection which was not readily treatable before.

Mr. GORDON. You state that a few years ago there was a spate of expensive highly touted antibiotics which turned out to be valueless and subsequently disappeared. Could you give us the names of some of these?

Dr. MAGEE. Yes. I had two particularly in mind. One was Carbomycin. It became evident in the course of time that Carbomycin was not as effective as an existing antibiotic, Erythromycin. When it became evident that there were staphylococci that were resistant to penicillin or became resistant, a spate of drugs was developed, each of which was said to be effective against penicillin-resistant staph. In the course of time it became evident that staph resistance developed to these as well. Carbomycin was one which produced a cross-resistance to Erythromycin such that Erythromycin, which was a reasonably good drug, was no longer effective against a staphylococcus organism which had previously been treated with Carbomycin. Then this drug disappeared. But the advertising did not.

Mr. GORDON. That was actually a harmful drug, wasn't it, because it made a person resistant to the application of a good drug?

Dr. MAGEE. Yes, that is true. In that sense it was harmful, because it did displace a better drug. But this better drug in the course of time was shown to have toxicity of its own. It took time to appear also.

Another one was a drug which is called Sigmamycin. You may remember that this one had some notoriety, because the Saturday Review looked into some of the advertising testimonials that were used in its advertisement.

Senator NELSON. Thank you very much. We certainly appreciate your taking the time to come before the committee today. Your testimony has been very useful to us.

Dr. MAGEE. Thank you.

Senator NELSON. Our next witness will be Dr. Lloyd C. Miller, director of the Revision and Acting Secretary of U.S. Pharmacopeial Convention.

Dr. Miller, we appreciate very much your taking the time to come over this afternoon. You may present your statement in any fashion that suits you. We may have a question or two, if you don't mind being interrupted. I think there is going to be a roll call vote in the Senate before very long, and it may require me to absent myself temporarily.

STATEMENT OF LLOYD C. MILLER, PH. D., DIRECTOR OF REVISION AND ACTING SECRETARY OF THE U.S. PHARMACOPEIAL CONVENTION, INC., NEW YORK, N.Y.

Dr. MILLER. Thank you very much, Senator Nelson. I appreciate greatly the opportunity to come here. I will preface my remarks by putting into the record a brief comment upon my training and background.

My name is Lloyd C. Miller, and I reside in Westchester County, N.Y. My advanced academic training, leading to a Ph. D. in 1933 from the University of Rochester, was in biochemistry and pharmacology. My experience has included 8 years on the headquarters staff of the Food and Drug Administration and 9 years as a research investigator in the pharmaceutical industry. Since 1950 I have served as director of revision of the U.S. Pharmacopeial Convention, an independent, nonprofit scientific organization devoted to providing standards of strength and purity for drugs. Since 1962, I have served also as acting secretary of the USP Convention.

I am a member of several scientific societies. I will mention only the American Society for Pharmacology and Experimental Therapeutics. It is an organization in which membership is by invitation.

In the present discussion of drug prices and drug quality, there is an acute need for bringing proper perspective to certain aspects of standards of drug quality. In view of the frequent mention of the standards of the U.S. Pharmacopeia in the discussion, we propose to explain briefly how these standards come into being and how they serve to determine the quality of drugs generally.

In 1960, we presented a rather comprehensive statement on the pharmacopeia to the Senate Subcommittee on Antitrust and Monopoly which was holding hearings under chairmanship of the late Senator Kefauver. On the assumption that the record of those hearings is readily available, our remarks today are intended mainly to update and amplify the 1960 statement.[1] Some recapitulation may be helpful, however. We wish also to correct some rather serious erroneous impressions that have been created of late to the effect that the USP standards are too lax, too few, or quite unequal to the task for which they are intended. An erroneous impression seems also to have gained credence that the USP is dominated by the pharmaceutical industry; the falsity of that, too, will be shown.

Senator NELSON. Do you know of any witness who has made that statement before our committee?

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[1] See p. 1161, pt. 21, hearings before the Subcommittee on Antitrust and Monopoly of the Committee on the Judiciary, U.S. Senate, 86th Congress.

Dr. MILLER. I have had access to Dr. Modell's statement, and from the way it was worded it might have been so interpreted; in fact, some of those who were in the hearing room at the time gained that impression on their own, and they suggested that I take this opportunity to dispel any misapprehensions that may have been given by Dr. Modell. I know he did not intend to give that impression, but the wording of his reference to the USP might have possibly been misinterpreted to mean that USP is supported by the industry. I will deal at some length with that.

Senator NELSON. I see. I didn't have that impression.

Dr. MILLER. Good, I am glad you didn't.

Senator NELSON. My interpretation of the references made by the various witnesses was that the USP was an independent, highly reliable source of information, and so I was curious where your impression came from.

Dr. MILLER. Thank you. It was a matter of precaution rather than apprehension on my part.

By the simplest definition, a pharmacopeia is a book that lists medicinal substances but the term is now generally restricted to drug lists that include standards of strength and purity, which in addition are produced under recognized authority. Thus the current U.S. Pharmacopeia is a book of some 1,200 pages. I have a copy here, that describes about 900 articles of therapeutic significance and provides for them appropriate tests and standards. This latest edition, USP XVII, was compiled, as were preceding editions, by a revision committee composed of 60 elected but unpaid medical and pharmaceutical experts who serve on the revision committee. These experts, and many others, take part in USP work not only because they are public-spirited but also because the Pharmacopeia is recognized as a legal compendium. That is, the USP standards are designated in the Federal Food, Drug, and Cosmetic Act for use by the Food and Drug Administration. As a result of this recognition by the Congress, the U.S. Pharmacopeia is regarded as an authoritative, quasi-legal compendium and no effort is spared to make it scientifically sound and accurate.

The revision program, incidentally, is supported not by tax funds, grants or contributions but rather by the sale of the Pharmacopeia and from fees charged for USP Reference Standards that are used in the laboratory in conducting the USP tests. The Pharmacopeia and the Reference Standards are used in all parts of the world. About two-thirds of the Pharmacopeias are bought by pharmacists, while nearly all of the Reference Standards are used in testing laboratories of the Government and the pharmaceutical industry.

I mention that fact to show the source of our support.

The organization responsible for this program is a nonprofit corporation that is constituted anew every 10 years by delegates from all of the colleges of medicine and pharmacy in America, from State and national medical and pharmaceutical associations, from several units of the Government, and from a limited number of professional and trade associations. Without doubt, the USP stands on a foundation of deeper roots and broader representation in medicine and pharmacy than anything else of its kind.

The revision program is entirely the concern of the USP Revision Committee, which is made up of 20 medical specialists and 40 special-

ists in pharmacy, chemistry and biology. A nine-member board of trustees handles all business affairs of the USP Convention.

At the time our statement was made in 1960, the 16th revision of the Pharmacopeia had just appeared; now, in 1967, the 17th revision has been out 2 years and work is well along on the next edition. These editions are not mere reprints; they are almost totally rewritten from cover to cover. The fact that the USP comes out at regular, 5-year intervals, with supplements intervening, and one just recently came out for the edition that is in force, amply supports the first point we wish to stress; namely that USP standards are kept current and are responsive to everyday needs.

Senator NELSON. May I interrupt?

Dr. MILLER. Surely.

Senator NELSON. How often does the supplement come out?

Dr. MILLER. Supplements come out as needed. This latest one came out after the main volume had been in effect for 18 months, so that generally we come out with two or three supplements during the 5-year period. There is no regular schedule for supplements. It is just that as we accumulate some 40 pages of material, we make the effort to publish it. The supplements incidentally are sent free to all holders of the Pharmacopeia who return a postcard in the back of the book that lets us know where they are, so that there is no excuse for anyone's not having a current supplement.

An outline of how the standards are revised may be helpful. To start with, the USP headquarters office in New York stands ready at all times to receive inquiries and suggestions, compile data, and develop sources of aid for the revision committee. If laboratory testing is needed, it may be carried out by a revision committee member himself or by the drug standards laboratory, a fully-equipped laboratory facility maintained here in Washington by three-way financial support from the U.S. Pharmacopeia, the American Medical Association, and the American Pharmaceutical Association Foundation.

The prestige of the USP is such that the revision committee has free access to the Nation's most competent experts on any relevant matter. There is no hesitancy in seeking expert opinion outside the revision committee; advisory panels are set up, often jointly with the National Formulary where the problem is common to both compendia. Possibly the fact that industry scientists are often consulted on drug assay problems had led to the notion that the revision committee is industry-dominated. In refuting the suggestion, we need only mention that we also consult FDA scientists often and receive invaluable aid from them. Revision committee members are drawn from industry and academic laboratories alike, but it is clearly understood that all members serve as individual experts and not at all as representatives of their colleges or companies. Of the 60 members, only 13 are now in the employ of pharmaceutical firms. And one of them is retiring at the end of this month.

Senator NELSON. The drug standards laboratory is maintained and staffed by the scientists by that laboratory?

Dr. MILLER. Yes; the funds come entirely from the USP, the AMA, and the American Pharmaceutical Association.

Senator NELSON. But the testing is done by the employees of the drug standards laboratory, and not by employees of the pharmaceutical industries?

Dr. MILLER. Yes; this laboratory is wholly independent and it responds to the needs of the three sponsors. It is concerned with the products that are put out by the pharmaceutical industry, but the testing it does is at the request of the sponsors. It has a small staff, and a small budget, but up to now it has met its needs rather adequately.

Proposals for revision are submitted to a two-layer screen of approval within the revision committee. A revision can be processed in a matter of weeks where a clear course is apparent, or may require years of study.

We take seriously the responsibility of keeping the studies in motion and in seeing that the results are translated into tests and standards as promptly as possible. In the 29 years since the passage of the Food, Drug, and Cosmetic Act in 1938, six entirely revised editions of the Pharmacopeia have appeared and numerous supplements have been published.

Admittedly, the mechanics and apparatus of the USP revision program are very simple; our headquarters staff is small. Although we must depend greatly upon voluntary efforts, our resources are substantial. We submit that the system has worked, is working, and will continue to work in providing the standards for drugs that are not exceeded anywhere in the world.

WHAT ASSURES DRUG QUALITY?

Great stress has been placed on drug quality in these hearings to date. The importance of quality in drugs is beyond debate, for in scarcely anything else in everyday use is the attribute of quality so vital and so difficult to measure, even for experts.

The elements that determine quality are several, but identifiable. This holds true for drug products made by large and small manufacturers or those compounded locally in the community pharmacy or hospital. The first requirement is the will to make a good product and the unswerving adherence to a creed that ranks high quality above all other considerations. Second is flawless procedure, usually called good manufacturing practice in the drug factory or good technique in the pharmacy. Then, in order of utilization and certainly in importance, come high standards of purity and potency; these are necessary to insure that only the best materials are used and that the final product comes up to expectation. It goes almost without saying that high standards are valueless unless they are put to use in a vigilant and rigorous testing program. Finally, once a product of high quality has been obtained, it must be protected by proper packaging, handling, and storage.

These, in broad outline, are the minimum elements needed to assure a quality drug product. The neglect of any one will almost certainly result in an inferior drug product.

Of all these elements, the most objective and most amenable to precise specification are the standards of purity and the conditions of proper packaging and storage. To provide these is the function of the U.S. Pharmacopeia and its sister compendium, the National Formulary. As a result, these books are recognized as "official compendia" in the Food, Drug, and Cosmetic Act.

We find it helpful to explain this situation by saying that the USP and the NF provide the yardsticks against which the FDA measures the quality of drug moving in interstate commerce. This recognition is in keeping with the three-way separation of powers in our Government, since it results in having the standards set up by an agency other than the one charged with applying them. Mr. Walter G. Campbell, who served as the first head of the Food and Drug Administration and was its head for a longer period than anyone else, often expressed the view that the existence of the official compendia and their creation by an independent agency relieved the FDA of playing the dual role of sitting as a council that promulgates ordinances that it must, acting later as police, proceed to enforce. Regrettably, this concept was disregarded when batch certification of the antibiotics was decreed in the 1962 amendments to the Food, Drug, and Cosmetic Act, and we are aware of more recent suggestions that the Congress should authorize further extension of batch certification. If this course is followed to any significant degree, it will sound the death knell of the Pharmacopeia and the National Formulary as non-Government sources of drug standards.

Senator NELSON. I don't exactly follow that. Are you saying that the Government should not batch-test antibiotics, or that nobody should batch-test antibiotics?

Dr. MILLER. That is a two-way question. If I answered the second part first I would probably be answering the first part. We don't think batch certification of antibiotics is especially necessary, because we don't think antibiotics, as a class of drugs, are particularly different from other classes of drugs. There are many reasons why they came to be regarded as special and different, but penicillin is just about as stable as sugar, and it was on the basis of a lack of stability that the certification program was set up in 1944 as an exigency measure, a wartime measure, then it got written into law later, and was extended in 1962.

We do not think that as a class the antibiotics are particularly different from any other drugs that we use. Now that view is in conflict with that of the Food and Drug Administration, but there are obvious reasons why they should have an interest in retaining an authority that they have been granted, and of course don't want to give up.

Mr. GORDON. Dr. Miller, in the FDA drug recall list that we have, it seems as though penicillin contamination is one of the most frequent causes for recalls.

Dr. MILLER. But that is not an antibiotic certification problem whatsoever.

Mr. GORDON. Is it not?

Dr. MILLER. No, of course not. If you were to look for it, you would probably find other drugs contaminating other drug products just as much as you can find penicillin in other drugs. But it happens that penicillin contamination of other drugs is an important public health problem, because many people are sensitive to penicillin, and they should not be subjected to penicillin willy-nilly. It is just good manufacturing practice not to mix drugs, and penicillin was a particularly bad one to have mixed in with any other drugs.

Mr. GORDON. Are you saying that all drugs should be batch tested or no drugs should be batch tested? I am not sure I understand exactly what you mean.

Dr. MILLER. The USP position is that no drugs need to be batch tested. It is a very expensive way. At one time I calculated, as close as we can get the figures, that it costs about 30 times as much to administer the control testing of the antibiotics as it does for the other drugs, many of which are just as important to public health as the antibiotics.

Mr. GORDON. Does the USP have any means of knowing that its standards are being adhered to? How can we insure that all products conform to the USP standards except through batch testing or some other way?

Dr. MILLER. Well, you certainly have the reports of the Food and Drug Administration, of their results of applying the USP tests to drugs in interstate commerce. It is their job to see that they do measure up to the USP standards.

Mr. GORDON. How do they do that?

Dr. MILLER. They do it by spot testing.

Mr. GORDON. By spot testing?

Dr. MILLER. Yes, spot testing is the process of collecting samples on the open market and testing them for compliance with label claims. They do it to a very large extent by factory inspection. They have the option of going in to any factory in the country, and asking to see the results of the tests that have been applied. Now, that can be done without requiring that once having completed those tests in the factory, any place in the country, a sample be sent to Washington, the testing be done all over again, at the manufacturer's expense, which means in turn at the public's expense, because certainly the manufacturer is going to have to get that money back in the price of the drug. In other words, it is retesting to an extent that we feel is considerably unnecessary.

I am just as much in favor as anybody could be of ensuring that every drug on every pharmacist's shelf in this country shall be just exactly as potent as it is supposed to be, but there are ways to do it that do not include batch certification.

Senator NELSON. I am not informed as to how much testing of drugs is done. Are all drugs that go on the market at some period or another inspected by some independent agency or the Government? In other words, some company is in the business of manufacturing a particular drug, and the FDA has the authority to spot check. Now, if this compound is being manufactured by a company that is on the market year after year, how do we know that it complies with the USP standards, for example?

Dr. MILLER. Well, in the first place the manufacturer has the responsibility in introducing a drug in interstate commerce, assuming he is going to do that, to see that he meets the published standards, if such there be. He doesn't need to test to do that. He can risk his reputation, risk being thrown into jail literally, if he is willing to take the chance, in not carrying out tests before he ships the drug, or at any time. Very few manufacturers are willing to take that risk. I know of none.

Senator NELSON. Are you saying that each batch of drugs by any manufacturing firm is batch tested?

Dr. MILLER. Oh, yes.

Senator NELSON. By the firm?

Dr. MILLER. Absolutely, tested all along the line. The raw materials are tested when they come to the door of the plant before they are used, and the components as they are manufactured are tested at various stages, and then if the product is USP the USP tests are generally applied in the finished form, and all of that testing is done in the course of manufacturing.

Now, it may not be. If a man is willing to cut corners for various reasons, he can get along without testing to a remarkable degree, but he will be risking putting out an inferior product.

Senator NELSON. The law does not require, then, that the manufacturer test each batch of drug?

Dr. MILLER. No.

Senator NELSON. But the law does require that it meet the USP standards?

Dr. MILLER. Yes.

Senator NELSON. If it is in the Pharmacopeia?

Dr. MILLER. Yes.

Senator NELSON. Is that correct?

Dr. MILLER. Yes.

Senator NELSON. Then how do we know that they do reach the standards, if there is not inspection of each batch by the manufacturer or by somebody else? How can the public be sure that a drug of improper potency is not being put on the market?

Dr. MILLER. By seeing that the Food and Drug Administration has the facilities for testing as often as it feels it is necessary and where it feels it is necessary, where the risk is greatest of the products that are offered for sale. Now, the expansion of the FDA testing that will be possible by the setting up of this new central testing laboratory in St. Louis will go a long way towards achieving this purpose. They will be increasing, if I have the figures correct, the amount of testing by about 10 times that which has been done in the past, and that will accomplish much in giving the public a chance to be perfectly confident that the drugs that are offered are right up to standard.

Senator NELSON. I don't know how important this really was, but in any event, you recall the publicity a few weeks or months back of the test of some 4,600 drugs by FDA?

Dr. MILLER. Yes.

Senator NELSON. And on that what they said was that 7-plus-percent of the generics were subpotent or maybe excessively potent and 8-plus-percent of the trade name drugs, so they were pretty close together. Are those significant percentages, and how do they get onto the market if they were subpotent or too potent, if the controls by the generic manufacturers and trade name manufacturers were adequate?

Dr. MILLER. Well, I would suggest that you get Commissioner Goddard here to discuss that, but the facts are coming out with respect to these 4,600 or 4,800 analyses, and there have been some reports which this committee may want to look into, that the work was done by summer help—but it couldn't have been summer help because the work was done from March 1 until about June 1 last year—to give the Commissioner an idea of just what the market situation was.

It was a crash program. We have seen data made available by some of the manufacturers involved which contradict, refute completely, the data on these very same lots that are supposed to have been found in violation. So the least we can say is that the subject is quite controversial at the present time, but I think it will be safe to predict that there will not be much difference between the two general groups of the manufacturers that you just mentioned, those that sell under brand names and those that sell under nonproprietary names. But I think all the facts are not in yet as to the result of this comparison. But there is a lot of difference between a substantive violation, that is one in which the potency was down far enough to be a worrisome thing, and a violation just beyond the line. Now, that too will have to be looked at. Where the USP lower limit was 95 percent and a product was found to be 94½ percent that technically would become a statistic on the violation side. Surely it is something that no one wants. But a product that is 94¼ percent is certainly not in as much violation as one that is 75 percent, and how many were down in that 75-percent range has not yet been revealed. In fact, the data themselves have not been reported with very satisfactory completeness.

Mr. GORDON. Dr. Miller, the Food and Drug Administration has supplied us with information to the effect that there are about 1,300 drug recalls in the past couple of years.

Dr. MILLER. Yes.

Mr. GORDON. Some of which caused death and serious injury. How can we insure that that does not happen?

Dr. MILLER. I wish I knew, because I am just as deeply concerned over an injury or a death by a subpotent drug as anyone can be.

Mr. GORDON. Don't you think batch testing could help?

Dr. MILLER. No. You will find that there have been just about as many recalls among batch-tested drugs in proportion to the number that are on the market as there were of those that were not batch tested. No, batch testing is not the whole answer.

Mr. GORDON. Is it a partial answer?

Dr. MILLER. It is a partial answer.

Mr. GORDON. A partial answer.

Dr. MILLER. If the American public is willing to pay the price that will have to be charged for testing every drug twice, every batch of drugs twice, then that is the way we perhaps should go about it. We don't think it is necessary.

Mr. GORDON. One more point. As I understand it, in this batch testing it is the FDA who sets the standards, is that correct?

Dr. MILLER. Yes, that is the thing of course that annoys the USP, because it took the authority away from us. It is just a matter of professional pride, but we think with almost 150 years of experience, we have a background of setting up standards that should not have been disregarded.

Mr. GORDON. Are the FDA standards lower, higher, or just about the same as the USP standards?

Dr. MILLER. Actually I think they were lower in many cases. The FDA was willing to settle for 85-percent penicillin, and our committee men never wanted to see less than 90, and yet the 85-percent figure prevailed.

Senator NELSON. You still list the antibiotics?

Dr. MILLER. Yes, but we do not provide any standards.

Senator NELSON. You don't provide any standards?

Dr. MILLER. We don't provide the standards. We simply say, "Look to the Food and Drug Administration for the standards, because our standards would have no force."

Senator NELSON. Thank you.

Dr. MILLER. I was about to talk about standards of clinical performance or equivalency.

Senator NELSON. Yes.

Dr. MILLER. While standards of chemical purity or potency are now highly developed, a need is recognized in the case of a limited number of drugs for some measure of clinical performance. This reflects a desire for a demonstration that a given lot of a drug product, or preferably every lot of each brand of that product, is capable of performing as effectively as any other lot or brand of it. To satisfy this desire fully might require going so far as to use human beings who were ill with the disease for which the product was intended. Needless to say, this is scarcely practical and something short of that is being sought.

The scientific principle involved here is physiological availability, and standards for clinical equivalency rest in large measure upon clearer elucidation of the factors that affect it. Physiological availability is a characteristic of a drug product that determines the extent to which the active ingredient of the product may be absorbed by the body in a useful form. It is thus a measure of the utility of a drug product to the sick patient when and where needed.

USP STANDARDS AND PHYSIOLOGIC AVAILABILITY

It is perhaps not surprising that scientists and laymen alike generally pay more attention to the spectacular natural phenomena, such as an eclipse of the sun or the appearance on schedule of a comet, than they do to other less breathtaking and more frequent events. Some of the latter may actually have enormously greater effects on man and his environment, as for example a prolonged drought or deluge. Similarly, in pharmacy, the failure of some drug products, mostly tablets, to yield the expected effects has stimulated pharmaceutical scientists to undertake studies that have generally explained the failures in a fairly satisfactory way.

A whole new sub-branch of pharmacy thus sprung up for which the term "biopharmaceutics" has been coined. Without doubt, the world is much better off as a result of these biopharmaceutic studies, for the drugs concerned are important and physicians now can use them more intelligently and effectively. However, an aura of mystique arose that has tended to blur our perspective at times. In consequence, there has been a tendency to extrapolate the findings unduly; indeed, there are some among us who would cast doubt on every drug offered for the physician's use.

Regardless of the complexity of the pharmaceutical aspects, a very simple physiologic fact is concerned here. That is, some patients get less benefit from certain oral medicinal products because, contrary to expectation, the helpful part of the medicine stays in the gastrointestinal tract and fails to get into the blood. Obviously, this applies

only to drugs that are given as capsules, tablets or pills and exert their effects following absorption, a process that is seldom 100-percent efficient. It may be an individual matter involving only a few patients or may hold true for all patients who get the same batch of tablets. Regardless of whether the failure of absorption is an individual or a general characteristic, the end result is that one or more patients fail to get well. The physician has reason to be perplexed, and at the very least, his therapeutic plan has gone awry.

Generally less frustrating to the physician are the situations in which the effect exceeds expectation as the result of better-than-expected absorption. This has been reported for at least three drugs. In each case, physicians were accustomed to using a specific dose that suddenly proved to be too much. Immediate checks showed that the right amount of drug was present and that other relevant USP standards were met. In due time, allowance was made for the more complete absorption by reducing the dosage and thus restoring the desired level of effect. The only possible explanation was that greater efficiency had been achieved as the result of some subtle change. Subsequently, it was confirmed that the manufacturer had changed his process of making the tablets and accidentally has discovered how to make a smaller amount of drug do what had required a larger amount previously. Greater physiological availability had been achieved, which simply means that the absorption of the tablets was more nearly 100-percent complete.

The important point, however, is that not more than a dozen drugs have presented problems with respect to physiological availability. Thus, to damn the entire Pharmacopeia of some 2,000 drugs for the failure of a mere handful is unscientific in the extreme. It would be just as illogical to strip a regiment of its honors each time one of its privates went AWOL. Yet this is what is suggested by those who would destroy our faith in all USP standards because pharmaceutical and medical science has not yet advanced to the point of providing the required test methods for the few demonstrated cases that require extra precaution. In short, let us not throw out the baby with the bath water.

Now I would like to turn to something that has been mentioned in these hearings and concerns a special area of the pharmaceutical world. and deal at some length with that, because I have had rather close experience with it for some years. It is drug nomenclature.

Drug Nomenclature

Drug nomenclature is an area in the pharmaceutical world that is distinguished by a maldistribution of too little information among too many self-styled experts. Suggestions are being made for more laws on the subject; but it will be a pity if more legislation is added before we learn to cope with the unfortunate enactments of 1962.

Senator Nelson. Why were they unfortunate?

Dr. Miller. They were unfortunate because they put the emphasis in the wrong place. I am confining my remarks here to drug nomenclature. Some two pages of the Kefauver-Harris Act are devoted to drug names.

Senator Nelson. What is that?

Dr. Miller. Drug names, how to correct difficulties with drug names.

Senator NELSON. And you are referring in this comment of yours about the 1962 act only to that aspect of the act?

Dr. MILLER. That is right, a page and a half of those two pages were concerned with official names; half a page was concerned with what I believe is the real problem, getting improper names assigned to new drugs. That is where the real problem is.

Senator NELSON. I thought you were referring to the whole act.

Dr. MILLER. No, I am not at all talking about the whole act. There were some other unfortunate parts about that, too, one of them being the extension of certification that we just talked about a few moments ago; but this subject of nomenclature was an area in which the Congress was not very well informed. There was very little discussion actually on that part of the act, and no one came up with quite the right formula by the time it went to the floor.

As a means of improving communication of information of all sorts on drugs, no one can quarrel with the one-drug, one-name concept. However, this best of all possible worlds is clearly unattainable. First of all, most drug substances are chemical entities and as such are known by names that are generally lengthy and comprehensible only to those highly trained in chemistry. The fact that few of those who deal with drug products are so trained makes it imperative to coin other, much simpler names. Disagreement seems on exist on whether these other names are nearly simple enough.

I would like to insert here a comment with respect to this element of simplicity. One factor that works against very short names is the principle that the names should show any important interrelationships that exist between the drugs. Thus within the group of the sulfonamides, the wonder drugs of the 1930's which gave man the first means of combating pneumonia and other serious infections, all nonproprietary names of the sulfonamides start with the prefix sulfa. There are sulfanilamide, the original member of the series, and those that have now replaced it, sulfadiazine, sulfamerazine, sulfathiazole.

If we were to undertake to shorten the name of this large group of drugs by chopping off the prefix sulfa, we would at once lose an important common bond of identity. Many other examples of this sort of thing could be cited, but the essential point is that brevity in drug names could come only at the expense of the informative capacity of the name. Bits of information are conveyed by syllables, and syllables are useful only if they are recognized and can be fixed in memory rather readily. But those of us who have undertaken to coin drug names learned quickly that the way to any really simple nomenclature is strewn with roadblocks of all sorts. Chief among these blocks is the existence of so many names that are in use or have once been used; trademarks may not be infringed and old names may not be applied to new drugs because of the confusion, that would result. In short, just as old skins are not safe for new wine, old names are useless for new drugs.

A second point is that critics seem never to take into account the fact that catchy, two-syllable, contrived names like Kodak or Ansco come to mean cameras only as the result of costly and ceaseless advertising. Hundreds of two-syllable trademarks are in use for drugs but they have mnemonic value only because they are heavily promoted. No nonproprietary name, short or lengthy can compete for public acceptance

without equally heavy promotion and no one has come forward with suggestions for financing the gigantic promotion effort that would be required to make them familiar.

The USP is engaged in a promotion campaign of sorts for the nonproprietary names known as the United States Adopted Names. In cooperation with the American Medical Association and the American Pharmaceutical Association, we sponsor a program that is aimed at selecting and publicizing a nonproprietary name for every new drug substance. The Food and Drug Administration has recently joined the three original sponsors but does not contribute financial support. The program is now in its 6th year and, to date, some 600 names have been selected and made public. The Fifth Cumulative List of U.S. Adopted Names has just appeared in booklet form.

I would like to make this copy available for the committee's use.[2]

The cost of this entire program, including publication and distribution of the just-mentioned list, is probably less than the cost of the preparation and postage of a single direct mailing on any drug with a sales volume of upwards of $1 million annually. The three organizations that are concerned with publicizing the nonproprietary or generic names simply do not have the resources to compete with the promotion efforts of the pharmaceutical industry in this regard in any way.

The alternative has been suggested that some limitation be placed on the free choice of clapping a brand name on any drug product. Such a limit might be of the sort that the French have used; namely, only the firm that introduces a drug product may use a trademark name, and all who follow must market the same product under a common, nonproprietary name.

Others seem to advocate the elimination of all trademarks for drugs. The latter course would force greater use of institutional advertising such as one sees for aspirin. This nonproprietary name was once a U.S. trademark, and while it still has exclusive status in many countries, it is in the public domain here in the United States. Thus we see many "brands" of aspirin, each clearly labeled to show the maker, so that we have Bayer aspirin, St. Joseph's aspirin, and Squibb's aspirin, to name but three of the many sources. A casual check will reveal that the use of the common name has not served to prevent substantial price differences between the makers of aspirin tablets.

Such revolutionary changes in our trademark laws as we have mentioned would apply not just to drugs alone, I should suppose, but to all products, and would surely require long and careful study. All these considerations lead us to believe that tinkering with drug nomenclature is scarcely a promising way to reduce drug prices.

In summary, our position is that the USP and NF standards for drugs are not only unsurpassed but they are reliable measures of drug quality. The standards should not be cast out because of the rare findings that a drug product which meets them fails to produce the expected clinical effect. Finally, the way to lower drug prices, if such there is, will not be found in the thicket of drug nomenclature.

Thank you.

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[2] Retained in committee files.

Senator NELSON. I am not sure I really understand that last statement. "Finally, the way to low drug prices if such there is will not be found in the drug nomenclature."

According to the Medical Letter, if I were a physician and wrote a prescription for Paracort, the price to the pharmacist is $17.88 for 100 tablets, but if I used the generic name prednisone, it is being sold to the druggist for as low as 59 cents. So that is a case where the name makes all the difference in the world.

Dr. MILLER. No, the name has nothing to do with it. There is nothing in the world to prevent the firm that sells at the lowest price from putting a trademark on its product and selling it under the trademark. As far as the laws are concerned, and the economics of the situation go, there is nothing that says a trademark product need cost a cent more than one sold under the nonproprietary name, or vice versa. There are other factors that determine what the prices are. It is not nomenclature.

Senator NELSON. I suppose there is no price attached to nomenclature, but the fact of the matter is that Paracort costs the pharmacist $17.88 and Meticorten $17.90, and prednisone by a number of companies listed in the Medical Letter study is selling for 75 cents a 100.

Dr. MILLER. I have seen that list.

Senator NELSON. It appears to me the name you use may very well make all the difference in the world as to what you are paying for that drug.

Dr. MILLER. The name you use may make a difference in what the patient has to pay, but the fact that a name differs does not mean that the price would have been different.

What I am trying to say is this. That had one of these firms that happens to charge more decided to sell its prednisone, and this is the position that Dr. Modell took here a couple of weeks ago, as prednisone, Upjohn or prednisone, Smith or prednisone, Jones Pharmaceutical Co., they would have thereby been able to identify the product with their firm, and whatever price they chose to charge would be the price charged the patient, simply because the doctor wanted the Smith product, the Jones product, or whatever firm was concerned.

What I think you are observing here is that to establish a trademark in the marketplace, and in the mind of the physician, is an expensive operation. It takes a lot of promotion, a lot of reminder, maybe a lot of stethoscopes, as was mentioned here this morning. That costs something, but there are other things that go into the price of a drug, too. But the question is how one might establish the practice of a physician of prescribing a particular drug without promotion.

Senator NELSON. What can't be done without promotion?

Dr. MILLER. Establishing a desire on the part of the physician to prescribe a specific brand of a drug. It isn't the name. It is promotion, and promotion is made easier by the use of a trademark, but it is not necessary. A firm could establish its name so well that a physician would buy that firm's drug under a nonproprietary name, if he were completely convinced that he wanted that particular firm's products, and he would get them if he put the firm name on the prescription.

Senator NELSON. If a good drug is patented, is exclusively held for 17 years, and is a widely used drug, then even at the end of 17 years when the patent no longer protects him from competition, the only name known to practicing physicians is the trade name. There are innumerable examples of major companies, all highly respected, coming into the market with their own brand name and with the generic name at a fraction of the price. Yet the other one still remains on the market.

Dr. MILLER. Yes.

Senator NELSON. The other one still sells because that is the only name the doctor knows. So knowing what the drug is and knowing the generics, the generic name, and knowing the various prices is certainly a very important factor to the physician and to the patient, I would think, wouldn't you?

Dr. MILLER. I don't know whether I can answer your question intelligently, but let me make this comment. The reason the price is different, the reason the latecomers into the market lower their price, is that that is the easiest way for them to get into the market.

Senator NELSON. But they aren't selling at a loss, are they?

Dr. MILLER. That I wouldn't be able to tell. I would assume not, or else they wouldn't go into business.

Senator NELSON. The opening sentence in the Medical Letter is that "Tests made for the Medical Letter on prednisone tablets USP purchased from 22 different pharmaceutical companies showed that all of them conformed fully to the requirements of the U.S. Pharmacopeia."

Dr. MILLER. Yes.

Senator NELSON. When you look at the 22 drugs, you find that they vary in price, all meeting the standards of the U.S. Pharmacopeia, from 59 cents per 100 to $17.90 for a 100. The Medical Letter is saying that they all meet the USP standards.

Dr. MILLER. Yes.

Senator NELSON. One is as good as the other. Therefore, isn't it important that the doctor who is prescribing for his patient to know which is which in the price variation, and why should the patient be paying $17.90, or rather a price based upon $17.90 per 100 to the pharmacist when there is an equivalent drug available at 59 cents a 100 to the pharmacist?

Dr. MILLER. I can't answer that in any satisfactory way. I myself wouldn't want to pay $17.90 for a drug that I was just as sure I could get for 59 cents.

Mr. GORDON. Dr. Miller, I would like to give you another example where the name is important. When the city of New York buys Benadryl from Parke-Davis Co., it pays $15.63 for 50 milligram, 1,000 tablets. When it is bought generically from the same company, the city pays $3. Now, how can we say that nomenclature is irrelevant to price?

Dr. MILLER. My position is that actually nomenclature has nothing to do with it as far as the buying of the drug is concerned. It is what you order. If you ordered Benadryl, you would be insisting that the trademark product be provided—what is the USP name?

Mr. GORDON. Diphenhydramine.

Dr. MILLER. If you ordered diphenhydramine hydrochloride, you might no get Benadryl but if you bought it from Parke-Davis the chances are pretty good you would get exactly the same product that they sell under the trademark Benadryl. To clarify my statement here, what I am trying to say is that abolishing trademarks and trying to make names simpler so doctors will remember them and things like that actually may be desirable for some reasons, but it should not be approached from the standpoint of trying to make drugs cheaper, because I don't think that will necessarily follow. We have too many examples, like the aspirin situation, where they are sold under the same name, and price differences do exist. Here you have price differences in that Medical Letter list, where they are sold under prednisone as such but they are all prednisone tablets. If you took away the ones where they are sold exclusively under trademarks and just looked at the ones that are sold under the nonproprietary name prednisone, you will find price differences there, and that is the point I am trying to make, that price differentials will exist, because of the differences in manufacture, differences in costs of other sorts, differences in distribution, differences in service. Some of the firms that sell for the least do not have a distribution system. You can buy them in only a half-dozen places in the country, and to make it available in 36,000 places in the country is expensive, a very expensive thing.

Mr. GORDON. Who has been complaining, as you previously stated, that the USP standards are too lax, too few, and cannot do their job? Who made that statement?

Dr. MILLER. One of our friends up in Buffalo, Dr. Gerhard Levy, is one of those who says that the USP standards do not guarantee clinical equivalency, and yet many times I have asked him for help in improving the USP standards, and his answer always is "Well, that becomes a research project," and he has never been very helpful in providing us better standards. We are working hard on it within our committee. We have one of the country's experts.

Mr. GORDON. You disagree with Dr. Levy; don't you?

Dr. MILLER. I don't disagree with him completely. I think he is overemphasizing these few shortcomings.

Mr. GORDON. Yet you say here on page 4 that "The USP standards for drugs are not exceeded anywhere in the world."

Dr. MILLER. That is true. Nobody else has any of these standards that he complains we should have. We have standards that no other pharmacopeia in the world has, and yet he thinks we should still be better. We agree with him on that. We wish we were better. But he among others has not been able to provide us with objective methods that FDA could go into court with, to improve, to make certain, doubly sure that these products were clinically equivalent and absolutely physiologically available.

Senator NELSON. Is the question of clinical equivalency considered in establishing the USP standard?

Dr. MILLER. Oh, yes.

Senator NELSON. Then, do you do clinical tests yourself?

Dr. MILLER. We do not.

Senator NELSON. Or do you rely upon the literature?

Dr. MILLER. We rely upon the literature, we rely upon experts on our committee, and we do have tests that have been shown in the past

to be important. One example is the drug Griseofulvin which is an antibiotic. It is available in two forms, tablets made of what are called large crystals, and tablets made of microcrystals. The tablets of large crystals require a dose of twice as much as of the small crystals. In other words, the small crystals are more completely absorbed than the large crystals.

In view of that, the USP recognizes only the small crystal Griseofulvin, whereas FDA continues to certify both the large crystal and the small crystal product. We think that, and it couldn't have been done within the law so that FDA is not lax in that respect, it is a pity that the large crystals continued on the market once it was discovered that the small crystals did the job better. We have been asked recently why the USP can't recognize the large crystal. Our experts think that that would be a medical mistake. There is no reason to give 500 milligrams when only 250 milligrams will do the job.

Senator NELSON. Have you found in your experience that if the drugs meet the potency standards, meet the standards established by the USP, that these drugs are also clinically equivalent?

Dr. MILLER. By and large, as I say, there are not more than a dozen examples where the difficulty has been discovered, and it is not generally true even for all of them. I don't know whether you want to get into examples. There are experts you can call upon to do that. It is a technical matter. But we feel that for the most part the problem has been met by the dissemination of information, the scientific information that has been developed on these examples, and no one is making those mistakes now.

Senator NELSON. Are there drugs that go into the Pharmacopeia for which you set standards, on which you do not have clinical tests?

Dr. MILLER. No, I do not think—by the time our physicians will vote its admission to the USP, a drug has to be pretty well established, and so I think that there are very few instances of USP drugs in which any question exists on clinical equivalency.

Mr. GORDON. Although these tablets vary within the bottle?

Dr. MILLER. Excuse me; well, all right.

Senator NELSON. They vary within the bottle, they still meet the USP standards. They are not identical, but as I understand it, they are therapeutically effective, isn't that correct?

Dr. MILLER. I didn't mean to give the impression that this was an intra-bottle variation.

Senator NELSON. Or intra-batch.

Dr. MILLER. We have a very good test that rules out the differences from tablets within a given bottle. No, the problem generally is a variation that exists between all the bottles of one batch and as contrasted with all the bottles of tablets in another batch.

Senator NELSON. I am talking about prednisone. Now, here you have tablet variation within a bottle. They all meet USP standards. Now, obviously they are not identical. According to you as I understand it, they are therapeutically effective, is that correct?

Dr. MILLER. Well, there are two things that happen to prednisolone.

Mr. GORDON. I am talking about prednisone.

Dr. MILLER. I will try to cover both of them, so that the record will show——

Mr. GORDON. One other question, Dr. Miller. If a drug meets USP standards, can we rely on the drug to do the job it was intended to do?

Dr. MILLER. We think so, by and large with very few exceptions. I have to qualify to that extent. Now, prednisolone is one of the cases.

Mr. GORDON. I am talking about prednisone.

Dr. MILLER. All right, prednisone. Yes, it was prednisone. Prednisone is a drug that is effective in very small amounts. One milligram is enough to do the job. A firm, a very highly respected firm, was putting out 1-milligram tablets of prednisone. The Food and Drug Administration discovered that within a given bottle some of those tablets had only a half a milligram of prednisone. Others had a milligram and a half. On the average, there was a milligram per tablet. But we considered that poor practice, and we now have a test that rules that out. We have a test in the USP which applies to prednisone tablets that prevents that happening again.

Mr. GORDON. What do you mean by exceeding USP standards?

Dr. MILLER. If I used the word exceeding USP standards I apologize because we don't recognize——

Mr. GORDON. You didn't use it.

Dr. MILLER. Oh, we don't think that there is such a thing as exceeding USP standards, because the USP standards are so written that anything—we say "not less than" a given percentage, and in the case of aspirin, for example, aspirin shall be not less than 99.5 percent pure. Now, that other half percent does not allow very much leeway for being better than USP standard.

Senator NELSON. I have seen some industry literature critical of USP in the sense that they say their drug exceeds USP standards. Are you saying that any further purification and any further this or that has no clinical or chemical meaning so far as the drug and its use is concerned? Is that what you meant?

Dr. MILLER. Yes, that is partly the view, but the main point is that anything between the minimum that we state and 100 percent is still USP, and when I have time, whenever I see one of these ads, I generally call the attention of the firm to our position, and as a rule, the advertising changes.

Senator NELSON. Thank you very much, Dr. Miller, for coming over here today. Your testimony has been very helpful.

Dr. MILLER. We appreciate the chance to come. Thank you.

Senator NELSON. We will adjourn until 10 o'clock tomorrow morning.

(Whereupon, at 3:50 p.m. the subcommittee was recessed, to reconvene at 10 a.m., Wednesday, June 28, 1967.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

WEDNESDAY, JUNE 28, 1967

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

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

Present: Senators Nelson and Hatfield.

Also present: Benjamin Gordon, staff economist; Daniel T. Coughlin, minority counsel; Susan H. Hewman, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. The subcommittee will resume hearings.

Our first listed witness is Dr. Solomon Garb.

Dr. Garb, the committee is pleased to have you appear here this morning. Dr. Garb is professor of pharmacology and associate professor of community health, University of Missouri Medical School, clinical pharmacologist at the University of Missouri, Columbia, Mo.

We have your biographical data here. Would you like to state briefly your biographical background for the record? You may proceed to present your statement in any fashion you wish. I have read it and I think it is the clearest explanation we have had for the question of generic brand, chemical names, and so forth, and a very good one. You may proceed to read it or extemporize from it. If you have no objection, as questions occur to Senator Hatfield or myself we may interrupt you to ask them unless you would prefer to present your whole statement without interruption.

(The biographical data referred to follows:)

DR. SOLOMON GARB—CURRICULUM VITAE

Present address: 101 Gipson Street, Columbia, Missouri 65201
Phone number: 314-442-3701
Birthdate: October 18, 1920
Place: New York, New York
Citizenship: U.S.A.
Sex: Male
Married: 3 children
Present position: Professor of Pharmacology and Associate Professor of Community Health—University of Missouri Medical School; Clinical Pharmacologist—University of Missouri Medical Center
Education:
Cornell U. College of Arts & Science, Ithaca, N.Y., A.B.—1940
Cornell U. Medical College, New York, N.Y., M.D.—1943
Cornell U. Medical College, Special Student in Pharmacology, 1947

Academic appointments:
- Research Fellow in Pharmacology, Cornell U. Medical College, 1949–1950
- Instructor in Pharmacology, Cornell U. Medical College, 1950–1953
- Assistant Professor of Clinical Pharmacology, Cornell U. Med. School, 1953–1956
- Assistant Professor of Pharmacology, Cornell U. Medical College, 1956–1957
- Associate Professor of Pharmacology, Albany Medical College, 1957–1961
- Associate Professor of Pharmacology, University of Missouri, 1961–1966
- Professor of Pharmacology and Associate Professor of Community Health, University of Missouri, 1966–on

Basic clinical medical training and experience:
- Internship—Beth Israel Hospital, Boston (Harvard Medical Center), 1944
- Residency in Medicine—Montefiore Hospital, N.Y., 1948

Clinical Pharmacology Experience:
- Clinical Assistant in Cardiology, Research Unit, Hospital for Joint Diseases, N.Y. (Part-time), 1949–1951
- Assistant, Cardiovascular Research Unit, Beth Israel Hospital, N.Y. (Part-time), 1949–1951
- Assistant Professor of Clinical Pharmacology, Cornell U. Medical College (Full-time), 1953–1956
- Clinical Pharmacologist, University of Missouri Medical Center, 1964–on

Military Experience:
- Active duty, A.U.S. in World War II. Commissioned 1st Lt. Medical Corps, October 6, 1944. Promoted to Captain, February 28, 1946. Discharged, December 26, 1946. Service in U.S., Philippines and Japan. Awarded Combat Medical Badge, May 27, 1945, by 126th Infantry, 32nd Division.

Research prizes and research fellowships:
- 1943—William M. Polk Prize for Research, Cornell University Medical College
- 1949—Henry M. Moses Prize for Research, Montefiore Hospital
- 1949–1951—New York Heart Association Research Fellowship (U.S.P.H.S. Post-Doctoral Fellowship awarded and declined)
- 1952–1956—American Heart Association Research Fellowship
- 1957–1961—United States Public Health Service Senior Research Fellowship
- 1962–1967—United States Public Health Service Career Research Development Award

Medical licensure:
- New York, Missouri, California

Membership in scientific societies:
- Society for Experimental Biology and Medicine
- Society for Pharmacology and Experimental Therapeutics
- American Federation for Clinical Research—Senior Member
- Sigma Xi

Fellowships in medical and scientific organizations:
- Fellow—American College of Physicians
- Fellow—American College of Clinical Pharmacology

Membership in medical societies:
- Boone County Medical Society
- Missouri Medical Association
- American Medical Association

Consultancies and related activities—Pharmacology and clinical pharmacology—Government and medical groups:
- Consultant to Senate Committee on Antitrust and Monopoly (Kefauver) 1960, 1961
- Member of Ad Hoc A.A.M.C. Committee on Relations with Pharmaceutical Industry 1961
- Consultant to A.M.A. Council on Drugs 1965, 1966
- Consultant in Clinical Pharmacology to Cancer Research Center, Columbia 1966, 1967

Faculty committee assignments—University of Missouri:
- MEND Committee (Secretary)—1961 to date
- Civil Defense Committee (Campus-wide)—1962 to date
- Research Development Committee—1961–1965
- Student Research Subcommittee (Chairman)—1964–1965
- Safety Committee—1967
- Human Experiment Committee—1965 to date

STATEMENT OF DR. SOLOMON GARB, DEPARTMENT OF PHARMACOLOGY, UNIVERSITY OF MISSOURI MEDICAL SCHOOL, COLUMBIA, MO.

Dr. GARB. No, that would be fine, sir.

Senator NELSON. If you will speak into the microphone so we can hear you, go ahead and proceed.

Dr. GARB. Do you want my biographical sketch, sir?

Senator NELSON. We have a detailed biographical sketch, but we should be pleased if you would give us a brief résumé of your professional background.

Dr. GARB. All right, sir. I received my M.D. degree from Cornell University Medical School approximately 24 years ago. I have had an internship, residency, military experience as a battalion surgeon, and a certain degree of clinical experience testing drugs in various medical centers. I have been a full-time teacher and researcher in pharmacology and clinical pharmacology since approximately 1950. I taught on the staff of Cornell Medical School, then Albany Medical School, and I am currently professor of pharmacology and associate professor of community health at the University of Missouri Medical Center. I am also clinical pharmacologist for the University of Missouri Medical Center and I am a consultant to the AMA Council on Drugs.

Senator NELSON. Thank you, Doctor.

Dr. GARB. It is an honor to be invited to testify before this subcommittee, and I hope that the information which I am able to present will help you in your deliberations.

The key point which I would like to emphasize is that the names of drugs are unnecessarily confusing. They are confusing not only to the layman, but to the physician as well. Furthermore, I believe that the existing confusion plays a major role in preventing the operation of the usual American marketplace checks and balances. As a result, many drug prices are excessively high. The point that I want to make here is that I don't feel that drug prices are excessively high simply because somebody is out to make a killing with them. I think that the economic structure of the industry tends toward high drug prices, and this is a point which I think will become clear as we go along.

There are several kinds of drug names for us to consider. They include: chemical, official, generic, USAN, brand, and private product names. And each drug can have one or more of each of these kinds of names.

The chemical name is a long, complex affair which identifies the specific chemical structure of the drug molecule. Fortunately, it is used only by chemists, and we need not consider it further.

The words official and generic are often used interchangeably in relation to drug names. The word "generic," is a poor one in this context, and hopefully, the term "official" will take its place. As commonly used, the term "official" and "generic" refer to names of drugs which can be used by any manufacturer, and which serve to identify the drug and distinguish it from others. There are, however, some differences in the meanings of generic and official. At one time the word "official" referred to a name approved by the U.S. Pharmacopeia. Today, it

refers to a name approved by the FDA. Since most people still use the term "generic" I will do so in the remainder of this testimony.

Our older drugs have simple, clear, and useful generic names. These include: Morphine, codeine, insulin, barbital, reserpine, and atropine.

Senator NELSON. May I interrupt a moment?

Dr. GARB. Yes, sir.

Senator NELSON. Why did the older drugs have simple, clear, and useful generic names and new drugs do not?

Dr. GARB. I will come to this subsequently, but to give a brief answer, I would say that there probably were a combination of two circumstances involved. At one point in the past, the AMA set up certain recommendations about drug names. They were only recommendations, they had no real force, and they involved some rather complicated thoughts about generic names being somewhat similar to chemical names or derivatives of chemical names. The drug manufacturers, following this, developed some very complicated generic names.

It turned out that the development of complicated names, which you can't pronounce and can't remember, tends to push doctors to the use of what I call private product names instead of generic names, and I think that when it was discovered that it worked this way, it was just too advantageous to the manufacturers for them to let it go.

Senator NELSON. What does the word morphine or codeine or insulin or barbital or reserpine tell a physician that another more complicated generic name does not, or what does a more complicated one tell the physician?

Dr. GARB. Morphine tells the doctor enough to identify the specific drug. Morphine is morphine. Morphine is morphine in Washington, in San Francisco, in London, and Australia. It is the same identical material. Morphine was the same thing in 1900 as in 1967. If we made the name morphine longer or made a longer name for the chemical which we call morphine, it would tell us nothing further. It would tell us nothing that is more useful. It would simply confuse the issue.

Senator NELSON. But the question I am getting at is, supposing you have a chemist who never heard of morphine.

You gave him the chemical name and then you gave him the name "morphine," would he recognize what the chemical name was from reading the word morphine? Does morphine tell you anything as a chemist, or is this simply——

Dr. GARB. No, morphine does not tell a chemist what the chemical structure of morphine is. On the other hand, these long generic names also do not tell the chemist the chemical structure of the molecule.

Senator NELSON. What does any of these generic names tell a chemist or a physician that a trade or brand name doesn't tell him?

Dr. GARB. Are you speaking now of morphine, a simple one like morphine?

Senator NELSON. Any one of them. What does reserpine tell you that Serpasil does not? One is the generic name and one is the brand name.

Dr. GARB. Well, the private product name tells you less, unless you happen to know the code. In effect the private product name that you have just mentioned, Serpasil, can be thought of as a code, which includes the identity of the manufacturer and the official or generic name. But if you happen not to know the code and most people do not know the code, it tells you just about nothing.

Senator NELSON. Let me put the question the other way. Supposing somebody had decided that the generic name ought to be Serpasil, and some company decided that their brand name ought to be reserpine. Would it make any difference?

Dr. GARB. No. A name is a name. The whole point is that you cannot rely upon names to give you chemical structures or anything else unless they are the long chemical names. The name of a drug is exactly as useful as the name of a person. You can call a person John, or you can call a person Dick. The names tell you nothing more than the identity of the individual.

Senator NELSON. So then in devising an official name or a generic name, the idea ought to be to devise a simple, pronouncable name; is that correct?

Dr. GARB. Yes, sir. It should be simple, it should be pronounceable, and above all, it should be so designed that it cannot be confused with another drug. This is a key point. We do have a case where there are two drugs with similar generic names. This is bad. One is digitoxin and one is digoxin. They are both cardiac glycosides. The names are so close together that confusion exists at times and doctors might make a mistake or pharmacists might make a mistake, and this is not good. So the names should be distinct enough so that they cannot be confused with any other drug by any person.

Senator NELSON. Does there have to be approval by FDA or any other official agency of the trade name or product name that a private manufacturer attaches to a generic drug?

Dr. GARB. To the best of my knowledge, no, but this is not an area I am familiar with. I am not familiar with the law in this respect.

Senator NELSON. The two names you gave, digitoxin, and what was the other?

Dr. GARB. And digoxin are generic names.

Senator NELSON. Are generic names?

Dr. GARB. Are generic names. They go back into history, and it is unfortunate that we have two generic names which are so close that they can be confused.

Senator NELSON. Who created those names?

Dr. GARB. I don't know.

Senator NELSON. They are old?

Dr. GARB. They are old.

Senator NELSON. Go ahead.

Senator HATFIELD. Excuse me, doctor.

Dr. GARB. Yes, sir.

Senator HATFIELD. Are there any generic names, or rather brand names that through long usage have become generic names?

Dr. GARB. The only one that I can think of offhand is aspirin.

Senator NELSON. Go ahead.

Dr. GARB. Most of our existing drugs, however, have long, complicated, almost unpronounceable names such as sulfamethoxypyridazine, zoxazolamine, bendroflumethiazide, benztropine methanesulfonate, oxyphencyclimine hydrochloride, methylbenzethonium chloride, chlorzoxazone, iodochlorhydroxyquin, triacetyloleandomycin, and so forth.

Senator NELSON. What do these generic names accomplish?

Dr. GARB. Well, theoretically they should identify the drug just as the name morphine identifies the drug morphine. They give you no more information about the constitution of the drug chemically or otherwise than do names like morphine, insulin, atropine. What they accomplish——

Senator NELSON. Or Dexedrine, which is a trade name.

Dr. GARB. Yes, sir; Dexedrine is a trade name.

Senator NELSON. I know. Does it give you any more information than that?

Dr. GARB. Well, yes. Again, it is the matter of a coding system in effect.

Senator NELSON. Does Dexedrine tell you any more than dextroamphetamine does?

Dr. GARB. It probably tells you less, unless you happen to know what the code means.

Senator NELSON. What do you mean by code?

Dr. GARB. The private product name such as Dexedrine, if you know all about it, tells you that it is a dextroamphetamine which is made by Smith, Kline & French, but you have to memorize these things, you see.

Senator NELSON. But this is what I am getting at. Couldn't Pharmacopeia or FDA have suggested the official name or the adopted name and have said Dexedrine should be the generic name and then the company Smith, Kline & French could come along and say we will call it dextroamphetamine.

Dr. GARB. That is right.

Senator NELSON. And neither one tells you more than the other.

Dr. GARB. Neither one tells you more than the other, that is correct.

Senator NELSON. Each one has to be memorized.

Dr. GARB. That is right. That is exactly correct, yes, sir.

Senator NELSON. Now where did these complicated names that you just listed come from?

Dr. GARB. These particular names were made up by the manufacturers. In the days before the Kefauver-Harris law, the responsibility for making up the generic name was left to the manufacturer, who first produced the drug, and in those days there were even drugs which had more than one generic name. I mean if two manufacturers developed the drug at about the same time, they could each give it a different generic name and they could even change generic names. This has been changed now in the law, and today the FDA has to approve the new generic names.

Senator NELSON. Who proposes the generic name that the FDA approves?

Dr. GARB. The company proposes it, I believe, but there are certain guidelines now that didn't exist before. Names today are getting a little less complicated than they used to be. They are still a little more complicated than I would like.

Senator NELSON. Don't they continue to be more complicated than the trade name?

Dr. GARB. Oh, yes.

Senator NELSON. Well, what is the explanation for that?

Dr. GARB. I think you would have to ask the FDA that. I couldn't tell you the explanation. I know that the FDA now has the power to

insist on simple, direct, easily-remembered names. Now there are certain problems that they have to face, because as you get more and more drugs, it becomes more and more difficult to devise simple names that don't conflict with other names, and that cannot be confused with them. But I would like to see generic names made as simple as possible. I see no reason for making them multisyllable or having lots of X's, Y's and Z's.

I am always amused by the fact that X, Y and Z are rather rare letters in most languages, but when you come to generic names of drugs, I would say about 75 percent of all of them have either an X, Y or Z in them and some of them have all three. Zoxazolamine has two Z's and an X.

Senator NELSON. This is your field. Is there a possibility for a pharmacologist to be familiar with all of the generic names?

Dr. GARB. It is possible for a pharmacologist to be familiar with the generic names. I don't know if it is possible to pronounce them.

Senator NELSON. So if we had to write it down on a prescription without looking up the spelling we couldn't do it in many cases; is that correct? I don't want to test anybody here.

Dr. GARB. I think I would have some trouble. I think, however, that a physician who has a particular type of practice and who is only using say 40 or 50 drugs altogether would become familiar enough with them so that even with these spellings he could handle them.

Senator NELSON. Go ahead.

Dr. GARB. These names are difficult because of two considerations. First, most of them were invented by the drug manufacturers, who found it financially rewarding to make generic names hard to remember, pronounce or write, so that physicians would be more likely to prescribe by private product name. Until 1962, the FDA did not have authority to specify simple, meaningful generic names. It now has that authority.

The second reason is that the FDA has been slow about using its authority to simplify generic names.

Senator NELSON. Are you referring to——

Dr. GARB. The old names.

Senator NELSON. The old names? Do they have the authority to go back now and establish simpler generic names than those that have already been adopted?

Dr. GARB. I believe they have. I am not a legal expert. My understanding of the law is that they do have that authority. If they don't, they should have.

Senator NELSON. But they do have the authority to approve it——

Dr. GARB. The new ones.

Senator NELSON. The new ones. Does that sole authority rest with the FDA?

Dr. GARB. Yes. They have a mandate now.

Senator NELSON. Do they work in cooperation with any professional groups?

Dr. GARB. I believe they work in cooperation with the AMA and other groups because frequently they will take the USAN name and make it a generic name. I am sure there is a great deal of cooperation.

Senator NELSON. I guess that is a question for the FDA when they come up here.

Dr. GARB. Yes, sir.

Senator NELSON. Thank you.

Dr. GARB. The USAN name is a temporary drug name adopted by the AMA Council on Drugs, the Pharmacopeia Committee and the American Pharmaceutical Association. USAN means United States Adopted Name. It is used for new drugs before a generic or official name is selected. Often, the USAN later becomes the generic or official name.

The term "brand name" apparently means different things to different people. In the classical sense, a brand is a name or device which identifies the manufacturer or other agency responsible for placing the product on the market. In most areas of commerce, the brand name is used as an adjective to modify the common name of the product. Some examples are: Florsheim—shoes, Eversharp—pens, Eveready—batteries, Heinz—ketchup, Heinz—vegetarian beans, Heinz—kidney beans, Heinz—vegetable soup, Campbell's—beans, Campbell's—vegetable soup, Campbell's—tomato soup, Libby—beans, Ann Page—beans, and so forth.

Note that the brand names above are the names of the manufacturers.

Other manufacturers chose to use devices rather than their own names as a brand. Examples are: Arm & Hammer—bicarbonate of soda, Bumble Bee—tuna fish.

Sometimes, the product is natural, rather than manufactured, such as: Sunkist—oranges.

This use of a brand name stems from old English common law and is specifically protected by congressional act.

I want to make it clear that I am 100 percent in favor of this brand-name usage. I consider it to be helpful to the consumer and a major factor in encouraging manufacturer reliability.

Let us take note of some of the features of this system, even though they may seem obvious.

First, and most important, the brand name is almost always used with the common or official name. A person would be unlikely to ask a grocer for a "can of Heinz"—he would ask for Heinz vegetarian beans, or Heinz vegetable soup, and so forth. Therefore, the use of this kind of brand name does not in any way obscure, hide, or confuse the true nature of the product.

Second, this use of the brand name permits the consumer to compare prices in a rational manner. He or she realizes that there are differences between Heinz beans, Campbell's beans, Ann Page beans, Libby beans, and others. However, the consumer also realizes that the products are, nevertheless, basically similar. If the price difference is 1 cent per can, the consumer might decide and often does, that the flavor of one brand is worth the extra 1 cent, and purchases it. On the other hand, if one brand of beans sold for 19 cents per can, while another sold for 69 cents, few consumers would be willing to pay over three times as much, even if the more expensive bean tasted a little better.

Mr. GORDON. May I interrupt here?

Dr. GARB. Yes, sir.

Mr. GORDON. Now this wouldn't apply to drugs, would it? That is consumers can't flit from one——

Senator NELSON. You cover that in your statement, I believe?

Dr. GARB. Yes, sir, as we go along.

Thus the proper use of a brand name is fully consistent with the operations of a free competitive market.

Third, the proper use of the brand name helps the consumer choose new products. Let us imagine a consumer who has never eaten clam chowder, but who has eaten and enjoyed Campbell's tomato soup, vegetable soup, and other soups. That consumer, seeing a can of Campbell's clam chowder in a display would be more likely to buy it than to buy an unknown brand, because of previous satisfaction with Campbell's other soups.

Fourth, by a similar mechanism, the proper use of a brand name is a stimulus to a manufacturer to keep his customers satisfied, and to keep all his products up to the highest standards.

Fifth, this use of the brand name can be applied to mixtures as well as single products. Thus, vegetable soup is a mixture, and Campbell's vegetable soup and Heinz vegetable soup differ slightly in the kinds and proportions of vegetables included. Nevertheless, they are similar products and the similarity is evident to the consumer.

Finally, the proper use of a brand name does not make it necessary for the consumer to memorize a large new vocabulary. Beans are called beans, not sneabs, nabes, anebs, ebans, hi-pros, or lo-cals. This is a point which is quite obvious in relation to foods, but not in relation to drugs. I will return to this point later.

In the drug field, the proper use of the brand name involves exactly the same arrangement as the proper use in other areas—that is, the name of the manufacturer, plus the official or common name of the drug. Some examples are: Lilly—secobarbital, Armour—thyroid, Wyeth—meprobamate, Lederle—tetracycline.

It is also permissible to reverse the names, as follows: secobarbital—Lilly, thyroid—Armour, and so forth.

Let me reiterate that I am completely in favor of this sort of brand-name use for all products—drugs, beans, vegetable soup, tires, anything you want to name.

Now we come to the private product name, which many people also call "brand name." I am using the term "private product" to distinguish it from the classical brand name discussed before.

The private product name is a noun which is substituted for the official, generic or common name, and which is the private property of the manufacturer who registers and uses it. Private product names are used primarily in the drug, detergent, and breakfast cereal industries, although a few other industries also use them occasionally. Their use for detergents and breakfast cereals is not particularly objectionable. After all, it hardly makes much difference if a housewife knows the names of the active ingredients in Duz, Rinso, Cheer, Fab, Bold, All, Dash, and so forth, nor is it necessary that she know the name of the manufacturer.

However, in the drug field, the use of private product names produces serious effects which work against the patient's best interests.

Let us look at some private product names for drugs. Here are some which are or have been in fairly common use: Achromycin, Seconal, Kynex, Miltown, Madribon, Equinal, Midicel.

Obviously, these names do not indicate the identity of the manufacturer or the nature of the active ingredient, unless you happen

to have memorized what I consider to be a form of a code. Furthermore, the relationships between the drugs is often obscured and confused—not deliberately, but by the operation of the system.

For example, looking at this, how many people not knowing the system would realize that Kynex is the same thing as Midicel in terms of chemical nature? Well, if a patient has been taking Kynex and develops a drug reaction from it, he will probably develop the same reaction if he gets Midicel, since the activities of each are absolutely identical.

The patient may know that in the past, after taking Kynex, he became ill. And therefore, if he sees a prescription for Kynex he might say to the doctor: "This made me sick last time." However, if he goes to another physician and receives a prescription for Midicel, is he likely to realize that the two drugs are the same? The chances are not. Will the doctor? Sometimes, perhaps, but not always. And I should add that there is evidence in the record that this is the case.

Senator NELSON. Just for clarification of the record, the list of seven drugs that you list on page 6 of your statement are not all the same generic drug.

Dr. GARB. No, no, I have several groups there. Incidentally if I had a list of seven different kinds of beans you would know that they are all beans you see.

Senator NELSON. I can see they weren't, but it doesn't appear clear from the statement.

Dr. GARB. Kynex is the same as Midicel; Miltown is the same as Equanil; Madribon is related to Kynex and Midicel, but is not the same thing.

If a doctor prescribes Achromycin for a patient with an infection and it doesn't help, might he switch to Tetracyn? Both are really tetracyline hydrochloride, and there are other private product names for the same medication.

The use of these private product names prevents the operation of a free competitive market in drugs. Few if any physicians can keep up with all these names, let alone the prices of each product.

Let us suppose that Equanil sold for 50 percent less than Miltown. A doctor accustomed to prescribing Miltown would be unlikely to change, if he did not know that Equanil was essentially the same thing, producing exactly the same result, but cheaper. I doubt if there are many physicians who know the composition of all the private product named drugs. In fact, I rather doubt if there are any physicians who know the composition of all those drugs.

The confusion which results from the multiplicity of private product names has been mentioned by many, and is thoroughly documented in the record of the hearings of the Kefauver committee. Should this committee wish, I will submit page citations. However, the evidence in the Kefauver hearings referred to happenings before 1961. The question

before us now is whether there is still significant confusion about private product drug names. I believe that the answer is definitely affirmative, and to support my statement, I wish to offer a copy of an article by Doctors Azarnoff, Hunninghake, and Wortman entitled "Prescription Writing by Generic Name and Drug Cost," which appeared in the Journal of Chronic Disease, volume 19, pages 1253–1256, 1966.

Senator NELSON. The article will be received and will be printed in the record.

Dr. GARB. Here is the article.

(The article referred to follows:)

PRESCRIPTION WRITING BY GENERIC NAME AND DRUG COST

(Daniel L. Azarnoff,* Donald B. Hunninghake† and Jack Wortman, Departments of Medicine and Pharmacology, University of Kansas Medical Center, Kansas City, Kansas, and St. Francis Hospital, Wichita, Kansas)

When a problem reaches such stature that it becomes a subject for the cartoonist (Fig. 1), we can be assured that it is either a significant social or political issue or an absurdity. Many, many words have been written concerning whether drugs shold be prescribed by generic or brand name. A variety of reasons can be offered for both. One factor frequently listed as a reason for prescribing by generic name is the lower cost of these preparations. There is little doubt that the wholesale cost of many drugs sold by generic name to pharmacists is less than the same drug sold under a trade name [1]. The real question, however, concerns the cost of the drug to the consumer and whether or not the decreased cost of a generic drug is passed on to him. In a recent popular book by Morton Mintz [2], it is categorically stated that the price of drugs when prescribed by generic name is cheaper than the same drugs by brand name. This investigation will show that for at least one drug the statement is true in a large midwestern city.

METHOD

A *bona fide* prescription for fifty tablets (400 mg) of Miltown® (meprobamate) was filled and purchased at 23 pharmacies. At least a week later, a prescription for a similar quantity of meprobamate was taken to the same stores by a different individual. If the source of the medication was not discernible by markings on the tablet, the pharmacist was asked for the name of the manufacturing pharmaceutical company. In all instances, this information was made available.

RESULTS

The mean cost of Miltown at the 23 pharmacies was $4.94 while meprobamate purchased by generic name was $3.88, a saving of 21 per cent (Table 1). The mean cost at pharmacies of two chain drug stores was $4.49 and $4.40 when prescribed as Miltown and $2.93 and $3.22 when prescribed as meprobamate. This represents a saving of 35 and 27 per cent respectively. At pharmacies composed only of prescription shops and other individually operated drug stores, the cost for each prescription was higher, although the saving on generic name prescriptions averaged 17 per cent. At 18 of the 23 pharmacies, a generic name product was dispensed when ordered in this manner. Of these, only one charged the higher price of a brand name product while he dispensed a generic name product. Of the remaining pharmacies, the brand name products were dispensed at their regular price in three and at a higher price in two.

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TABLE 1

Miltown		Meprobamate	
Retail stores	Price	Source	Price
Chainstores A:			
1	$5.75	Davis-Edwards	$2.55
2	3.83	Wyeth Laboratories (Equanil)	3.83
3	4.55	Davis-Edwards	2.77
4	3.82	do	2.55
Chainstores B:			
1	4.50	American Pharmaceuticals	2.90
2	4.25	do	2.90
3	4.25	Wyeth Laboratories (Equanil)	4.50
4	4.50	American Pharmaceuticals	2.90
5	4.50	do	2.90
Individual pharmacies:			
1	6.10	West-ward	4.90
2	5.50	do	3.65
3	4.40	Wyeth Laboratories (Equanil)	4.40
4	4.35	Schein	4.35
5	4.20	Riverton	2.38
6	4.00	McKesson Laboratories	4.00
7	5.75	West-ward	4.25
8	5.50	Wyeth Laboratories (Equanil)	5.50
9	6.50	McKesson Laboratories	5.25
10	6.00	do	4.35
11	6.35	Roder	6.35
12	6.50	McKesson Laboratories	4.25
13	3.95	Wolins Pharmacal	2.40
14	4.50	Wallace Laboratories (Miltown)	5.50
Mean	4.94	Mean	3.88

DISCUSSION

Since meprobamate purchased by generic name is cheaper than the brand name product, the crux of the problem is whether the two are identical in therapeutic efficacy. Several examples have been reported [3–5] for other drugs which demonstrated that neither the United States Pharmacopeia (USP), National Formulary standards, nor Food and Drug Administration regulations assure the therapeutic equivalence of generically identical pharmaceutical products. The therapeutic effect of a drug preparation depends upon the compatibility, purity, solubility, particle size, vehicle, percentage of active ingredient, melting point, pH, allergic effects, disintegration time, quality control, and effect of storage to name only a few of the factors involved. Although we did not analyze the tablets we purchased for meprobamate content, a survey reported in *Medical Letter* [1] showed that meprobamate tablets from all ten companies checked by them met USP standards for content. There can be little question of differences in the quality of the meprobamate powder itself in generic and brand name products since it is all prepared by a few manufacturers according to specifications of Carter Wallace, the parent company of Wallace Laboratories.

Although our study demonstrated that meprobamate could be purchased more cheaply by generic equivalent, this is admittedly a small survey and involves only one drug. In an editorial in the *Rhode Island Medical Journal* [6], a survey of the Division of Public Assistance of that State is quoted as indicating that the saving from prescribing by generic name, where possible, in 10,000 prescriptions would be only 5 per cent. However, in a recent report to Congress, the U.S. Comptroller General indicated that if drugs for the welfare recipients of the State of Pennsylvania were prescribed by generic equivalent, the State could have saved $722,000 to $1,500,000 in fiscal year 1964.

One factor against prescribing by generic name has been the complexity of this name supposedly making even the organic chemist cringe. To some extent this has been true in the past. However, the nonproprietary nomenclature has been simplified and standardized by a committee composed of representatives of the USP, National Formulary, and American Medical Association. The names adopted by this committee are designated as United States Adopted Names (USAN) [7]. The guiding principles of this committee are that the names should be distinctive in sound and spelling, conveniently short, should indicate general pharmacological or therapeutic class, and the general chemical nature of the

compound. The implementation of these rules by the Kefauver-Harris bill of 1962 has done much to correct this difficulty for the prescribing physician.

On too numerous occasions, we have seen patients simultaneously receiving a similar drug in two preparations of different brand name. Meprobamate, for example, can be prescribed by at least 33 different brand names either alone or in combination with a variety of other drugs.[1] Many of these names give no indication of the active ingredients. It is most often when a combination of drugs is prescribed by a single brand name that the physician may lose sight of the various components and prescribe one of the ingredients again in a separate preparation. In addition, the increasing knowledge of the effects of drug interactions makes it imperative for the physician to be acutely aware of all drugs the patient is receiving. We have noticed a similar difficulty particularly when antibiotics have been prescribed by brand name. Following an inadequate therapeutic effect, the patient may be given another brand name antibiotic without the physician realizing the same antibiotic is being given. Although such errors are not frequent, prescribing by generic name would do much to stop these instances of poor therapy. Therefore, we strongly recommend that all drugs be prescribed by generic name. In those instances where the physician feels a specific company's product is best for his patient, the generic name of the drug should be followed by the name of the company whose product he wishes. This appears to us to be a logical solution. After all, if a physician has determined that a specific manufacturer's product is best for his patient, he should at least know the name of the company.

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Dr. GARB. There is much of importance and interest in this article and I will return to it again. At this time, there are two statements that I wish to quote. (They use the term "brand name" to refer to what I have called "private product name." They are using it in the usual fashion.) These doctors say:

> On too numerous occasions, we have seen patients simultaneously receiving a similar drug in two preparations of different brand name.

They go on:

> We have noticed a similar difficulty particularly when antibiotics have been prescribed by brand name. Following an inadequate therapeutic effect, the patient may be given another brand name antibiotic without the physician realizing the same antibiotic is being given. Although such errors are not frequent, prescribing by generic name would do much to stop these instances of poor therapy.

Much of the public discussion of brand versus generic prescribing have assumed that there are only two basic ways to prescribe drugs. Instead, there are three. Let us assume that a physician wishes to prescribe a particular medication.

One way would be to write: meprobamate.

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[1] Apascil, Atraxin, Biobamat, Calmiren, Cirpon, Cyrpon, Ecuanil, Equanil, Equanil LA, Harmonin, Mepantin, Mepavion, Meproleaf, Meprosin, Meprospan, Meprotabs, Miltown, Nervonus, Neuramate, Oasil, Pamaco, Panediol, Perequil, Perquietil, Pertranquil, Placidon, Probamyl, Quanil, Quilate, Sedabamate, Sedasil, Urbil, Viobamate.

This is called generic, or official prescribing, and means that the pharmacist may dispense any manufacturer's make of meprobamate.

A second way would be to write: Equanil.

This is called brand, or private product name prescribing and means that the pharmacist must dispense the product distributed by Wyeth.

The third way, which I consider the best way would be to write: meprobamate (Wyeth).

The pharmacist would then dispense the Wyeth product.

For at least 25 years, medical school facilities have been teaching and urging that prescriptions be written in this third way. Unfortunately, our recommendations have not been widely followed, and I believe that this lies at the root of most of the difficulties with drug prescriptions.

On May 11 of this year, I participated in a dialog on drug marketing at the University of Missouri, sponsored by the American Marketing Association. It was a most valuable experience.

One of the representatives of the pharmaceutical industry asked about the difference between prescribing Seconal or secobarbital (Lilly). Would the patient not receive the identical medication either way? My answer was "Certainly."

Senator NELSON. Who makes Seconal?

Dr. GARB. Lilly. Seconal is Lilly's brand of secobarbital, and my point was that if the physician wishes to have the patient receive Lilly secobarbital he should write Lilly secobarbital.

So this gentleman commented, "Well, if the patient would receive the same medicine, no matter which of these two ways the prescription is written, why quibble over the way the prescription is written?" And apparently many people think this point we have raised is a quibble, or some sort of ivory tower perfectionism that professors like to indulge in.

It is neither—it is an issue of major importance, and I believe that we medical educators have been remiss in not explaining why. Therefore, I'd like to point out the importance of the proper prescribing method. To a large extent it is a matter of numbers.

First, let us consider the number of drug names. Let's assume that there are 100 drug manufacturers, each making the same 50 drugs. If prescriptions are written in the meprobamate (Wyeth) fashion, the physician needs to know only 100 plus 50, or 150 names in order to prescribe any combination of any drug made by any company, and of course a physician can easily handle 150 names. However, if prescriptions are written by private product name, for example Equanil—the physician must know 100 times 50, or 5,000 names in order to prescribe any drug made by any company.

Senator NELSON. Any drug made by any one of these 100.

Dr. GARB. Right, any drug made by any of these 100; yes, sir. There are actually more than 100 manufacturers using private product names and more than 50 drugs. It was my understanding that the total number of different names for prescribed drugs is today somewhat over 7,000. I heard a disturbing report that I may have underestimated this, but 7,000 is I think a serious enough problem.

Senator NELSON. Are you saying there are 7,000 different drugs or 7,000 different brand names?

Dr. GARB. There are more than 7,000 different private product names on the market today.

Senator NELSON. How many different drugs are on the market today?

Dr. GARB. This will depend on how you define a different drug really. In other words, do you want to consider sodium penicillin to be different than potassium pencillin? Depending on how you define your terms, I would say around 900, something in that range.

Senator NELSON. We are talking about prescription drugs.

Dr. GARB. Yes, sir. The average physician probably uses not more than 50 different chemical entities. As I say, there are probably more than 7,000 different private product names on the market today, and there are somewhere between 500 and 600 changes per year.

These changes may be additions, subtractions, or alterations. A manufacturer can change the name of a mixture that he has already on the market, or he may keep the name and change the mixture if he chooses to, or of course, he may develop a new drug or he may drop an old drug.

Let's consider what's involved in trying to learn that many names, and their meaning. Since the words themselves are newly coined, they are the equivalent of a foreign language vocabulary. I consulted some of my colleagues in the language departments of the University of Missouri and asked how many new words a bright student was expected to learn per year. I was told that for French, Spanish, Russian, and German, the range was 1,000 to 1,200 new words in terms of recognition, but less, in terms of full understanding. Thus, I estimate that, conservatively, the time, energy, and study needed by a doctor to learn 7,000 private product names would be equivalent to that needed for a student to obtain an "A" grade in more than 5 years of college French, Spanish, German, or Russian. If a doctor did take the time to do this, he would then find at the end of the 5 years, that 2,500 to 3,000 of the drug names had been changed.

The fact is that doctors cannot possibly keep up with the flood of private product names, and this situation leads to poor medical practice. It is not that the doctors are ignorant, it is not that the doctors don't want to know what is going on. The situation is simply that doctors are human beings, not computers and they have certain limitations, and they can't possibly learn this. Therefore they must compromise. They learn a few names and they work with those few. Unfortunately, the names that they learn and work with are not always necessarily the best ones for the particular patient that they are treating, and the doctor just has no way of encompassing the total amount of information needed in order to handle this.

It is difficult enough to practice medicine with all its complexities, without having the names of drugs made so confusing that you can't keep up with the field. I was here for part of the testimony yesterday when Dr. Williams from Emory University said that he had difficulty keeping up with all the names, and I will say that I have at least as much difficulty. I can't keep up with these names, although this is my job. It is just not feasible.

Mr. GORDON. At present there are thousands of drug names. You mentioned 7,000. I have heard a figure of 14,000.

Dr. GARB. Which is much worse.

Mr. GORDON. If we had a system of generic names, how many would the average practicing physician need to know to practice good medicine?

Dr. GARB. Not more than 50.

Mr. GORDON. Not more than 50?

Dr. GARB. Not more than 50.

Senator NELSON. I take it it would vary.

Dr. GARB. It depends on his specialty.

Senator NELSON. On the specialty of the physician?

Dr. GARB. Yes, sir, it would depend on the specialty. Some physicians would get by with not more than 10 or 12, but somebody with a very busy practice might have to thoroughly understand about 50 generic names. There is a big difference between 50 and 7,000 or 14,000.

Mr. GORDON. What do you mean by poor medical practice when the doctors cannot keep up with private product names?

Dr. GARB. Well, I have mentioned two examples of these. One is prescribing two private product name drugs for the patient, not realizing that both of them contain the same active ingredient, or similar active ingredients, which will cause toxicity.

Another one is starting a patient on a drug, finding that the drug is either toxic or ineffective, and then switching him to another drug, not realizing it is the same thing.

A third example is giving a patient a drug which is not the best possible one for that patient, because the doctor simply has to focus on something, and he may learn to use one particular antibiotic, and not realize that for one patient's infection, another antibiotic would be better.

Just keeping up with the private product names of all the antibiotics on the market is too much, and therefore, the doctor uses what he knows, although it may not be the best one for a particular patient. I do not feel that this is the fault in any way of the doctor or the medical profession.

Doctors are having a very difficult time with the enormously complex problem of helping sick people, and this name situation is just making it harder.

Senator NELSON. With respect to your statement that you don't think it is in any way the fault of the practicing physician or the medical profession, I certainly don't see how the private practitioner could solve the problem, but doesn't the profession itself have more of a responsibility to do something about this than it has thus far assumed? Or has it assumed all the responsibility you think it should, in terms of clarifying this problem?

Now we have had several witnesses of great distinction in addition to yourself who have made exactly the same point, that there is no way for physicians to learn all these names; that as a consequence of this, there is bad medical practice occurring that shouldn't occur; that there is overmedication; that there is duplication of the same drug, unknowingly to the doctor; that the doctor prescribes a drug and there is an adverse reaction and then he prescribes another one, because he doesn't know it is the same composition, and you get a bad result.

Doesn't the medical profession have some responsibility to be vigorously pursuing the solution, and if it is, have you heard anything about it? I certainly have not.

Dr. GARB. Well, sir, I would have to answer you in this way. Those of us who are coming here to testify about this are largely members of the medical profession who have looked into this, and we feel that we are discharging our responsibility by doing so.

Furthermore, I will say that many of us have been working in this field, studying it and trying to be heard for long years before the Congress took interest in it. So I don't think it would be fair to try to place the burden for the situation on the medical profession.

In fact, in the record which I submitted for the Kefauver hearings, was a statement made in 1902 by Sir William Osler, in which he said virtually what we have been saying here in this testimony.

My feeling is that a large part of the responsibility for this does not lie with the medical profession because we are fundamentally powerless.

Senator NELSON. Pardon?

Dr. GARB. I say the medical profession is fundamentally powerless to handle the problem as it stands today.

Senator NELSON. When you say the medical profession, are you talking about the profession as a whole or individual members of the profession? Are you saying the AMA, for example, is powerless to do anything about this?

Dr. GARB. Well, in terms of the AMA perhaps the word powerless is too strong, but I would say it has very little power in this area, if any.

Senator NELSON. In terms of education of the physician, for example?

Dr. GARB. Yes, in terms of the education of the physician too it has very little power. It is I think, doing a good job as it can with the facilities and funds available to it, but you see, in my view, this is not primarily a matter of the education of the physician. There are problems in terms of the medical school and the continuing postgraduate education of the physician, but this is not what I am directing my testimony toward, at this moment.

I believe that the fundamental problem which exists is a matter for Congress and the courts, because this misuse, as I call it, of the brand name privilege is a situation which came about because of a series of judicial decisions which extended the meaning of laws. This goes back to the *Upton* case in 1869, and to the best of my knowledge, Congress has never given a monopoly in law to any company to use a coined name, a noun, as a private product name.

Congress has given a monopoly in the use of a copyright name which identifies the manufacturer, but starting back in 1869, the courts have extended by interpretation the monopoly that is vested in a private product name, and I think this is the problem, and I don't think the medical profession has any power to handle this other than to come before Senate and House committees, as we are doing, and asking that this situation be remedied.

Senator NELSON. Yesterday, Dr. Williams of Emory University, testified along similar lines to what you have been saying. He pointed out that the American Medical Association did what he thought was a splendid job in this field of identifying drugs, informing the physician about their effect some 15 years ago, and that it was his judgment that it was beyond its capacity now, because of the great multi-

plicity of drugs that have come onto the market. Is that what you are saying about the lack of the power of the AMA?

Dr. GARB. No, sir.

Senator NELSON. I think I am quoting him roughly correctly.

Dr. GARB. Yes, I heard that part of his testimony, Senator. I would say that I agree with him in part. I think that the AMA could probably do more than it is doing, but I think we could say this about anybody or any group.

However, I don't think that the AMA has the power or ever had the power to recitify the present situation in relation to these brand names.

Senator NELSON. I wasn't really referring to that. I was referring to the fact of furnishing information to doctors.

Dr. GARB. The AMA is doing a good job on that. They have been improving considerably over the last few years. They now have a feature which I find most helpful, a short one or two page summary of new drugs as they come out, I think they are probably doing as much as they can do in this particular area.

Senator NELSON. You were here yesterday during Dr. ——

Dr. GARB. During most of Dr. Williams' testimony.

Senator NELSON. He spoke also about the tremendous dimensions of the problem, and again his testimony speaks for itself so I hope my paraphrasing doesn't distort it. But to summarize what I understood him to say, he thought that the Government, through various ways, should test drugs, to do it by contracting, but in any event, it could test the drugs chemically. It could contract for clinical tests in addition to the chemical evaluation of the drugs. That it could out of all of this prepare what in effect would be a national compendium I suppose, which listed all the drugs generic and trade name, and listed the side effects and composition and the use of the drug, and as I understood him to say, he thought that was an absolutely necessary thing to do, that it would cost a considerable amount but it was necessary to do for the good practice of good medicine, and that it ought to be done, and that he thought the Government was the only one that could do it. Now I think I have roughly summarized it.

Dr. GARB. This was my impression of his testimony also.

Senator NELSON. Do you agree with that?

Dr. GARB. 100 percent, absolutely.

Senator NELSON. Thank you.

Senator HATFIELD. I would like to pursue with you this thought for a moment. If I understand you correctly, you do agree with Dr. Williams and others who have testified that there has been on the part of some physicians misprescribing and ill effects that have come out of that. It could be classified as lack of understanding on the part of the physician, ignorance and other such matters relating to certain drugs.

You also testified I believe today that you are a counsel, you are a consultant to the AMA.

Dr. GARB. Consultant.

Senator HATFIELD. I understand also from your testimony today that you feel that this is a problem that is far too large and complex for the profession alone to handle.

Dr. GARB. It is not simply that it is large or complex, Senator. I don't think that a private organization of citizens has the power to

change laws. That is the point. I think that the problem here lies in the way the law has been interpreted by the courts, and I think that this has to be corrected first.

Senator HATFIELD. But don't you agree that there are professional responsibilities?

Dr. GARB. Yes, sir.

Senator HATFIELD. In helping to find a satisfactory change in that law.

Dr. GARB. Yes, sir.

Senator HATFIELD. If this be so then, why has not the American Medical Association indicated some interest by appearing before this committee or indicating involvement of their profession in seeking the proper solution to this?

Dr. GARB. Well, I don't think I ought to try to interpret motivations of other people, Senator. I don't know why the AMA does a lot of the things that it does. I am a member of the AMA, but I am just one member, and I don't form their policy. I think this is a question which they ought to answer directly. I wouldn't want to guess as to why they do or do not do certain things.

Senator HATFIELD. What is your particular area of counsel in the area of pharmacology?

Dr. GARB. Sulfonamide drugs.

Senator HATFIELD. Have you counseled the AMA along this line, in your role as a consultant?

Dr. GARB. Yes. What they do is this. They prepare a book which comes out every year on new drugs, and this is a very useful book for the physician, telling him about the characteristics of new drugs, and so forth.

In preparing it, they take the information which is submitted by the manufacturer and they mail it to various consultants in the country, and they ask us to read it over and make comments. Do we think the information is clear? Do we think that the information holds together? Is it consistent with what we know about the group of drugs as a whole, and so on?

For example, I got a stack of literature about that thick on some new sulfonamide drugs and I sent back a list of comments that I believed that the manufacturer's claim was not substantiated for various reasons, and so on.

But the area—and there are many consultants for the AMA council on drugs—the area in which we are consultants is the technical one, not policymaking. Nobody has ever asked me about policies, and I have never discussed policy with any official of the AMA. I have no way of knowing why they make the decisions that they do.

Senator HATFIELD. Do you think it would be helpful to this committee to have the counsel of the AMA on this problem?

Dr. GARB. I certainly do, sir, and I think——

Senator HATFIELD. Do you think it would be in keeping with the standard, or rather, the objective of improving standards of practice that the AMA has as part of its responsibility that it should be here and represented here in these hearings?

Dr. GARB. I had assumed that they were going to be here.

Senator NELSON. They will be. The AMA representatives will be here. We have been discussing it with them.

Dr. GARB. I think probably he will be able to answer your questions much better than I could possibly guess at the answers.

Senator HATFIELD. The point that I would like to make very clear though in my own thinking this morning with you, Doctor, is that you have stated these matters to us and other doctors have likewise as individuals, as individual practicing physicians or teaching physicians.

I am concerned that, from the professional viewpoint or from the viewpoint of the profession itself, we get the fullest and complete counsel. I think it is very important to have your views as individuals—you have been most helpful—but I should believe and hope that the profession would assume more responsibility than you indicated that you think the profession has thus far assumed in this problem.

I cannot agree with you that the profession, even though technically it may not be empowered as a private association to act upon the problem, I believe that from a professional viewpoint, the profession should be intimately involved in all this, because it does involve the profession and its practice and its relationship to its patients and all the other things that go with professional life, and I would feel that the profession should be the first in line to initiate action, to counsel action, especially where it does not feel it is empowered to act, rather than standing off and asking to be invited.

Dr. GARB. Well, sir, I can understand your point of view, but I am afraid I can't quite agree with it, knowing how busy doctors are, how they practice, how they relate to their various associations, and so on.

Senator HATFIELD. But they were much in evidence in the halls of Congress during the medicare program and debate. They weren't reticent then to not appear here in these halls, so I am told. I wasn't here at the time.

Dr. GARB. Well, this is something which I think they had better explain themselves. In this area, in the drug area, there are so many complexities that I rather doubt whether the average practicing physician can keep up with them. It is becoming almost a full-time job just to keep up with the names, and realistically, I don't see how a democratically elected professional association can do very much, as an association, in an area of this sort. It seems to me it has to rest on individuals coming and testifying as individuals. I just can't see any other way of doing it.

Senator HATFIELD. I couldn't disagree with you more, and for this reason. Let me say it as a former professional person, as one in a profession. I think that when a profession recognizes a specific problem relating to its practice and its profession, and recognizes its own inadequacies or constrictions on its actions, it should take the initiative to move some way to solve that problem and to take the action to incorporate into the format those agencies that can be helpful to it.

You see the situation as it appears today to much of the public is that a committee of the U.S. Congress has intervened or has invaded or has injected itself into a professional matter. I think that this is unfortunate, because many times Government will tend to do this without any encouragement. On the other hand, there are many times when Government must do this because of the inaction of either the profession itself or that part of our society which should have taken action or should at least have raised the issue and asked for the cooperation and the partnership action of Government. In this in-

stance, you as physicians have come before us and you have told us that there have been inadequacies in your profession, you have told us there have been dangers to the people, to the patients because of these inadequacies, and because of this ignorance in the profession, and yet the profession has not done anything to my knowledge to try to correct this on a major base nor has it invited Government to help. We have initiated the action, and then in some instances some of these professional people come in here and criticize our chairman or other members of this committee or Government in general for having injected itself into a professional problem.

You see it creates the confusion and the difficulty that does not give real aid to solving the problem with the professional counsel and the professional partnership role that I would like to see.

Dr. GARB. I see your point, Senator. First of all, I do not think anybody could conceivably be justified in considering these hearings or any of the congressional activities relating to drugs as invasions of a professional prerogative.

To me this is an absolutely necessary thing which the Government must do to protect the health of the people. I think perhaps the area in which we may be seeming to disagree is not really disagreement.

You have used the term profession when I suspect you probably mean professional association. To me the medical profession consists of the doctors of medicine, whereas I think you are using the term to refer to the official professional association of those doctors, and I distinguish between the two. You are speaking, I think, of the AMA, are you not?

Senator HATFIELD. Well, I would not restrict my comments merely to the AMA, but I believe that where you have a professional society or a professional organization which has a large staff or at least has a staff to research problems and expresses the thinking of the individual doctors through composite action, that this can be used interchangeably, because I know that many physicians do expect their views to be expressed through their professional association.

Dr. GARB. Well, in this area it would be difficult, not impossible, but very difficult to determine what a consensus of opinion of the practicing physicians in the country would be. I don't think, for example, that I would have any right to say that I am speaking for anyone other than myself, and people whom I know agree with me.

I doubt very much if the average practicing physician has had the time or the opportunity to look into this problem to the extent that those of us who are professors have had, and in a democratically elected organization you have to go by what the majority are concerned with. So I don't feel that I have any right even to make guesses as to why the association or any other group of physicians do or do not do certain things. I think that they ought to explain that for themselves.

Senator HATFIELD. I don't want to press the point too far, but let me just say as a former Governor I recall many times when we had problems that confronted us at a State level that involved the medical profession, and we had every reason to expect and we did receive counsel from the medical profession acting through its own societies, and we gained their cooperation.

We had their active role participating in solving these problems, and I came to expect this because they performed, always performed

in a most notable and credible way, and I am just concerned that we work with them.

I am not here criticizing the doctors. I have great faith in them. I only want to see an active role on the part of the profession, acting through any channel or mode that it wishes to act through, both as individuals as you have appeared here, but also as a profession, because we need their counsel and we must have it, and I think they should be just as concerned about this problem as we who are political officials are concerned. In fact, they should be the first to be concerned, because they are most intimately involved and most technically qualified to counsel on this problem. That is my point.

Dr. GARB. Well, I hope it turns out that way.

Senator HATFIELD. You sound very, very encouraging this morning.

Dr. GARB. But again I would just have to wait and see what they say.

Senator HATFIELD. All right. Thank you.

Senator NELSON. I would like to interject for just a moment. We have had here, as you well know, in addition to yourself, a number of very distinguished authorities in the field of pharmacology and clinical medicine. They have all, without any exception that I recall, generally stated that there is great confusion in this field, that something ought to be done about it, and that it is a very serious matter.

I would like to say first that I am inclined to agree with Dr. Williams' testimony yesterday, and your endorsement of it, that it is a problem that needs to be dealt with at some central level. I don't think, for example, that it is a problem you can blame the drug industry for.

I am told there are a thousand or two who manufacture, at least several hundreds competing with each other, and under the law they have got to add some name to their drug. That is their responsibility, so there isn't any way for an individual company, and it is unrealistic to expect, the group to get together and settle this problem. In fact, they don't have the legal power to settle it. Fifty of them might agree on what the answer ought to be and then you would have 50 competitors who wouldn't agree and the confusion continues.

So I think that is the nature of the problem, and that is the reason for these hearings. It needs a careful evaluation. We need the best testimony of all the people who are involved, the medical profession individually and as an organization, the drug companies, the pharmacists, the retail druggists, independent professors and teachers in the field and that is what this hearing aims to do: to get the best information we can from all of these people.

I think I should clarif y one point. The AMA as such or any professional group related to the AMA, has not asked to testify. Whether it would be appropriate at this stage or not I am not prepared to say, but none of them has asked to testify. I may have interjected a confusing note when I said we were discussing it.

What has happened is that Dr. Annis, former president of the AMA, wrote a letter to his Senator in which he said that he wanted to testify. This was as an individual. We weren't prepared to put him on forthwith as he desired because of our schedule. I was advised yesterday that he has now said he would come as a representative of the AMA. I guess he is on the board. So that is the only note I have received from them. It was after Dr. Annis requested to appear as a

private individual and he subsequently said—he didn't tell me, he told a staff member of one of the Senators—that he would appear then as a spokesman and representative of the AMA. Of course, at some stage he will be scheduled.

However, on the point you made about the responsibility of the organizations, Dr. Thomas Hayes is secretary of the Council of Drugs of the AMA. The AMA has over the years, I believe I am correct, been one of the advisory groups to the Pharmacopeia, and they furnish the professionals who spend the time to decide what drugs should be approved for inclusion in the Pharmacopeia.

So I think if they are prepared to do that, they ought to be prepared to give advice on what ought to be done about this very difficult and confusing problem, and I assume that perhaps they are. Certainly we will request that the head of the Council on Drugs and anybody else that AMA wishes to send to appear and give us the benefit of their knowledge which I am sure is considerable.

Dr. GARB. I hope that this will be helpful to you. I would want to make a distinction between general advise which of course the Council of Drugs or any other person or group could give just in answer to a question, and the kind of advice they have been giving the Pharmacopeia Committee is largely in the nature of technical advice.

Senator NELSON. We have a rollcall and we will recess. If something doesn't follow immediately we should be back in 15 minutes.

(Recess.)

Senator NELSON. We will resume the testimony of Dr. Garb. There will be another rollcall within the next 30 minutes. At that time we will recess for lunch. Hopefully, we will be able to finish Dr. Garb's testimony so we will not have to hold him over.

Go ahead.

Dr. GARB. Let us return to the three ways of prescribing. The proper way—a combination of generic and manufacturer's name would, of course, be the best. If, however, I am asked to choose between the other two—simple generic prescribing or private product name prescribing, I must choose generic prescribing as being the lesser of two evils.

I am quite familiar with the drawbacks, real and imaginary, to generic prescribing. I have heard that generic-name drugs are sometimes made in bathtubs, garages, and basements.

Senator NELSON. Is it not true that you could add a trade name to that?

Dr. GARB. Yes, sir; and it is quite true that if generic-name drugs are made in bathtubs, garages, and basements, so may private product name drugs be made in the same places.

Senator NELSON. I just wanted to make the point very briefly that the witnesses come here and they make all the arguments that are made about generic drugs and they fail to say every single argument can be applied to a brand-name drug.

Dr. GARB. This is absolutely true, sir. I am not saying that the drugs are made there. I am saying that I have heard claims that they are. I am not a judge of the accuracy of the claims.

If this is still so and if these claims are correct, then the FDA has the power to correct it and should do so promptly. I have heard that generic drugs are not subject to the same quality controls as private product name drugs, and that generic drugs are of erratic potency and sometimes pass through the patient without being absorbed.

Senator NELSON. May I interrupt again for a moment.

It is correct, is it not, that many of the major, perhaps all of the major drug manufacturers make generic drugs too?

Dr. GARB. To the best of my knowledge, it is correct for most of them. I do not know about all of them. In fact, many of them make the drugs in bulk lots, and then sell them to small packagers.

Senator NELSON. I just want to point out that this criticism of generic drugs, I suppose, goes across the board. I do not quite accept the criticism, but if it does, it goes across the board for little generics, big generics——

Dr. GARB. Yes, it certainly does. Any criticism that applies to generic drugs could be just as——

Senator NELSON. Or to put it another way, if the quality control is not of a high standard it does not make any difference whether it is a generic or trade name drug or a big company or a little company, the result is exactly the same?

Dr. GARB. Exactly. I cannot judge the truth of these accusations which have been leveled at generic-name drugs. However, since a doubt has been raised about the purity and potency of generic drugs, that doubt should be settled at once.

After all, many patients today are receiving generic drugs. They are entitled to a wholesome, pure, effective and safe product. There is absolutely no excuse for having anything else on the market. The solution is inspection—not inspection 1 day out of every 2 years, which is the current approximate rate, but continuous inspection every day.

Senator NELSON. I assume that if you had adequate inspection, whatever that consists of, that that would be beneficial not only to the user of the drug, but to those manufacturers who had adopted the highest quality and most sophisticated standards, would it not?

Dr. GARB. Absolutely, sir.

I would say that I would look with suspicion on any manufacturer who was reluctant to have his product or his factory under continuous inspection.

Here is a label from a can of Ken-L Ration dog food, and there is a statement saying "Packed under continuous inspection of U.S. Department of Agriculture," I would like to submit this as a piece of evidence.

(The label referred to follows:)

Ken-L RATION

NET WEIGHT 15½ OZ.

Packed Under Continuous Inspection of U.S. Dept. of Agr.

Ken-L RATION

A NORMAL MAINTENANCE DOG FOOD

for variety

4 KINDS OF KEN-L RATION

Vary your dog's diet by feeding all 4 kinds of nutritionally balanced Ken-L Ration . . . it's Government Inspected.

Feed hearty **Hash**—savory **Liver Flavor**—succulent **Stew**—and delicious **Regular** Ken-L Ration. These 4 tasty varieties keep dogs eating well and in top condition.

REGULAR LIVER FLAVOR

STEW HASH

HOW TO FEED: Feed Ken-L Ration (all four varieties) according to age, size and activity of your dog. A mature 20 pound dog requires about 1 can to 1½ cans daily. Feed at room temperature.

WE GUARANTEE:

YOUR MONEY BACK WITH A SMILE IF YOU ARE NOT SATISFIED

GUARANTEED ANALYSIS Per Cent

CRUDE PROTEIN	Not less than 10.0
CRUDE FAT	Not less than 3.5
CRUDE FIBRE	Not more than 1.0
ASH	Not more than 4.0
CALCIUM (Ca)	Not less than 0.5
PHOSPHORUS (P)	Not less than 0.3
SALT (NaCl)	Not more than 0.5
DRY MATTER	Not less than 26.0
MOISTURE	Not more than 74.0
VITAMIN A	Not less than 600 U.S.P. Units per pound of Feed
VITAMIN D	Not less than 150 U.S.P. Units per pound of Feed

INGREDIENTS: Meat By-Products, Horse Meat, Soy Grits, Mule Meat, Heat Processed Soybeans, Oatmeal, Cracked Barley, Cracked Milo, Horse Meat By-Products, Mule Meat By-Products, Iodized Salt, Torula Dried Yeast, Dehydrated Alfalfa Meal with added Chlorophyllin, Onion Powder, Choline Chloride, Garlic Powder, Vitamin A Supplement, Irradiated Dried Yeast, Sodium Nitrite, Water sufficient for processing.

MFD. BY THE QUAKER OATS CO. CHICAGO, ILL.

Dr. GARB. Seven years ago I asked why we could not have the same safeguards for drugs that we have for dog food. Thus far, I have not received a satisfactory reply. Some drug company officers with whom I have discussed this problem have told me that inspecting drugs is much more complex and expensive than inspecting dog food. I am sure they are right. However, many companies today say that they have superior quality control inspections of their products.

If a drug company can make such inspections, why can't the U.S. Government?

I have also been told that the cost of continuous inspection would be astronomical. I cannot see why. Most drugs which are produced in this country today are being inspected by inspectors hired and paid by the manufacturers, and the costs are included in the price of the drugs. If we had continuous Government inspection, the costs should not increase, although they might come from a different pocket. But in the long run, the cost of inspection would still be paid by the person who uses the drugs.

I am convinced that there is no place for any kind of substandard drugs, no matter how they are named, anywhere in America, and I hope that prompt steps will be taken to eliminate this problem. I think that we ought not have any patients harmed by substandard drugs, and I think we ought not have any patients or any doctors with any misgivings or anxieties about whether the drug they are getting is a pure, potent, wholesome drug or not. When we sit down to eat some meat, we do not start to worry about whether the meat is wholesome or not. If it has been inspected, we are sure it is.

I think we ought to have the same safeguard for drugs. Indeed, we ought to have more safeguards for drugs.

The patient who is sick is a worried person. He ought not have the added worry about whether the drug he is getting is pure, wholesome, potent, and effective. He ought to be sure of it, and it seems to me that inspection, continuous Government inspection, the same kind that we have for dog food is the sort of thing that we need.

I have also been told that preparations of the same drug may differ in more than 20 ways, and that the physician is the person who can best judge which preparation is best for his patient. There is an element of truth in this assertion, but it is greatly exaggerated. If a physician prescribes digitalis leaf, it is advisable not to change brands except by plan. This is one of the areas in which there is an element of truth.

Also, about 10 years ago, one manufacturer, Wyeth, marketed a preparation of Salk polio vaccine which had no detectable penicillin in it. Other preparations of the vaccine contained penicillin, and therefore were dangerous for patients with a penicillin allergy. Under those circumstances, it is perfectly proper for the doctor to prescribe a particular manufacturer's product, and it is conceivable that such situations could arise again.

Senator HATFIELD. Senator Nelson, on this point that you are making now relating to the need for continuous inspection, and you use the corollary in the food field of dog food or food for human consumption, will this get to the problem of potency and efficacy, or will this be more in the line of purity and safety?

Dr. GARB. Purity, wholesomeness, and cleanliness.

Senator HATFIELD. Yes.

Dr. GARB. And potency in terms of active ingredient being what it is supposed to be.

Senator HATFIELD. Labeling?

Dr. GARB. Yes, not necessarily in terms of therapeutic potency.

Senator HATFIELD. No.

Dr. GARB. Questions of therapeutic potency will require another approach.

Senator HATFIELD. Do we have evidence or do you have evidence or any knowledge of drugs that have been used and have created illness or other ill effects due to the improper handling in the manufacturing of such drugs related to purity or cleanliness or wholesomeness?

Dr. GARB. Oh, yes. Recently many batches of drugs were recalled because they were contaminated with penicillin in the manufacture. That is, the machines making the tablets or vials had been used for penicillin and there were residues of penicillin around and they got into other medications.

Also, there have been recalls because small amounts of hormones got mixed in with other drugs. This is a common problem. You see, here is another problem that comes up, Senator. When we hear about a recall of a drug, we have to remember that that drug was probably not recalled until a large number of patients had already taken it.

Senator HATFIELD. They had evidence?

Dr. GARB. Sure.

Senator HATFIELD. That there was some ill effect?

Dr. GARB. It reminds me of a joke that we had as children.

"What is worse than biting into an apple and seeing a worm?" The answer is "biting into an apple and seeing half a worm."

I think the worst thing for a patient is to have taken a drug and then hear that that drug has been recalled, and then have to worry about what has happened to him.

Senator HATFIELD. Do I understand you then to say that manufacturers do not have sufficient quality control programs within their own structures?

Dr. GARB. Some do and some do not, but I have no way of knowing which do and which do not.

Senator HATFIELD. You have no way to identify except by the evidence of those manufacturers which have had to recall certain drugs?

Dr. GARB. Yes, but unfortunately, even the biggest and the best manufacturers have had drugs recalled, so this leaves me without clear-cut guidelines.

Senator HATFIELD. Do you know of any of them who have had to recall their drugs who have had quality control within their organization?

Dr. GARB. Yes, sir.

Senator HATFIELD. In other words, their quality control program did not prevent such drugs reaching the market?

Dr. GARB. That is correct, sir.

Senator HATFIELD. Was this an inadequate quality control of the human factor, or if Government had been in the picture on continuous inspection, would it possibly have been prevented?

Dr. GARB. This is a little difficult to answer. I do not know if it would have been prevented by Government inspection or not.

Some of these things probably would have been prevented and others probably would not. I do not think I could make a generalization there.

Senator HATFIELD. I think to be fair, as you know, we have had instances where certain food products have created ill effects upon the user, and they have been taken off the market, and in such instances there has been a quality control program on the part of the manufacturer, and there has been also in some of these same instances governmental inspection. But it slipped by both, so to speak, and so that we do not really have a complete blanket guarantee on that. Would you feel that by requiring a quality control program, it would receive the approval of FDA or some other agency of Government, it would be part of the private manufacturer's own organization, and that that would be sufficient?

Dr. GARB. I would not worry about who actually paid for it or how it was arranged as long as I was sure that there was some reasonable quality control.

Now, nothing is perfect, and I realize that things do slip by, and I do not want to leave the impression that I believe we have a lot of bad drugs on the market. I do not know.

My point is that I do not know and I do not see how any physician can possibly know what percentage of the drugs on the market are perfectly pure and satisfactory and what percentage are not.

There has been a challenge raised. The challenge has been raised to the effect that there are some small manufacturers who do not do a good job.

I just want to be sure that no member of my family and no patient that I have anything to do with ever gets these.

Well, how do I make sure?

There is no way we can do this in the absence of some kind of quality control. Now, I am not an expert on the mechanics of quality control inspection. I would simply take the word of somebody who is.

Senator HATFIELD. But you are not recommending that it specifically must be a governmental type of quality control supervision or involvement?

Dr. GARB. No, I am not recommending that specifically. It could be arranged with a Government inspector in the plant or it could be arranged with an inspector whom the Government approves or it could be arranged any other way.

I do not know enough about the details of quality control to make a recommendation as to the exact way it should be done. But I would like to have stamped on every bottle or box of medication the same sort of thing that is stamped on the cans of dog food.

Senator HATFIELD. Continuous Government inspection?

Dr. GARB. Yes, sir, it is Government inspection, but as I understand it, the meat companies pay for that service by the Government.

Senator HATFIELD. What about the Good Housekeeping stamp of approval; would that be helpful, do you think, that type of thing? I am not being facetious here.

Dr. GARB. No, sir, it is a very sensible point actually. I would not accept the Good Housekeeping seal of approval.

Senator HATFIELD. This is merely an example.

Dr. GARB. Yes, but I would accept the AMA seal of approval.

Senator HATFIELD. Aha, we are back to the AMA again.

Dr. GARB. We are back to the AMA again.

Now, unfortunately, the AMA gave up its seal of approval program years ago, which I think was a dreadful mistake.

Senator HATFIELD. That is what I am trying to get at, Doctor. It seems to me that we have to get a believable——

Dr. GARB. Exactly.

Senator HATFIELD. A believable stamp of approval.

Dr. GARB. Yes, sir.

Senator HATFIELD. And to me the word "Government" in itself does not necessarily answer all these problems.

Dr. GARB. I like that word "believable." I think that is a fine word and I like it very much.

Most of the time, however, the differences between drugs of different manufacturers are not apparent, or are trivial.

For example, what are the differences between Miltown, Equanil, and meprobamate sold by McKesson? If there are differences, how does the doctor find out about them? They are not described in the medical journals, in medical textbooks, or in PDR. How does the doctor decide which of these preparations is best for his patient?

What I am getting at here is that we are told that one drug may be put up in a somewhat different size of granule, that it may have more sugar in it than another drug, that it may be ground up a little differently, et cetera, and that only the physician can tell which of these drugs is best for his patient.

Well, I have heard this argument now for about 7 or 8 years, and so I began to wonder about it, and I have asked the question, how does the physician find out, and I have not been able to find out any way. There is no way to find out, unless perhaps if you write to the company's main offices directly. I have here, for example, a series of the package stuffers that are used for drugs.

These are supposed to contain all the pertinent information about the drugs. These are supposed to be the most complete thing which the doctor gets, more complete than any ad, for example.

I have here the one for Miltown and for Equanil, both of which are meprobamate. They do not tell you anything about which pill has more sugar in it or which pill has different size granules or anything else, and in fact I have a whole stack of these package stuffers, and none of them tell you this. So I do not see how this argument can apply.

It seems to me that if any group of drug manufacturers wish to use the argument that their brand name drugs are better because of certain differences, and that the doctor knows what these differences are, they should show how the doctor finds out these differences. They should be required to put those differences in writing in these package stuffers.

I have some of these here, if anybody would like to check them.

Senator NELSON. The trade association claims there are 20 to 30 ways in which one drug is different from another. Is it not likely that in whatever ways they differ, if they meet Pharmacopeia standards, the difference does not really make very much difference?

Dr. GARB. I think the differences are trivial, but my point is I do not know that they are trivial, because I cannot find out what they are. I have never been able to find out what the difference is between one brand of the drug and another brand of the drug.

Senator NELSON. Then if you cannot find out and have made a conscientious effort, can you tell us how a busy practicing physician can find out?

Dr. GARB. I do not know. Perhaps he can find out if he writes to the home office of the company and asks them, maybe they will tell him.

Senator HATFIELD. A trade secret?

Dr. GARB. I think it may be a trade secret in some cases actually, but I am not familiar enough with manufacturing processes to tell. All I know is that none of these package stuffers have ever told me what percentage of sugar is involved or what kind of sugar they use as the excipient to bind the active ingredients in the pill or anything else.

Senator NELSON. And whether it makes any difference?

Dr. GARB. I do not think it could make much difference, because after all, how much sugar can you get in a little pill?

I do not think it could make much difference, but I would not want to say definitely that it does not, since I cannot find out what it is in the first place.

Senator NELSON. The U.S. Pharmacopeia lists several hundred drugs, all of which have been on the market for their various physicians, pharmacists and pharmacologists to decide that it is a drug of therapeutic value. Then they establish in the Pharmacopeia standards for that drug to meet, whether it is a generic, one of a dozen trade names, and then they stand behind that as certain that there is not any difference, that the therapeutic clinical result is the same, that the differences are of such insignificance that you can use them all.

Dr. GARB. I see no reason to question the U.S. Pharmacopeia's statement on this at all. I would say that the burden of proof should rest on anybody who wishes to disagree with their statement.

Senator NELSON. Thank you.

Dr. GARB. I have also been told that with generic prescribing, the decision on which manufacturer's product to use is left to the pharmacist, and that the pharmacist may choose an inferior product. I cannot understand why a pharmacist should be considered less competent or less reliable than a physician in terms of choosing reputable manufacturers and good products. I had understood that pharmacists were the best trained persons in this field.

In this connection, I would like to quote an editorial by George P. Provost in the American Journal of Hospital Pharmacy, volume 24, March 1967, page 103. He says:

> To claim that pharmacists are not capable of selecting quality brands is to imply that physicians know more about pharmacy than do pharmacists and that pharmacists have gone to school 5 years for naught. Traditionally, pharmacists have compounded prescription medications and have dispensed generic prescriptions for codeine, phenobarbital, digitalis, and many other drug products. The inference that the ancient and honored profession of pharmacy now has so many unethical or incompetent practitioners that it cannot be relied upon is indeed disturbing.

And here is a copy of this editorial.

(The editorial referred to follows:)

[From the American Journal of Hospital Pharmacy, vol. 24, March 1967]

THE AMA AND GENERIC PRESCRIBING

(By George P. Provost)

The House of Delegates of the American Medical Association, at its meeting in Las Vegas, November 28–30, 1966, reaffirmed AMA's policy that physicans should be free to use either generic or brand names in prescribing and encouraged physicians to supplement medical judgment with cost considerations in making this choice. The action was taken as a result of a recommendation by the AMA Board of Trustees, whose report stated:

"The issue of cost is not simply a matter of prescribing drugs generically as opposed to brand name prescribing. Often there will be substantial variations in the cost of the same drug marketed under different brand names by a number of reputable manufacturers. However, generic prescribing alone will not assure that the least costly brand will be dispensed or that the savings will be passed on to the patient. Nor will generic prescribing alone assure the physician that his patient is receiving the product of a manufacturer in whom he has confidence . . .

"The attending physician should not delegate this choice—that is, he should not prescribe generically—unless he is convinced that he can rely upon the quality and purity of the drug that will be dispensed to his patient. If this is not the case, then the physician himself should designate the source of supply by prescribing by brand name or by adding the name of his choice of supplier to the generic name of the drug . . . .

"If medical considerations lead the physician to the conclusion that he can safely delegate the choice of supplier to a pharmacist, a hospital formulary committee or some other third party, he does not abrogate his responsibility to protect the economic as well as the medical interests of his patient . . . Thus, in choosing to prescribe generically, the physician should be assured that whoever actually make the choice of supplier can and will take into account not only the medical needs of his patient but will protect the patient's economic interests as well."

Unfortunately, but perhaps not entirely unrealistically, AMA's position is based largely on distrust or lack of confidence or understanding in the ability of the pharmacist. The selection of a brand of a drug is, after all, more of a pharmaceutical than a medical judgment. Drugs become *pharmaceuticals* after they are put into dosage forms. Physicians are trained in *drug therapy* but not in the area of *pharmaceuticals*.

The hospital pharmacist and the physician practicing in the hospital can take comfort in the fact that the Pharmacy and Therapeutics Committee, referred to as the hospital formulary committee in the AMA report, can "take into account . . . the medical needs" of the patient and "protect the patient's economic interests as well." This is one of the main reasons for its existence. Indeed, the AMA has endorsed the hospital formulary system by its approval of the Statement of Guiding Principles on the Operation of the Hospital Formulary System. According to the Statement, "The pharmacist, with the advice and guidance of the Pharmacy and Therapeutics Committee, shall be responsible for specifications as to quality, quantity and source of supply of all drugs, chemicals, biologicals and pharmaceutical preparations . . . ." The document concludes, "A hospital formulary system . . . is considered to be important in drug therapy in hospitals. In the interest of better patient care, its adoption by hospital medical staffs is recommended."

Hospital pharmacists operating under the formulary system are well aware that they have assumed full responsibility for the pharmaceutical quality of their products, those they purchase in finished form as well as those they finish in their pharmacies. If hospital pharmacists are not better prepared and more capable of assuming this responsibility than are physicians or nurses, there is little reason for having a pharmacist in a hospital.

Dr. GARB. Gentlemen, all the pharmacists whom I know are both ethical and competent, and I believe that they can be relied upon to dispense only wholesome, potent drugs.

I have also been told that generic prescribing will cause a shrinking of drug company research. I am heartily in favor of such research, but I believe that it should be rewarded by patents where appropriate, not by the present confusing and inequitable system.

Accordingly, I recommend that in any purchases of drugs from tax funds, whether direct or indirect, generic prescribing be made mandatory, with one stipulation. If the physician has reason to believe that a particular manufacturer's product is needed for his patient, he should be allowed to specify this by writing the manufacturer's name together with the generic name. However, under no circumstances should the private product name be acceptable as a substitute.

If this were acceptable as a substitute, we would be right back in the mess we are in now.

Doctors Azarnoff, Hunninghake, and Wortman, whose paper I have submitted, have made a similar recommendation. They say:

> Therefore we strongly recommend that all drugs be prescribed by generic name. In those instances where the physician feels a specific company's product is best for his patient, the generic name of the drug should be followed by the name of the company whose product he wishes. This appears to us to be a logical solution. After all, if a physician has determined that a specific manufacturer's product is best for his patient, he should at least know the name of the company.

I would also like to make a few comments on drug advertising. Since implementation of the Kefauver-Harris law, the grossly misleading ad has been virtually eliminated, and this is an important achievement of the Congress. However, there are still problems. The enormous volume of drug advertising and promotion is a force which tends to divert the physician from the best type of practice. It is also a major economic waste.

We have heard about the expenditures of the drug industry for research. We ought to remember, however, that the industry spends on advertising and promotion per year from three to five times as much as on research. I am referring only to the prescription drugs. That is, the drug industry spends three to five times as much each year on advertising prescription drugs as it does on its research.

Another comparison might be with medical education. The question of the education of the physician and the postgraduate of the physician was raised yesterday. A justification for this comparison is the repeated statements of drug industry spokesmen that their advertisements are educational.

Our medical schools graduate under 9,000 doctors per year, and expansion is slow because of the expense of educating a medical student—over $3,000 per year per student—which is only partly covered by tuition. Thus, we have a severe and growing shortage of physicians. If the money now being spent on drug advertising and promotion were spent on regular medical education, we could, as far as finances are concerned, graduate not 9,000 doctors per year, but over 50,000.

Of course, we do not have that many qualified applicants for medical school. I am not proposing that the drug industry subsidize medical schools. Indeed, I deplore the existing financial links between the industry and medical schools, however small.

I do, however, wish to point out that in the last analysis, the money being spent—and misspent—on drug advertising is money obtained from the sick American through excessive drug prices.

I raise this point here to give some notion of the amount of money being spent on drug advertising and promotion. The problem is not that the physician is uninformed. The problem is that the volume of advertising noise directed at him is so tremendous that it is very difficult to get anything else through.

I am not prepared at this time to suggest a remedy for the advertising expenditures. Hopefully, generic prescribing will help correct this problem. If not, it may be necessary for the Congress to scrutinize it again.

The reason I am hopeful that generic prescribing will correct the excessive volume of drug advertising, is that we have quite a few drugs still which are sold almost entirely under generic name, and the advertising for these drugs is well within reasonable bounds. It is not excessive. It is not inordinately expensive, and I am hopeful that if we have generic prescribing, this will in itself correct the overadvertising and overpromotion.

Senator NELSON. You made some comment in the latter part of the last page about deploring the existing financial links between the industry and the medical schools. In what ways specifically are they aiding financially, and what aspect of it do you think is not sound?

Dr. GARB. Well, there are actually many financial links between the drug industry and the medical profession, and I deplore all of them. I am in a minority here. I speak only for myself.

I am sure that most doctors and many, perhaps even most medical educators would disagree with me, but I think there is a principle involved.

I think when a patient buys a drug, and pays for it, he should not be taxed involuntarily to support anything else.

The financial relationship between the drug industry and medical schools is a rather minor and trivial one in terms of money, and it is not as objectionable to me as certain other things.

For example, every student, or almost every student, on reaching the second or third year of medical school will get a free doctor's bag with instruments and diagnostic equipment from a drug company. Well, now you can say "Why not?"

I think it is poor policy. Somehow or other it just does not seem right to me for drug companies to take money which they are getting from patients and turn it over to a medical student or a doctor. I think that the medical student should pay his own way through medical school or get a scholarship or a loan or something like that, but I do not think he should be supported by the sick people, except, when he becomes a doctor, by direct fees.

Now, this as I say could be considered minor.

Then we go a little further along the line, and we get into certain financial relationships which I think are absolutely abhorrent. We find, for example, that at many medical conventions free drinks and sometimes food are supplied by the drug firms. I think this is absolutely wrong and absolutely unethical.

I have heard the argument that it does not make any difference. "After all, do you really think any doctor is going to be influenced in

what he prescribes by the fact that we have given him a couple of free drinks?"

My answer to that is, "I hope not, but if giving the doctors free drinks and free barbecues and free parties influences their prescribing habits, then it is clearly unethical and wrong. If it does not influence them, it is a waste of the stockholders' money, or an overcharge to the patient on the price of the medication, and I just cannot see how any kind of moral society can accept this kind of an arrangement."

Doctors make a good living, and I do not see why they need any kind of charity.

Senator NELSON. That is another rollcall vote, Dr. Garb. We will recess until 1 o'clock. There will be another rollcall, I assume, another 40 minutes after this so we will resume at 1 o'clock.

Dr. GARB. I will be at your service, sir.

Senator NELSON. Do you have time to stay?

Dr. GARB. Yes, sir, I will be at your service.

Senator NELSON. We will resume at 1 o'clock.

(Whereupon, at 12:20 p.m., the subcommittee recessed, to reconvene at 1 p.m., the same day.)

AFTERNOON SESSION

Senator NELSON. We will resume the hearings. We will call Dr. Fitelson.

Dr. Garb, will you stay where you are?

Dr. Fitelson of the Fitelson Laboratories, Inc., of New York City.

Dr. Fitelson, we appreciate very much your taking the time to come here today. We thought we would ask Dr. Garb to sit there. He may have an observation to make or respond to a question or two, if you do not mind. Dr. Fitelson, you may proceed to present your statement which I see is very brief here, and I assume that you will want to present an explanation of the studies you made for the Medical Letter in addition to your statement; is that correct?

STATEMENT OF J. FITELSON, PH. D., FITELSON LABORATORIES, INC., NEW YORK, N.Y.

Dr. FITELSON. There will not be too much.

Senator NELSON. Go ahead and proceed.

Dr. FITELSON. I have a small food and drug testing laboratory in New York City. I myself am a Ph. D. in chemistry and my two associates have their master's degrees in chemistry. We have been in this laboratory now for some 16 years. Prior to that I was a chemist for the U.S. Food and Drug Administration, in New York City mainly. I was in charge of laboratories in New York for about 17 years.

As part of our work we test various drugs, and for the past years we have been testing drugs for the Medical Letter, which is a publication, a weekly publication put out by the Drug and Therapeutic Information, Inc., of New York City, which is a nonprofit organization.

The results of our findings have been published in various issues of the Medical Letter.

I might explain that our laboratories receive coded vials of tablets. We know what they are supposed to be; that is, prednisone or Miltown

or that type, but so far as we are concerned, we do not know whose tablets they are. They come in numbers or letters.

I understand that the Medical Letter obtains these tablets through various pharmacies, and then they repack them in these unlabeled vials, except for the code marks.

We follow the U.S. Pharmacopeia requirements and test exactly, wherever possible.

During the past 3 years we have made three series of tests. In 1964 we tested an antihistamine known as chlorpheniramine maleate. There we tested 20 samples of tablets from 20 different manufacturers.

The U.S. Pharmacopeia requires for this particular drug that first it shall contain that drug, and our tests showed that all of the samples did contain that drug; secondly, that the tablets disintegrate within a certain time limit, 30 minutes in this case, under certain specified conditions.

Senator NELSON. Was this the USP standard?

Dr. FITELSON. This is the U.S. Pharmacopeia standard, that when the tablets are shaken in water at a certain temperature in a certain way, they will fall apart completely within 30 minutes.

Senator NELSON. This is a test for this particular drug?

Dr. FITELSON. It is a test for a tablet.

Senator NELSON. A tablet?

Dr. FITELSON. The drug has nothing to do with it except that disintegration times may vary with different tableted drugs. In the case of this particular tablet, the U.S. Pharmacopeia requires 30 minutes as a maximum disintegration time.

Senator NELSON. For a different kind of tablet it may require——

Dr. FITELSON. Some disintegration times are more rapid, others are much longer. It depends on the tablet.

In this case all of the tablets complied with the U.S. Pharmacopeia requirement for disintegration time. The U.S. Pharmacopeia also requires that the tablets shall each have a certain weight within limits. The limitations vary with the size of the tablet. The smaller the tablet, the greater the percentage allowed because it is more difficult to maintain rigid limits there. The tablets did vary in size; some manufacturers prefer to put more excipient in the tablet so you will have larger tablets, with the same dosage of this drug.

Senator NELSON. But when you say weight, are you talking about the weight of the——

Dr. FITELSON. The weight of the total tablet, not the amount of drug in the tablet but the weight of the total table and the Pharmacopeia has certain ranges, and all of these 20 samples fell within those required ranges so far as the weight of individual tablets concerned.

Then we made the final test for assay, which is a chemical analysis of the amount of drug in the tablet. The Pharmacopeia has again a range limit for each particular drug. I do not recall what it is for this particular drug, but in most cases it is plus or minus 10 percent.

In other words, it may have 90 to 110 percent of the labeled amount of drug. In some cases it is a narrower range. In the case of chlorpheniramine maleate, all fell within the required range of the Pharmacopeia.

The results of this particular survey were published in the Medical Letter of February 26, 1965, on pages 18 and 19.

I might say that this Medical Letter, in addition to publishing my assay results, also publishes the price per 1,000 tablets.

Mr. GORDON. May I ask a question here?

I notice that the prices vary considerably, and the highest priced version of the drug had 101.4 percent of the active ingredient; that is, chlorpheniramine, and the lowest priced version had 103.7 percent.

Can you tell us if this has any significance?

Dr. FITELSON. No. They are both well within the Pharmacopeia limits in the first place, and then it is hard to believe that 1 or 2 percent makes any particular difference in a drug, particularly in a drug which is not a potent drug.

Mr. GORDON. So it is really not meaningful——

Dr. FITELSON. No.

Mr. GORDON (continuing). To say one is better than the other?

Dr. FITELSON. It is not meaningful at all. Anything within the Pharmacopeia limits is quite acceptable.

Sometime later we ran another series of tests.

Senator NELSON. You are going to a different drug?

Dr. FITELSON. Going to a different drug.

Senator NELSON. May I ask a question before you do?

Dr. FITELSON. Yes, sir.

Senator NELSON. These were the 20 companies——

Dr. FITELSON. Twenty different companies; yes, sir.

Senator NELSON. And all of them met USP standards?

Dr. FITELSON. That is correct.

Senator NELSON. Can it be concluded from that then that each of them had the same therapeutic value?

Dr. FITELSON. I am sure that is a correct conclusion, since they were exactly the same drug in all tablets, and the variations were not significant.

Senator NELSON. May I ask, this was not a test on all companies that make this drug, was it?

Dr. FITELSON. I doubt it. There must be others besides the ones we tested.

Senator NELSON. So do we have a situation where drugs meeting the same Pharmacopeia standards range in price from $1.40 for 1,000 tablets?

Dr. FITELSON. Per 1,000.

Senator NELSON. To $17.50 for 1,000 tablets?

Dr. FITELSON. That is correct.

Senator NELSON. Insofar as U.S. Pharmacopeia is concerned, they are of equal value as drugs; is that correct?

Dr. FITELSON. That is correct; yes, sir.

Senator NELSON. May I ask Dr. Garb a question?

Dr. GARB. Yes, sir.

Senator NELSON. As a physician, do you visualize that there would be any difference between these two drugs from a therapeutic value, or to put it another way, if you had this history before you and were to prescribe, would you have any hesitation about prescribing any one, regardless of the price here, for your patient?

Dr. GARB. I can see no reason to have any hesitation.

I would say that if anybody wishes to argue against the significance of this fine study, the burden of proof would have to be on them.

In other words, I think that Dr. Fitelson has produced concrete evidence that these particular drugs all fall within USP standards, and USP standards are more rigid than are absolutely necessary. They are not minimal standards. They are good standards.

He has here objective evidence that these drugs are equivalent. Now if somebody wishes to claim that there is some reason why they are not, I think the burden of proof ought to be on them, and they ought to come forward with objective evidence, not with testimonials and not with repeated claims.

I think this is the kind of thing that we have needed for years, objective evidence, and I am happy to see that we are now getting it.

Senator NELSON. This drug is in the USP, is it not?

Dr. FITELSON. Oh, yes, sir.

Senator NELSON. Yesterday Dr. Miller, testifying for the USP, said that all of the drugs in the USP are drugs with which there has been clinical experience, and again I am paraphrasing, I would not want to misstate it, but in any event they were satisfied therefore that the drugs that met USP standards were of equivalent therapeutic value, I think. Would you at least say that?

Dr. GARB. Yes. That is the reason why we have the USP. Otherwise, what good would it do to us to have a USP? It seems to me we have to assume that all drugs which meet USP standards are equivalent, and if they are not equivalent, I would like to know why they are not.

I know claims are made sometimes that they are not equivalent, and I have never been able to find out exactly why they are not, and here we have objective evidence that they are.

Senator NELSON. Are you satisfied that the kind of tests made by USP and the kind of tests made by Dr. Fitelson's laboratory, in terms of dissolution time and chemical contents and so forth cover the necessary spectrum of tests to give you some assurance that any one of them that meets this will have an equivalent therapeutic, clinical value?

Dr. GARB. I will put it this way.

The USP are much more qualified than I to select the tests which are pertinent. Dr. Fitelson has had much more experience than I in this area, and I would certainly rely on people like Dr. Fitelson and the USP and on their judgment as to which tests ought to be done. I have no reason to question their judgment as to which tests ought to be done. If these are the tests that the USP says ought to be done and Dr. Fitelson thinks ought to be done and they come out this way, I cannot see any reason to question it. If somebody has a reason, I think they ought to come forward and tell us exactly what the argument is.

Senator NELSON. So unless you heard a specific reason to the contrary, as a prescribing physician, you would be satisfied to rely upon the information furnished by USP or by this laboratory's tests in prescribing this particular drug from any one of the companies listed here?

Dr. GARB. Yes, sir.

Senator NELSON. Go ahead, Dr. Fitelson.

Dr. FITELSON. Our second survey was on meprobamate, of which Miltown is one, and here these were 400 milligram tablets, and there

were 19 different manufacturers' products tested. The U.S. Pharmacopeia has the same four tests for this product as it had for the chlorpheniramine maleate.

Senator NELSON. Which one is this?

Dr. FITELSON. Meprobamate or Miltown. It has the identification tests, the disintegration test, time for disintegration, the variation in weights of individual tablets, and finally, the assay of the amount of material in the product, and these tablets met all of the specifications of the USP. They are published in the Medical Letter of April 23, 1965, on pages 34 and 35. They also include the price, this table here includes the price per 100 tablets.

Shall I continue?

Senator NELSON. Yes, go ahead.

Dr. FITELSON. And finally, we recently made a test on prednisone tablets, these are 5-milligram tablets.

Prednisone is a rather potent drug and the U.S. Pharmacopeia, in addition to the four tests I mentioned before, has two additional tests.

One is a test related to foreign steroids. There are chemical compounds closely related to prednisone, which might be present, if the prednisone were not manufactured properly, and the U.S. Pharmacopeia permits up to 2 percent of such related foreign steroids. This is a special test, and none of the 22 different samples showed more than 2 percent of such related foreign steroids. They came within the Pharmacopeia limits.

Another special test on prednisone is a new one for this Pharmacopeia. The present Pharmacopeia is USP, Volume 17, which became effective September 1965, and at that time a new test was introduced entitled "Tablet Uniformity Test" or "Content Uniformity Test."

This does more than weigh each tablet. You must make a chemical test of each tablet to determine exactly how much drug is in that tablet. All of the chemical tests of the U.S. Pharmacopeia are really tests on composites. That is, we grind 20 tablets together, and then we mix it up and take a small sample for our chemical tests or assay.

In this new test you actually grind only one tablet, and use that whole tablet for the test to see exactly how much prednisone is in that tablet.

You also make what is known as the assay test, which is made on the composite of 20 tablets. On these individual tablets, the U.S. Pharmacopeia allows, permits not more than one out of 30 to show more than 15 percent variation from the declared amount.

On the composite it has a much narrower range. As I recall, it is 90 to 110 percent of the declared amount. This tablet content uniformity test is a very rigid test, and some years ago I recall running, oh, 7 or 8 years ago I recall finding quite a big variation in individual tablets, but these 22 tablets all complied with the U.S. Pharmacopeia test in all respects.

Senator NELSON. Did you only do one tablet for each company?

Dr. FITELSON. The U.S. Pharmacopeia requires testing 10 individual tablets for each company.

Senator NELSON. From the same batch?

Dr. FITELSON. Plus a composite.

In other words, you first take 20 tablets and mix them up, grind them, mix them up and run a test of that composite. Then you take 10 separate individual tablets and run each one separately.

Senator NELSON. How are the 10 individual tablets from the same company selected?

Dr. FITELSON. At random. I am given a vial of some 50 or 60 tablets to test and we pick out those 10 at random and run those separately, individually.

Senator NELSON. Is it known whether they came out of the same batch or not?

Dr. FITELSON. I presume they did because when they are purchased they are probably purchased out of one bottle.

Mr. GORDON. Although there are tablet variations within a bottle; that is, the tablets really are not identical, nevertheless, as I understand it, they are claimed to be therapeutically equivalent, are they not?

Dr. FITELSON. Oh, yes. The U.S. Pharmacopeia specifies a certain limitation on individual tablets as well as on the composite of the tablets, and they are all therapeutically equivalent so far as I know.

Senator NELSON. This was a test of 20 again, was it?

Dr. FITELSON. Twenty-two different pharmaceutical companies, and this is published in the Medical Letter of June 2, 1967, just a few weeks ago.

Senator NELSON. And you found that all 22 met USP standards?

Dr. FITELSON. All 22 met all of the U.S. Pharmacopeia standards.

Senator NELSON. And in this case, then, the price variation was from a low of 59 cents per 100 to as high as $17.90 per 100?

Dr. FITELSON. That is right.

Mr. GORDON. Dr. Fitelson, have you had any reaction from drug companies since this report has come out?

Dr. FITELSON. I personally would not have a reaction, since this comes through the Medical Letter. I do not know what reactions they have had.

Mr. GORDON. Did you want to comment, Dr. Garb?

Dr. GARB. I do have a comment.

This may illustrate one of the points I have been trying to make. According to this you will notice that the Merck product is $2.20 a 100, and the Parke, Davis product is $17.88 a 100. In other words, the Parke, Davis product is more than eight times as expensive as the Merck product.

Now here we have a fantastic spread. Both companies have good research programs. Both companies do promotion, et cetera. I would hardly think that anybody would ever complain that Merck is not as good or as reliable a company as Parke, Davis. Merck is selling this at one-eighth the cost of Parke, Davis, but how does the doctor know about this?

How does he even know that the two medicines are the same considering the way the names are confused?

In other words, if the doctor is thinking in terms of Deltra and Paracort, if he does not know they are the same material he may prescribe the more expensive one but if he knows they are both prednisone, if he knows that Merck's prednisone is one-eighth of the cost of Parke, Davis' prednisone, he would almost certainly prescribe Merck's prednisone all the way through. This is, I think, an excellent illustration of what happens when drugs are sold by private product name.

I am not saying that Merck is necessarily making a better prednisone than some of these other companies, but here you have two big companies.

Mr. GORDON. Upjohn is another, for $2.25.

Dr. GARB. Yes, there is Upjohn. I did not see them at the bottom of the list. There is Upjohn too.

Now I think this is a perfect example of how the confusion in drug names leads to a pricing structure which is not really a free market pricing structure.

Senator NELSON. That is a very good point. Did you have anything more?

Dr. FITELSON. No, sir. That completes the work I have done so far for Medical Letter.

Senator NELSON. How long have you been doing work for the Medical Letter?

Dr. FITELSON. Oh, for about 12 or 13 years on various products.

Senator NELSON. Does the Medical Letter have a continuous program of testing?

Dr. FITELSON. From time to time, they seem to get spurts. They decide to test certain drugs. I am now running a digitoxin survey for them.

Senator NELSON. I want to thank you very much.

Mr. COUGHLIN. Dr. Fitelson, I just have a few questions I want to ask you with regard to testing.

I notice on page 2 of your statement where you refer to the prednisone tablet test conducted, you were looking for various impurities. I would assume one of those impurities would be cortisone; is that right?

Dr. FITELSON. That is right.

Mr. COUGHLIN. Aside from cortisone, what other impurities were you looking for?

Dr. FITELSON. As I recall, the U.S. Pharmacopeia specifies each steroid to test for. I think it is hydrocortisone and cortisone. I am pretty sure they are. They vary with the steroid.

Mr. COUGHLIN. I also gathered from the first paragraph of your statement that you ran off chemical testing only; is that right?

Dr. FITELSON. I am a chemist; yes, sir.

Mr. COUGHLIN. And the results enumerated or enunciated on page 2 of the statement prove that prednisone tablets are chemically equivalent, is that right, as far as the steroid content is concerned?

Dr. FITELSON. Which are you referring to?

Mr. COUGHLIN. In other words, if you were conducting a chemical test, I assume on the basis of the conclusion you made on page 2 that you regarded the number of products tested as being chemically equivalent?

Dr. FITELSON. The prednisone you mean?

Mr. COUGHLIN. Yes; that is right.

Dr. FITELSON. Yes.

Mr. COUGHLIN. Now with regard to them being chemically equivalent as far as the steroid content is concerned, do these tests prove also that they are therapeutically equivalent?

Dr. FITELSON. I can only reason backwards.

If they all contain the same amount of drug, and if that particular drug is identical and is pure in each tablet, I can only assume all have the same effect.

Mr. COUGHLIN. Is there any way in which you would also test for therapeutic equivalency?

Dr. FITELSON. No, sir; I have no way of testing.

Mr. COUGHLIN. So this is an assumption you draw?

Dr. FITELSON. That is right, an assumption based purely on chemical tests.

Mr. COUGHLIN. Thank you.

I was also curious, Doctor. Are you affiliated with a hospital?

Dr. FITELSON. No, sir.

Mr. COUGHLIN. Thank you very much.

Mr. GORDON. These tests were based on USP standards?

Dr. FITELSON. We followed the U.S. Pharmacopeia test; yes.

Mr. GORDON. And is that not the assumption of the USP also, that if they fall within the USP standards, they should be clinically equivalent?

Dr. FITELSON. I think Dr. Garb is better qualified to answer that.

Dr. GARB. I will go further than that.

That is not only the assumption of the USP, that has been the assumption of the medical profession ever since the beginning of modern medicine. If you have a chemical on the one hand which is the same as the chemical on the other hand, and if they are not identical in their actions, there has to be a reason for it.

Senator NELSON. May I interrupt? You can complete your answer.

That is a rollcall. I am going to have to leave. I think that I have asked all the questions, but I want you to conclude your answer, and I want to say to both of you, I appreciate very much your coming here. The testimony of both of you is very valuable to our hearings and to this record. Thank you very much.

Dr. GARB. The conclusion of my answer is that if we cannot assume this, then we cannot practice any kind of rational medicine. We have to assume, for example, that a study which was done on phenobarbital 10 years ago still applies more or less to phenobarbital today, unless there is a reason for it being changed, and there can be reasons. There are changes, for example, in the antibiotics, as the bacteria adapt to them.

But this is a fundamental assumption in medicine, that unless there is reason given to the contrary, we must assume that an equivalent amount of a particular chemical at one time will do the same as the same chemical at another time.

Now, it is conceivable to be sure that there may be differences, but we have to start out on the assumption that there are no therapeutic differences when there is chemical identity, unless somebody comes forward with objective evidence to prove that there is a difference.

There have been a few rare cases in which differences have cropped up, but they were unusual situations in which a drug manufacturer used a particular chemical in the tablet, and in so doing he neutralized part of his active ingredient.

Mr. GORDON. That was calcium tetracycline?

Dr. GARB. That was some years ago; yes.

This was complete inadvertence, and not realizing this, the manufacturer added something else which neutralized the neutralizer, but by and large, unless there is objective evidence to the contrary, we must assume that a given chemical will do what that chemical is supposed to do, or else we could not practice any kind of rational medicine.

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

(Whereupon, at 1:45 p.m., the subcommittee adjourned, to reconvene at 10 a.m., Thursday, June 29, 1967.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

THURSDAY, JUNE 29, 1967

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

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

Present: Senators Nelson, and Long of Louisiana.

Also present: Benjamin Gordon, staff economist; Daniel T. Coughlin, minority counsel; Susan H. Hewman, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. The hearing of the subcommittee will resume.

Our first witness this morning is Dr. Leighton Cluff, professor of medicine, University of Florida. Doctor, the committee appreciates very much your coming here today to present your testimony. You may present it in any fashion you please, and speak extemporaneously from your statement or read it, elaborate on it, whatever way you wish. If you would, give a brief biography of your professional background.

STATEMENT OF DR. LEIGHTON E. CLUFF, PROFESSOR AND CHAIRMAN, DEPARTMENT OF MEDICINE, UNIVERSITY OF FLORIDA COLLEGE OF MEDICINE, GAINESVILLE, FLA.

Dr. CLUFF. I graduated from George Washington School of Medicine, took my house staff training, intern and residency training at the Johns Hopkins Hospital and Duke University School of Medicine. I had my research training at the Rockefeller Institute in New York. I then joined the faculty at Johns Hopkins University in 1955, and I rose in rank there until I became professor of medicine at the Johns Hopkins University in 1962. I was professor of medicine at the Johns Hopkins University until the summer of 1966, when I became professor and chairman of the department of medicine at the University of Florida.

Over the past few years, my major investigative interest has been in the epidemiological study of hospital acquired disease.

Senator NELSON. Of what?

Dr. CLUFF. Hospital acquired disease, and in the past 5 or 6 years one of my major areas of interest has been in the epidemiological study of drug usage and adverse drug reactions.

Senator NELSON. All right, Doctor. If you would, go ahead and present your statement.

Dr. CLUFF. I would like to read if I may, Senator Nelson, a very brief statement which summarizes the statement that I presume you have before you.

Senator NELSON. Yes.

Dr. CLUFF. I shall read this if I may. It is very brief, but I think it summarizes the position and interpretations that are predicated upon the statement that you have before you.

Senator NELSON. All right.

Dr. CLUFF. An important factor in the cost of drugs for the patient is the number of drugs consumed or prescribed as well as the cost of an individual drug. Drugs are used excessively by the public and are prescribed excessively by physicians.

Curtailment of excessive and indiscriminate use of drugs probably would have as great, if not greater impact upon expenditures for drugs as minor adjustments in drug prices.

A significant and lasting influence on drug consumption will occur only through changes in attitudes toward, and improve awareness of the uses and abuses of drugs by the public and medical profession. These changes could be fostered by development and use of educational media and by more judicious and rational drug advertising.

A cooperative venture by the Government, the pharmaceutical manufacturers, and the medical profession, providing for public education and medical education in therapeutics is needed.

Senator NELSON. I have some questions. It would be helpful if you would read your complete statement, Doctor.

Dr. CLUFF. All right, and perhaps you can interrupt me if you wish as I go along.

Senator NELSON. Yes.

Dr. CLUFF. The introductory comments are perhaps not pertinent because in essence I have already said that. This is largely biographical background.

While I was professor of medicine at the Johns Hopkins University, epidemiological studies of drug usage and adverse reactions to drugs were done on hospitalized patients during 1962 to 1966. These studies are now being continued at the Shands Teaching Hospital of the University of Florida. Observations made during these studies serve as the basis for this statement and are briefly outlined below. All of these statements are based upon the findings that I have obtained in my own investigative work.

Observations: (1) 4 to 5 percent of patients admitted to the medical service of a general hospital are found to have adverse reactions to drugs and 3 to 4 percent of all medical service patients are admitted because of illnesses caused by drugs. About 10 percent of patients experience ill effects from drugs while hospitalized.

Senator NELSON. What percentage of the patients who are admitted for adverse reaction to drugs, what percentage of that group could have avoided such reactions if the physicians prescribing——

Dr. CLUFF. You are asking for proportions and that is a difficult thing to give you exactly. I don't think there is any question but that some of these could be avoided by the more judicious use of drugs or at least the physician paying greater attention to ill effects that the patient had previously experienced. There are many examples of this which I could cite and I would be happy to do so if you wish.

Senator NELSON. I would like to have some examples, yes.

Dr. CLUFF. One patient that we have reported was a young pregnant woman being followed in the obstetrical clinic of the hospital. During the initial evaluation for her pregnancy she was found to have a urinary tract infection and for this she was treated with a sulfonamide drug. The urinary tract infection cleared but the lady developed a diffuse erythematous rash and the drug was discontinued and the rash subsided. The notation was made that the patient was allergic to sulfonamides.

Senator NELSON. Was this the way it read?

Dr. CLUFF. Yes. The patient was then followed through her pregnancy, had an uncomplicated delivery, but during the postpartum care she was found to have a urinary tract infection again. Because the patient was beyond the postpartum period and no further care was desired in the obstetrical clinic she was referred to the medical clinic in the hospital.

In the medical clinic in the hospital she was found to have the urinary tract infection as indicated, and the physician caring for the patient represcribed a sulfonamide drug. The patient this time developed a diffuse erythematous rash once more, a very high fever, passed blood in her urine, developed very severe hypertension, and was admitted to the hospital and subsequently died. She was found to have sulfonamide crystals in her urine and in her kidneys and diffuse vascular disease, undoubtedly a manifestation of allergic reaction to the sulfonamide.

The problem in this case was that in many hospitals, particularly the one where this study was done, on the initial occasion when the allergic reaction was found, the notation was made in the obstetrical clinic notes but the notes in this instance were kept in a separate part of the patient's chart. When the patient was seen in the medical clinic, the obstetric notes were not reviewed and in reviewing the facts the doctor was not aware she had an allergic reaction from the drug, nor had he inquired of the patient whether she had previous difficulties with sulfonamides.

I think this is a clear illustration of an avoidable situation where if there had been adequate notation the physician would not have represcribed the medication.

Senator NELSON. Yes, but that is really a case of carelessness in the medical history.

Dr. CLUFF. That is correct.

Senator NELSON. It is not a case of somebody being confused about drugs.

Dr. CLUFF. That is correct.

Senator NELSON. We have had testimony here from several physicians, pharmacologists, that one of the problems is that you end up with so many product names or trade names. We had a couple of specific illustrations of a patient who has had a bad reaction to some drug, and then gets another drug by another product name, the doctor not knowing that it is the same drug. That is quite a different case from one where the records are poorly kept.

Do you run into any problems like that?

Dr. CLUFF. Yes, but I think the problem, Senator Nelson, is equally the case not only with prescription drugs that the physician prescribes

but nonprescription drugs as well. I would like to cite an example of this, if I may.

Senator NELSON. Surely.

Dr. CLUFF. This is a man whom we had observed during the course of our studies, who was admitted to the hospital with a disease known as erythema multiforme, which is a peculiar skin disease associated with fever and glandular enlargement, and is known to be a common manifestation of an allergic reaction to a drug. One of the most commonly incriminated drugs in this instance is a constituent of laxatives commercially available, nonprescription laxatives.

Senator NELSON. What is that?

Dr. CLUFF. Phenolphthalein is the chemical substance that is a common constituent of many nonprescription laxatives. The patient was advised of the fact that he had an allergic reaction to this particular laxative and was told by the physician not to take it again.

Now he was advised not to take the drug again by trade name. The patient left the hospital, but was readmitted 1 month later with exactly the same disease again. He had not taken the same trade name product again which had previously caused his difficulty. He had taken another trade name product, a laxative which also contained phenolphthalein.

This time the patient was again advised by the physician not to take these two trade name laxatives. So the patient then returned home, but was readmitted again a short time later with a reoccurrence of the same illness. This time he had taken a third trade name product laxative which also contained phenolphthalein.

In order to avoid any subsequent difficulty for this patient, the physician then obtained as complete a listing as he could of all of the known preparations by trade name containing phenolphthalein so that the patient could avoid taking the drug again.

I think this is an illustration where designation of a drug by trade name rather than by chemical constituents can lead to serious difficulty.

Senator NELSON. Would this have been avoided if the doctor had used a generic or official name?

Dr. CLUFF. Only if the drug was obtainable over the pharmacist's counter by generic name. In this instance this is not, of course, the ordinary way in which the patient will have purchased the drug from the drugstore. In these instances the three different drugs were Ex-lax, the other trade name I can't remember, and one was the 4-way Cold Tablet I believe, and I have forgotten what the second one was, but in this instance these drugs contained more than one chemical constituent, so that in prescribing of the preparation, if prescribed by generic name, one would have to prescribe it by the name of all of the constituents.

In this instance it was just as important for the patient and the physician to be aware of the fact that there was more than one trade named product containing phenolphthalein.

Senator NELSON. Thank you. Go ahead.

Dr. CLUFF (reading.) (2) Approximately 20 percent of untoward reactions to drugs in patients requiring admission to the hospital are attributable to nonprescription, or over-the-counter drugs, including laxatives, analgesics, and antacids. The remainder are attributable to

prescription drugs, including penicillin, digitalis preparations, sedatives, anti-infective preparations, diuretics and tranquilizers.

Senator NELSON. You are saying 20 percent of the untoward reactions are from nonprescription drugs?

Dr. CLUFF. Of those reactions patients acquire outside the hospital which require admission to the hospital. This is a designation of a specific group of patients. They are admitted to the hospital because of an illness caused by drugs, and of those illnesses caused by drugs requiring admission to the hospital, approximately 20 percent are attributable to nonprescription drugs.

Senator NELSON. Are these statistics—were your studies such as to be able to say that these statistics would apply on the average?

Dr. CLUFF. Yes, I think so. No similar studies of this kind that I am aware of have been performed elsewhere, and I am sure that this committee has heard of the studies done by Schimmel at Yale. Other similar studies are now being conducted but I don't know of any specific study that designates the statistical data as I have indicated it to you thus far.

Senator NELSON. What are some of the drugs which cause bad reaction, nonprescription?

Dr. CLUFF. I have mentioned one, phenolphthalein. Some of the others are bromide-containing sedatives. I did not bring my data with me, Senator Nelson. If this kind of information is pertinent to your committee's deliberations I would be happy to provide such data for your committee by sending it to Mr. Gordon.

But the preparations that I can list which I do recall are bromide-containing sedatives as well as antacids. And the phenolphthalein laxatives, as I have indicated.

Senator NELSON. You say that 20 percent of the untoward reactions were nonprescription drugs and 80 percent were prescription drugs.

Dr. CLUFF. Yes.

Senator NELSON. What are the most common drugs that cause some untoward reactions?

Dr. CLUFF. Well, I will just list some of them. Again I don't wish to imply that the list I am giving you is necessarily complete by any means but these will serve as illustrative examples. If this is data you care to have, I will be happy to send it to you.

An example would be penicillin, tetracycline, sulfonamide, digitalis, phenylbutazone, and indomethacin.

Senator NELSON. What are they used for?

Dr. CLUFF. Penicillin, of course, is an antibiotic, indomethacin is a drug with the trade name, Indocin, a drug which recently has been under scrutiny by the Food and Drug Administration.

Senator NELSON. Recently what?

Dr. CLUFF. Under scrutiny by the Food and Drug Administration and is a drug used for treatment of rheumatic complaints. Phenylbutazone is similarly used for treatment of rheumatism.

Tetracycline is an antimicrobial agent. Digitoxin, often in combination with a diuretic drug with the generic name chlorothiazide and another quinidine, a drug used to control cardiac rhythm.

These give you some illustrations of the type of prescription drugs which we have observed to be involved in drug reactions producing illness requiring admission to the hospital, as well as reaction to drugs which we see occurring in the hospital itself.

Senator NELSON. I note that under item 3, where you stated that illness due to drugs was the seventh most common cause of hospitalization.

Dr. CLUFF. That is correct.

Senator NELSON. It is a rather startling statistic.

Dr. CLUFF. It was to me too, Senator Nelson, when I first uncovered it.

Senator NELSON. What you are saying is that this was the cause of the hospitalization.

Dr. CLUFF. That is right. This was the cause of the illness requiring hospitalization.

Senator NELSON. Do you have any judgment about how much of that would be avoidable?

Dr. CLUFF. That is asking for a value judgment. I would put it this way, Senator Nelson. I think that some of these reactions undoubtedly are due to excessive drug use. Some of it is due to excessive drug use by patients of over-the-counter preparations. Some of it I suspect is due to the excessive and indiscriminate use of drugs by physicians.

However, I think that it is very important to point out that illnesses due to drugs probably will never be completely abated, and the point here is it is not so much elimination of the problem as it is reduction of the significance and severity.

I think there is no question but that some of the reactions occurring in patients requiring hospitalization are probably unavoidable, with the present knowledge that we have. But I think some of them are probably avoidable, illustrated by the two examples that I cited to you previously.

Senator NELSON. In your studies did you get a statistical breakdown of, for example, how many of these patients who were admitted, experienced a second or a third reaction to a drug? In other words a circumstance such as the one you mentioned earlier?

Dr. CLUFF. Yes.

Senator NELSON. Where the patient knew or the doctor knew or both knew that the patient had had a reaction before, and for one reason or another the drug was administered again?

Dr. CLUFF. Well, I have cited two examples where this occurred. I don't think there is any question but that in some instances the administration of digitalis preparations, this is a drug necessary in many instances for the treatment of heart failure. In the administration of this drug commonly the physician feels that he can't obtain effective therapeutic action of the drug without increasing the dosage of the drug to the point of toxicity. He may then reduce the dosage of the drug.

But subsequently the patient's heart failure may increase, and the physician may then correspondingly increase the dosage of digitalis again to reintroduce the problem of intoxication. I think there are certain instances where this undoubtedly occurs.

On the other hand, the question you are asking is relevant circumstances where the physician knew the patient had trouble with the drug on one occasion and then readministered it to the patient again. The physician may occasionally knowingly do this.

For example, there have been many reports in the literature and many physicians have had such experiences. A patient, for example, may have had a serious problem with allergic reaction to penicillin.

Then the patient subsequently gets an infection in which penicillin is the only drug that can be considered effective in the treatment of the illness, and the physician is loathe to readminister the drug to the patient. But if it is a life-threatening illness, he may be forced to do so anyhow.

Here is another instance I think where a reoccurrence of a reaction can occur, knowledgeably and rationally. The physician then, of course, will do what is required to control the reaction.

In terms of the frequency or rates or proportion of patients who have reactions to drugs being attributable to the indiscriminate readministration of the drug to a patient known to have previously reacted to it, I don't know of any such data.

Senator NELSON. Isn't there an effective antidote for penicillin? Doesn't Schenley Laboratories have it?

Dr. CLUFF. Schenley Laboratories some years ago introduced a drug, the generic name is penicillinase. Subsequently, this drug has lost favor for the simple reason that it, too, is potently antigenic. It can produce an allergic reaction so that the drug is not commonly employed anymore. Furthermore, subsequent control studies have generally revealed that the drug probably has little effectiveness in the control of penicillin allergic reactions.

Generally, the mechanism whereby a physician controls allergic reaction to pencillin today is by the administration of potent pharmacological agents which can treat the manifestations of the allergic reaction without necessarily completely reversing it. Such drugs as the antihistamines, cortisone, and its analogs as well as epinephrine in the treatment of anaphylactic shock but there are no specific antidotes to pencillin reactions.

(3) In our studies on a general medical service, illness due to drugs was the seventh most common cause of hospitalization, ranking ahead of blood, musculo-skeletal, genito-urinary, and cutaneous diseases in frequency of admission.

(4) Among 714 hospitalized medical patients, observed over a 3-month period of time, eight of 36 patients admitted with drug induced illness died and three of 97 patients died with an adverse drug reaction acquired during hospitalization. These reactions were attributable to a variety of different drugs, including both prescription and nonprescription drugs, the ones that I have already indicated. The point in making this, of course, is to emphasize that not only is the problem of trouble with drugs an important cause of admission of patients to the hospital, but it is also an important cause of reactions in the hospital, and it is an important cause of death.

(5) Patients admitted to the hospital with an adverse reaction to a drug were about three times more likely to acquire a reaction to another drug during hospitalization.

When I say another drug here, Senator Nelson, this refers to a drug of a different pharmacological characteristic. The explanation for this is not entirely clear, but suggests a peculiar predisposition of certain patients to the occurrence of ill effects of drugs. What the factors responsible for this are and their identification I think is a matter for further investigation. But patients who have once experienced ill effects from a drug are potently susceptible to the occurrence of ill effects from other drugs that they might subsequently receive.

(6) The average number of different drugs administered during hospitalization to patients on the medical service was 10 to 12, ranging as high as 42. That number now should be increased to 52. The drugs given most often were sedatives and tranquilizers, analgesics, digitalis preparations and other cardiac drugs, antacids, and anti-infective drugs, in the order listed.

I think that a part of statement No. 7 perhaps ought to be combined with this, and that is that the patients receiving the most drugs were sicker than those receiving fewer drugs, at least as measured by duration of hospitalization and mortality rate. This is pretty much as you would expect that the sickest patients are the ones who are going to get the most drugs in the hospital.

Nevertheless, the point here that I wish to emphasize is that patients receive a large number of medications in the hospital, and indeed the number at times seems excessive—52 different drugs, which I think is a little hard to justify.

In addition to this statement, I think that it is important to point out that at the present time I know of absolutely no data to indicate the number of drugs that the patient outside of the hospital uses which he buys over the drugstore counter.

My own personal experience about this and my personal concern about this was recently reinforced when a pharmaceutical representative came to my office and I was speaking to him about what I considered to be the excessive use of nonprescription drugs by patients outside of the hospital, and he was intrigued by this and went home and counted the number of drugs he had in his drug cabinet at home, and he had 90.

Whether or not this is illustrative of the public at large I have no idea, but I have made it a practice over the past few years whenever I visit a friend to go to their bathroom and look in the drug cabinet, and it is impressive to note the abysmal chaotic characteristic of nonprescription drugs that families ordinarily keep in their homes.

The next point (7). When increasing numbers of drugs were given to patients, there was an increasing likelihood of adverse reactions occurring to at least one drug during hospitalization. Seven percent of patients in the hospital given 6 to 10 different drugs had an adverse reaction, while 40 percent of patients given 16 to 20 different drugs had an adverse reaction.

This is as much as you might expect, that you increase the number of drugs that the patient takes and you increase the total number of reactions that you can anticipate observing. The problem here is that the rate rises so rapidly it almost becomes logarithmic, and I think one must raise the question as to whether or not there are other factors than just additive which are important in increasing the rates of adverse reaction to drugs in patients taking many medications. Our present interpretations are that at least one of the factors which may play a role here is the simultaneous administration to the patient of more than one drug, resulting in an inadvertent interaction of two drugs, resulting in an ill effect that neither drug alone might have produced.

I can give you certain examples of that. One of the most common interactions that we observe resulting in ill effects in patients is the simultaneous administration of a drug such as digoxin or digitalis

to a patient simultaneously receiving or subsequently receiving a diuretic such as chlorothiazide. The mechanism of the interaction here is primarily because the chlorothiazide reduces the serum potassium level and this potentiates the reaction of digitalis.

One other such example is the simultaneous treatment of the patient with streptomycin and kanamycin for infection. Both have significant toxicity upon the eighth nerve, the hearing nerve, and indeed this still is an important cause of deafness in such patients.

In addition, we see patients who are treated with more than one drug for premedication in a variety of instances causing ill effects. I would like to cite for you here one specific example to illustrate the point.

During the course of our studies we observed one patient, for example, who was in the hospital because he had chronic pulmonary disease and he had a lesion in his lung. The lesion in the lung needed investigation because the physician thought it might be a tumor. So he ordered that the patient be bronchoscoped—which is putting a tube down the breathing tube—and taking a look in the bronchial tree to see whether or not he can see a tumor or any other lesion.

Premedication for bronchoscopic examination commonly employs the use of a barbiturate narcotic such as Demerol, or frequently another agent which may include atropine, phenothiazine, or other drugs. He was given such medication prior to his bronchoscopic examination but he developed respiratory arrest. He stopped breathing. He was given artificial respiration and recovered but it was decided he should not be bronchoscoped because he couldn't be without this premedication.

The physician still had no interpretation as to the nature of the man's lung lesion. It was decided to do a bronchogram, which is putting a dye down into the bronchial tree and taking an X-ray of the chest.

But unfortunately, the physician prescribing the bronchogram didn't realize it required the same premedication as did the bronchoscopy. The three medications were given as premedication. The patient not only developed respiratory arrest but also developed cardiac arrest and died.

This illustrates the synergistic effect of different drugs which have a very profound effect upon the respiratory-cardiac functions in an individual who is inordinately predisposed to reaction. This gives you some indication as to the nature of the drug mixtures or the administration of more than one drug to a patient at a time which can result in ill effects which neither drug alone necessarily would produce. Obviously, in a patient who is receiving 16 to 20 drugs or more, one correspondingly increases the risk of synergistic drug reactions that can produce ill effects.

(8) Some of the factors influencing rates of adverse reactions to drugs were: renal failure, gastrointestinal disease, previous history of drug reactions, allergic disease, acute and chronic infection, liver disease, in addition to other factors mentioned above.

Interpretations: From the observations we have made, the following interpretations seem warranted:

(1) Adverse effects of drugs are an important health problem.

(2) Adverse effects of nonprescription drugs, as well as prescription drugs, are responsible for hospitalization and death of a significant number of patients.

(3) It is unlikely that the large number of nonprescription drugs taken by patients, and prescription drugs administered by physicians are necessary or required.

(4) The number of different drugs taken by, or given to, patients undoubtedly contributes to the total cost of drugs for the patient.

(5) Reduction of the number of drugs taken by or prescribed for patients would undoubtedly reduce the frequency of adverse drug effects and also reduce total drug costs.

(6) Continuous evaluation and study of drug usage and ill effects of drugs in sick persons treated by various physicians should provide increasing understanding and elucidate measures to reduce risk from drugs and prevent indiscriminate drug usage.

(7) Development of procedures for public instruction about drugs, their proper and improper use, is necessary.

(8) Development of better methods than now available for informing physicians about rational and irrational drug usage is required.

(9) Continued reliance upon pharmaceutical manufacturers and their representatives as the only major source for public and physician instruction about drugs is unwise. Much information provided by manufacturers is quite useful, but profit motive and bias are not proper bases for guiding the public and medical profession about the use of drugs.

Obviously, there are certain kinds of individuals who when given drugs will have trouble with them, whereas other individuals given the same drugs will not. What the factors are that increase the susceptibility of one person to the ill effects of the drug and why another person is spared these ill effects I think at the present time is not completely understood, but we do have some information as to what these factors are.

Senator NELSON. I notice on item 3, page 2, that you state:

> It is unlikely that the large number of nonprescription drugs taken by patients and prescription drugs administered by physicians are necessary or required.

How serious, in your judgment, is the problem of overprescribing or misprescribing of drugs?

Dr. CLUFF. I would say overprescribing is probably a greater problem, at least as I see it, in the hospital. I can't speak about outside of the hospital because I have not studied the problem out of the hospital and I don't know of anyone who has. But in the hospital I would say that the major problem is overprescribing rather than misprescribing. There are innumerable illustrations of this that I think one could cite. I would like if I may to cite some of my own personal opinions about it.

For example, it is common practice in hospitals for the physician to write an order for the patient to receive a sedative at night if the patient doesn't sleep.

Now I don't know if any of you have ever been in a hospital. I work in one. I have been in one as a patient. But commonly in the hospital lights are turned out at 10 o'clock or 9, and indeed it is expected that the

patient can go to sleep at that time. Now generally my sleeping habits are such that I don't go to bed until 12:30 at night, and in the hospital I find it very difficult to go to sleep before 12:30 anyhow. I think it is a little disconcerting to have the physician order a sedative that the nurse can administer at 10 o'clock at night when indeed I don't feel like going to sleep until 12:30. In essence I think this is a manifestation of indiscriminate prescribing.

In addition, another illustration of this would be the common habits of physicians in hospitals to order laxatives, what they call PRN—if necessary. And indeed this leaves the decision as to whether or not the patient should get a laxative up to the nurse. Now the nurse generally walks around the wards every day and asks the patients if they have had a bowel movement.

Now many nurses feel that it is absolutely necessary that every patient have a bowel movement once a day, but it is not uncommon at all to find some patients in the hospital whose natural habits are to have a bowel movement every 3 days. But, because the nurse feels that it is important that they have a bowel movement every day while they are in the hospital, they are forced to have one by being given a laxative every night. So that in essence I think this is again excessive use of medication.

Sedatives I think are equally overused. It is common when patients are in the hospital for them to be disturbed, particularly if they are elderly. Many patients admitted to the hospital are frightened and anxious, and in order to maintain quiet in the wards, the physician may administer sedatives and tranquilizers to the patient merely to maintain adequate comfort for the environment of the ward, when indeed there are many other ways in which the patient's anxiety and fear could be allayed without the administration of drugs.

In addition to that, I think that the use of antimicrobial drugs in the hospital is markedly excessive. As an illustration of this——

Senator NELSON. What kind of drugs?

Dr. CLUFF. Antibiotics. As an illustration of this, in the surveillance of the use of antibiotics at the Johns Hopkins Hospital in the months of December and January, it is not at all uncommon for 40 percent of the patients in the hospital to receive at least one antibiotic, and it is inconceivable to me, because one of my major interests is infection, to believe that 40 percent of the patients in the hospital require an antimicrobial drug, so that in this instance I think that there is no question but that these drugs are also used excessively.

It is not at all uncommon for a physician in practice to administer penicillin, for example, or any other antimicrobial drug to patients with viral respiratory disease when it is patently clear from the scientific literature this is absolutely of no value. So in essence I think it is perfectly obvious that drugs are used excessively by physicians.

In addition to that I think it is important to emphasize as I hope I pointed out before that the population as a whole, the public itself, seems to have the very distinct impression that you can cure almost any ill out of a tube, box, bottle or can and indeed it is very common for patients as I have indicated before to buy nonprescription drugs excessively in the drugstore, in order to treat whatever ill they happen to think they may have.

So I think that the problem is very much broader than just over-prescribing by the physician. I think that the public at large also uses drugs excessively.

Mr. GORDON. Dr. Cluff, one of our witnesses a couple of days ago stated that the enormous pressure of advertising and promotion causes the use of unnecessary or unsafe drugs. Would you comment on this please?

Dr. CLUFF. Well, I can cite an opinion here if I may, because I don't know of much data on this. I can cite one thesis study that I have read since I have been at the University of Florida, done by a Dr. Murphree, who examined a rural population of Florida as a part of a sociological study. She tried to get some idea as to what were the factors that influenced the population in the use of drugs, and there was no question that the single most important factor which she uncovered was advertising.

I would agree that advertising is probably the single most important force influencing the use of drugs. Many personal examples one could cite about this as well. I am sure that any of you who have families at home whose wives and children go to the drugstore occasionally to buy things are as aware as I am that they too are strikingly influenced by the advertising of the products they buy and the number of products they buy when they go to the drugstore. So I would have to admit that this is a factor about over-the-counter and prescription drugs.

There is also no question but that it has a pronounced influence on how physicians use drugs. Many examples of this I think I can cite.

I became interested a few years ago in Baltimore of why it was that one of the most commonly used drugs for the treatment of diarrhea disease was a drug named Donnatol, and in this instance I began to make inquiries about this, and it seemed to me, after looking into the situation, that the factor most influential in determining use of this particular medication for diarrhea was that the pharmaceutical representative for a long time had made it a practice to keep boxes of the drugs in the emergency room at the hospital so that the residents would have it available to treat patients who come in with diarrhea without having to write a prescription for them.

This practice we did curtail. Subsequently I believe, the use of this medication did decline in the hospital. These are largely opinions again let me point out. I don't have any factual basis nor any published papers establishing this point, but I don't think this can be argued.

One other example of this which recently came to my attention, which I will be happy to cite if you wish, involves a drug called Declomycin—it is an antibiotic—very commonly used in the State of Florida. Coming from a little further north where the winters are much more severe, we were very much concerned even there about the use of Declomycin in the summertime because it is a drug known to be a potent photosensitizer. By that I mean that when this drug is taken, and the patient is exposed to sunlight, he very commonly will have a marked acute skin eruption.

But in Florida, where the sun is out so much of the time, the use of Declomycin in that State seemed to be a little unwarranted when other drugs, most of the other tetracyclines, are pretty well known to be equally as effective against infection. But I suspect the reason for this

is that the pharmaceutical detail man in the State of Florida, who is interested in making sure that Declomycin is sold, is a very forceful, a very aggressive, and a very charming person.

I wouldn't be a bit surprised, again opinion mind you, not statement of fact, I rather suspect that this is an important determinant as to why it is that in the State of Florida, a drug such as Declomycin is used when my own experience would lead me to believe that this is not a drug that should be employed in people who are readily exposed to sunlight.

Senator NELSON. Why wouldn't the prescribing physician be aware of the photosensitive side effect of this drug?

Dr. CLUFF. Well, generally it is deemphasized, of course, by the man trying to sell the drug. He is interested in seeing that the physician buys the drug. He isn't interested in discouraging his use of the drug, so generally he will deemphasize it. The usual approach is that most of the patients requiring this drug are sick enough so that they are likely to be in the house and not outdoors. But that doesn't seem to me to be necessarily a justifiable use either.

In addition to that, of course, he uses other types of information which may be pertinent. He has certain data on absorption, frequency of administration of the drug and blood levels which he assumes are important in evaluating the efficacy of the preparation, and these are impressive pieces of evidence when one looks at it, but they may not be the important reasons why the physician uses the drug when his concern is the treatment and the cure of the patient's disease and these may have no relevance to that.

Senator NELSON. Is this Declomycin?

Dr. CLUFF. Yes.

Senator NELSON. As a matter of ordinary practice, this drug comes to the attention of a physician. What does he rely upon to make his determination as to whether or not he will use that drug?

Dr. CLUFF. He evaluates the information provided by the pharmaceutical representative. Now I am speaking here primarily of the physician out in practice. Within the hospital we have other means of controlling this. But outside of the hospital the physician is to a certain extent dependent, as a matter of fact I know he is pretty heavily dependent upon, the pharmaceutical representative for information about new drugs, even information about old drugs. And if he evaluates the information provided to him, he will try the drug and gain some personal experience with its use, and predicated on his experience with the drug he will either then continue its use or discontinue it.

Senator NELSON. The drug Declomycin, for example, comes to the attention of a Florida physician you say, the drug causes a problem from a photo-sensitive standpoint and it is used a lot there. Where else can the doctor readily look to find out about the drug other than the detail man or the advertising of the company?

Dr. CLUFF. Well, if he happens to come to one of the symposia, seminar or local hospitals that I happen to be speaking at or visiting, he will hear about it from me. If he happens to read the New England Journal of Medicine or the American Journal of Medical Sciences or the other established medical journals, the Annals of Internal Medicine, he can acquire the information in this regard. Generally, how-

ever, a busy physician in practice doesn't have the time to devote to reading the available literature.

Senator NELSON. Of course, it would only be accidental whether or not he attended a conference at which——

Dr. CLUFF. Of course, my concern about this, Senator Nelson, is that from the studies that have been done, the physicians who go to symposia and seminars for educational purposes are generally the same 10 percent, so in essence one is reaching a very small segment of the total population of physicians. The person who on a person-to-person basis attempts to keep the physician informed about drugs by visiting him in his office and in the hospital where he works is the pharmaceutical detail man.

Senator NELSON. It may be very good from his point of view if he has a special case to be made in behalf of whatever product he is handling.

Dr. CLUFF. He is interested in selling it and I would never argue with a man's capacity to sell a product. My concern is really summarized in item 9 of my interpretation which indicates that continued reliance upon pharmaceutical manufacturers and their representatives as the only major source for public and physician instruction about drugs is unwise. Much information provided by manufacturers is quite useful, but profit motive and bias are not proper bases for guiding the public and medical profession about the use of drugs.

Senator NELSON. What, in your judgment, is the solution to this problem, which has been raised with identical observations made by a number of very distinguished witnesses—pharmacologists and physicians? What is the answer to this problem?

Dr. CLUFF. Well, I think that one can look at this in two ways. One, a personal opinion as to about what I think ought to be done. Second would be to examine what efforts are being made to do this.

I think we might examine the latter first. The American Medical Association Council on Drugs has established a series of panels on a variety of different kinds of drugs and the reactions they cause. I happen to be chairman of one of those panels, and indeed a great effort has been made by the use of the Journal of the American Medical Association to make available to the practicing physician expert opinions and expert guidance on the use of drugs by publication in the Council of Drugs reports in the Journal of the American Medical Association.

In addition to that, the Food and Drug Administration, as you know, is making some effort in the distribution of advisory comments and warnings to the medical profession about certain types of drugs.

In addition to that, the National Academy of Sciences' National Research Council Drug Research Board, of which I happen to be a member, also has currently under consideration establishment of a few centers trying to explore the methods that might be better employed to guide physicians in practice about the use of drugs.

My own personal feeling about this is this—in addition to that, of course, there are skads of publications and many brochures. A physician could fill his office up with these. Personally, I don't think these are very effective.

The thing that the pharmaceutical representative has done, which is the major reason why he is so effective as an educator of the physi-

cian, is his person-to-person contact. As you will note from the data available, there are many thousands of pharmaceutical representatives in the country whose sole purpose is to visit physicians in their offices and talk to them about drugs.

Somehow or other, I don't wish to necessarily imply that we ought to stop this, but somehow or other we have to provide some more rational basis for advising physicians about the use of medication, and I think that somehow or other we must try to foster and capture the methods of the pharmaceutical manufacturers' detail man by establishing some mechanism for better relationship between those individuals who are capable of instructing physicians in practice by making available the opportunity to them to visit the physician in their area of operation and work.

Senator NELSON. Whom are you talking about now?

Dr. CLUFF. The Drug Research Board has a proposal under consideration at the present time to establish a few such pilot programs to develop programs of what we might call therapeutic consultants, associated with medical centers. Persons whose primary responsibility would be to visit physicians in their hospital and provide rational information on drug use. Conceivably, this could be one way of approaching it. I suspect there are others.

My other attitude about this is that the medical profession itself must begin to assume an increasing responsibility for its own education about the use of drugs. I think the medical schools in the country generally have adopted methods of education of the physician in practice which we have already recognized as archaic and no longer used in teaching medical students, and that is the didactic lecture system which is, in essence, what we generally employ when we go out into communities to talk to physicians.

We all recognize that this is not the most effective way to teach, and furthermore, as I have indicated, only a small proportion of all of the physicians that practice generally attend such symposia and seminars.

In addition to that, I think that medical schools must begin to assume some increasing roles in this as well as the American Medical Association.

In terms of advice to the public, how the public can be guided about drugs, I am very much concerned about the fact that the only things they read either damn drugs or praise them. Neither the advertising material of the manufacturer or the damning articles that are published in the common journals.

I think that the public needs to be informed that they have a responsibility to be discriminating in the use of drugs, but they need to be advised as to how to be discriminating. I personally feel that the education of the public should be a joint enterprise between the pharmaceutical manufacturers, the Food and Drug Administration, and the medical profession. How this should be structured I don't know, but I rather suppose that the Food and Drug Administration should take the leadership.

Senator NELSON. If a physician is practicing in a large hospital where you have a formulary, a formulary committee, and a number of specialists of various kinds recommending what goes in the formulary, you have the situation where clinical studies can be made

and information given, it is a relative simple matter for the physician practicing there to be informed.

Dr. CLUFF. Well, I would challenge that to a degree. I would agree that the larger the medical center and the more closely it is affiliated with a medical school, the more likely is there to be an effective formulary and educational system. On the other hand, I think that it is important to recognize that the majority of hospitals in this country are not major medical centers, and they are not associated with medical schools, and in these hospitals generally they are operated by very busy physicians in practice, and they are dependent upon themselves for controlling this problem, and for the most part I doubt if such institutions have done well.

Senator NELSON. I was only as a preface saying that in those hospitals where they do have a formulary, it is relatively easy.

Dr. CLUFF. Yes.

Senator NELSON. Compared to what the individual private practicing physician's situation is.

Dr. CLUFF. Yes.

Senator NELSON. What puzzles me is why, if it is possible for a New York City hospital or some large group health organization with 94,000 members, over 200 doctors, and a large formulary committee, if it is possible for them to establish a formulary, based upon their experience and the specialists they have, why isn't it possible to have a national formulary that names all the drugs, generic as well as trade name, attest as to their reliability, gives all of the side effects that are known about the drug, so that the physician, when he is prescribing, can open up an index to the book and see the generic name, all the various trade names, the side effects, and so forth? Why isn't it possible to do that?

Dr. CLUFF. Well, I might just make one or two comments about that, because I was involved in the development of a formulary at the Johns Hopkins Hospital.

In the development of this formulary we took it upon ourselves to review the formularies presently available or at that time presently available in other major medical centers. One of the important things is that the formulary we came up with specifically met the needs and requirements and interests of the physicians on our staff. In other words, they were the ones who decided what drugs were essential in their practice.

The formulary that we adopted was not necessarily similar to the one, for example, in a major New York hospital. I think in a sense that the physicians who are requesting the drugs should have the opportunity to participate in the drugs that they select to use, and indeed, if you establish a national formulary, you take away from the physician in these various hospitals where they are functioning, the opportunity to participate in the decisions.

Senator NELSON. Why would that take that away?

Dr. CLUFF. Well, because presumably if you are going to have a national formulary, you are going to have to have some body of people that can't represent all of the many thousands of hospitals in the country involved in the production of such a formulary.

I think you could end up with a very desirable and interesting formulary to use, but I do believe that it is desirable to provide the physician with some flexibility in the selection of the medication.

Senator NELSON. I am not suggesting that even the doctor would have to pay any attention to it. We have an abundance of testimony from very distinguished professors. Dr. Modell, Dr. Burack, and a whole series of pharmacologists simply saying really that the doctor doesn't have any basis, good basis for making judgment between drugs as to relative efficacy, that there are so many drugs that he really doesn't know. In effect, in his testimony he said—he didn't put it that way—that the doctors really don't know what they are doing with drugs.

All I am saying is give them a formulary and let them be guided by it if they wish to. Nobody suggests that a formulary be imposed on the doctors. What basis could a doctor have for making a judgment among 7,000 drugs?

We had pharmacologists here who spend fulltime in this field, and they say they can't keep up with the drugs. Obviously, the physician can't either, so, as you said earlier, what he is really doing is that he is relying on the detail man. The detail man is incompetent to make the decision. And if he does make it, he makes it in behalf of the company he represents. That is the name of the game.

It just seems scandalous to me that a private practicing physician really has no place to turn. You say that he can go to attend a conference. But you also say this is the same 10 percent. He really doesn't know what he is doing in a substantial number of cases.

He doesn't know all the trade names, so he may have a patient with a trade-name drug that has a side effect and the same patient goes to another physician and that doctor prescribes another drug that is the same. He has no way of knowing that it is the one the patient had a side effect with. The doctor is just in a jungle in this field I think. According to the distinguished witnesses we have had, a major percentage of physicians really don't know what they are doing.

Dr. CLUFF. I agree.

Senator NELSON. I say what is the answer. Do you agree with that?

Dr. CLUFF. I agree completely with what you have said. I think the real difficulty is, can you solve the problem that you have cited by just establishing a formulary, and that I am not convinced of.

Even at my hospital at the present time or even at Johns Hopkins where we established a formulary, I don't think that necessarily controlled or prevented the indiscriminate and unwise use of drugs.

Senator NELSON. At least it is a source of information for the physician, isn't it?

Dr. CLUFF. Well now, it depends on what you mean by a formulary. If you are talking, and perhaps this is a point where we need some definition, if you are talking about a formulary as being a text on pharmacology which in essence has a listing on all of the available drugs by generic name, let's say, and has a description of the pharmacological action and indeed has information about side effects, their chemistry, and so on; we have some superb books available at the present time to provide such information for physicians. The classic in the field is "Goodman and Gilman on Therapeutics," so in essence such texts are available.

My only question is, just providing the book won't necessarily make the physician read it, and thereby won't necessarily improve the wise use of drugs.

Senator NELSON. Is there a readily available source of information so that the doctor can open up a book and see a listing of all generic names and all trade names and readily available summary as to what the side effects are, a scientific evaluation of the clinical information that is available from experience with this drug from all over the United States. It is one thing to go to the New England Medical Journal, it is another thing to read a medical letter one month and miss it the next month. But we have drugs. They are used all over the United States, and I suppose a relatively tiny, small number cover 90 percent of the treatment, it may be 100 drugs, it may be what, I don't know, but what does the private practicing physician do?

Can he turn to an index and see them all listed and a patient comes in and says "I have had Pentids." The doctor knows Pentids but there are 10 other trade names he doesn't know. It doesn't strike a point with him that the person is allergic to, in this case, penicillin.

Senator LONG. Could I just interrupt you, Senator Nelson?

I want to make a brief statement. I am participating and cochairing a hearing taking testimony from Dr. Galbraith, Mr. Turner, assistant attorney-general, Dr. Mueller of the Federal Trade Commission, and a number of others, dealing with a monopoly problem.

I just wanted to pay my respects to the magnificent job you are doing. I was once chairman of this subcommittee, and I must say that I think it was a wise decision that you, Senator Nelson, are now chairman of this subcommittee, because you have found the time to do a magnificent job.

As chairman of the Finance Committee and assistant majority leader I have been very busy, as members of the committee so well know, and haven't been able to participate in these hearings as I would have wanted to do.

May I say that Senator Nelson and the staff working with him have done a magnificent job in developing this record about drugs and drug prices. We have been keeping up with it in the Senate Finance Committee, and I really believe that the results of the work done here will have a great deal to do with proper Federal legislation, particularly in the medicare area and the medicaid area, where we anticipate that we can find better answers to existing problems and perhaps ultimately save the Government hundreds of millions of dollars a year as a result of the fine job that is being done in exploring and understanding these problems.

One thought has occurred to me in connection with recent disclosures, particularly those that were the subject of press coverage in this morning's newspaper. We should not permit any company to put any drug on the shelves—any drug which is other than what it is supposed to be—to do so is dangerous. It is a hazard to health. Proper inspection of all drugs should be an absolute must in the future. It should be required. We should not permit someone to market any drug that is not what it should be, or is less than what should be required, and we should have adequate inspection to assure proper quality.

I believe that we will be achieving just those goals with legislation in the medicare and medicaid area as exemplified by the bill that the Senator from Wisconsin, Mr. Nelson, joined with me in cosponsoring.

Having done that, having assured that these drugs have the quality that they should have, it would then seem appropriate that we ought to

try to guarantee to the public and the Government the benefit of genuine competition in the drug field.

What you have done here, Senator Nelson, in bringing the facts out is extremely worthwhile and important. I would hope that when we look at this problem in the Finance Committee in connection with paying for drugs under medicare and medicaid, a great deal of the work will have been done for us by this subcommittee of the Committee on Small Business.

I am proud to be a member of this subcommittee, Senator Nelson, once having been its chairman. I think you are doing a magnificent job, and we are very proud that you could find the time and devote the energy to do this vital work along with the capable staff you have here, Ben Gordon and others, who are helping dispose of the old myths and bringing out the truth. I think you are doing a very good job and we appreciate it.

Senator NELSON. Thank you, Senator Long. The staff of the Finance Committee, through your direction and cooperation, has been very useful to the committee. We have had testimony, as you know, from a number of very distinguished witnesses, including the witness who is before us today.

I think it has developed some very valuable and a useful record for the committee, and out of it I think it will furnish the basis for some education plus, possibly, some useful legislation.

I appreciate your remarks.

Senator LONG. We are happy to make available such competence as our staff possesses in this area, and we would hope that at a suitable time, you could return the favor.

Thank you very much.

Senator NELSON. Thank you, Senator Long.

What I was getting at, Doctor, is this: We have had a number of physicians, pharmacologists in teaching institutions, who say the information isn't readily available to a doctor. All I am saying is, why couldn't something better than what we have got at least be made available to the physician?

Dr. CLUFF. I think it could be, and as a matter of fact, I know at the present time such a formulary as I think you are talking about is either under advisement or is very soon to be developed. My point here was that I had assumed that you were speaking about a restrictive formulary.

Senator NELSON. No; I was just talking about——

Dr. CLUFF. Now, I gather you are talking about an information formulary.

Senator NELSON. I wasn't using the term in the same sense as a hospital formulary——

Dr. CLUFF. No.

Senator NELSON. Where they may at a hospital say you may not, except with special permission or under certain conditions, use anything except what is in our formulary. I realize that each staff—and, perhaps, it depends upon the kind of hospital—determines the nature of the formulary.

I was thinking of one that would be informational and useful, particularly to a private practicing physician who doesn't have the benefit of a hospital staff and a hospital formulary and easily available

consultants who are specialists, pharmacists, pharmacologists, or physicians who have been using various drugs. I was thinking of something for him that would be advisory, not compulsory.

I am wondering why we couldn't develop, why it would be impractical, to develop something like that.

Dr. CLUFF. I think it would be quite practical and highly desirable, Senator Nelson, in view of that position. I think it was a misunderstanding on the interpretation of the word "formulary." In many hospitals, of course, a formulary is considered to be restrictive in terms that these are the only drugs that you can use. We won't give you any others.

An informational formulary you are talking about, or a drug compendium, it might be called. One providing discriminating information about drugs, their use, their problems, and their hazards, that indeed could be provided every physician in the country; I think is a very worthwhile endeavor, and you perhaps know more about this than I do.

But I know that this has been discussed by the National Research Council, Drug Research Board, and it was my understanding that there was at the present time collaborative effort between the pharmaceutical manufacturers, the Drug Research Board, and the Food and Drug Administration, in an effort to try to come up with just such a compendium as you describe.

Senator NELSON. I did not know there was this proposal. I have some legislation in a bill pending on that point. Well, go ahead. Do you have something you haven't covered?

Dr. CLUFF. I really don't know whether there is anything else I can add. I would like to summarize, perhaps, the statement that synthesizes my own feelings about this, and that is that one of my major concerns about drugs, and indeed this involves their cost, is what I would consider to be an excessive use of nonprescription drugs by the public at large and an excessive use of drugs by the physician.

Generally, I think this is attributable to unavailability and inadequate guidance and information about the actions and interpretations in the use of drugs.

I think in this instance that if something can be done to improve the present mechanisms of consumer buying, if one wants to use that point, for the public, about how they buy drugs and how they should not buy drugs, and how they make decisions about buying drugs, and what are some of the things that ought to be considered, this would be of great value.

The exact details and implementation of it is something that will have to be worked out. My own personal feeling is that the leadership for the development of such guidance for the public must come out of the Federal Government, probably out of the Food and Drug Administration.

So far as the physician is concerned, I agree the compendia would be a very desirable thing. Personally, I am not at all convinced that that would solve the problem of the excessive use of drugs by physicians.

I still think that one must recognize that some method must be provided for improving our present guidance to physicians about the use of drugs, rather than, as we do now, depending so heavily upon

the pharmaceutical manufacturers' detail representative for the principal education of the physician about drugs.

Senator NELSON. You are addressing yourself to the basic question of the continuing education of the physician in the field of drugs.

Dr. CLUFF. Yes; because I happen to feel that that is the only ultimate, permanent, long-lasting resolution of the problem we are talking about.

Senator NELSON. I would certainly defer to your judgment on that. It is correct, and perfectly logical, that that is probably something that is a responsibility in one way or another of the profession itself.

Dr. CLUFF. I agree.

Senator NELSON. It seems to me from everything that I have listened to over a period of time, that this is a problem of such size that it is necessary for FDA or somebody in a central place with the authority to test drugs, clinically, and chemically, and the resources to gather all such information together and then to put together a compendium with the advice of the appropriate authorities.

Dr. CLUFF. I think it ought to be more than advice, Senator Nelson, because in essence the Food and Drug Administration, does not now have, nor do I visualize it will ever have the necessary highly trained, qualified experts, to prepare such a compendium independent of active cooperation and collaboration by the medical profession at large.

Senator NELSON. I meant that.

Dr. CLUFF. Yes.

Senator NELSON. I meant it would have to go in the same way that the pharmacopeia——

Dr. CLUFF. Yes.

Senator NELSON. They would have to go to all the resources there are, private and public, in the country for assistance in drafting such a compendium and keeping it up to date.

Dr. CLUFF. Yes, this is the only way the medical profession will accept such a compendium as a legitimate guide, is if they were active participants in its structure.

Senator NELSON. They would have to be. That is where the source of the information, in fact, is.

Dr. CLUFF. Yes.

Mr. GORDON. Is there any information to indicate whether brand-name drugs are more likely or less likely to cause bad reactions than under the generic name?

Dr. CLUFF. I have no evidence to indicate that that is the case.

Mr. GORDON. Would it be possible to project on a national basis how many people are needlessly injured or killed as the result of poor drug therapy?

Dr. CLUFF. Well, you probably know these figures better than I do, Mr. Gordon, but if one just extrapolates the figure, of 5 percent of the patients being admitted to medical service in a hospital for adverse effects of drugs, and generally the medical service of the hospital will represent anywhere between one-third and one-half of all patients in the hospital, then extrapolation nationwide in terms of the total numbers of patients in hospitals in the country, I think these figures would stand up. Essentially comparable data has been obtained in three different institutions. I think one can get a rough estimation as to the total magnitude of the problem of the ill effects of drugs requiring hospitalization in the country at the present time.

Mr. GORDON. That would be?

Dr. CLUFF. It would be staggering, but I have never sat down and figured it out.

Mr. GORDON. But it would be a good, at least, first approximation?

Dr. CLUFF. Yes.

I happen to feel that the problems from the ill effects of drugs is a major public health problem at the present time.

Senator NELSON. A major?

Dr. CLUFF. A major public health problem.

Mr. GORDON. One other question: concerning false and misleading advertising, what effect does that have on drug-induced illness?

Dr. CLUFF. The way it has an influence on drug-induced illness is because it increases the indiscriminate and excessive use of drugs, and one of the premises of our observations is that you increase the total number of drugs that the patient gets, and you correspondingly increase the trouble you are going to have with drugs.

Mr. GORDON. When you use the term "education" with respect to the detail man as a source of education, are you using the word "education" with quotation marks around it, or are you not?

Dr. CLUFF. Well, even bad education is education, Mr. Gordon, and in this instance I would say that it is a matter of judgment as to whether what he is providing in the form of educational material is good or bad.

I personally feel that in every instance that I know of, it is always biased, it is always associated with profit motives, and for that reason, I don't think that it is good guidance alone for the physician in practice to use.

Senator NELSON. That is all the questions we have.

Dr. Cluff, we appreciate very much your taking the time from your busy schedule to come here. Your testimony has been very constructive and very valuable to us, and we appreciate your taking the time.

Dr. CLUFF. Senator Nelson, I appreciate the opportunity to come here. Thank you.

Senator NELSON. We will take a 5-minute break, and then we will take the next witness. I have some other business this afternoon.

(Whereupon, there was a short recess.)

Senator NELSON. We will resume the hearings.

We will now hear from Dr. Margaret McCarron, associate clinical professor of medicine, University of Southern California School of Medicine.

Dr. McCarron, we appreciate very much your taking the time to come and testify today. You may present your testimony in any way you wish. If you don't mind, we may interrupt from time to time with questions.

STATEMENT OF DR. MARGARET M. McCARRON, F.A.C.P., ASSOCIATE CLINICAL PROFESSOR OF MEDICINE, UNIVERSITY OF SOUTHERN CALIFORNIA SCHOOL OF MEDICINE; ASSISTANT MEDICAL DIRECTOR AND CHAIRMAN OF THERAPEUTIC COMMITTEE, LOS ANGELES COUNTY GENERAL HOSPITAL, LOS ANGELES, CALIF.

Dr. McCarron. I would prefer to read it. The first paragraph is an explanation of the size of the hospital and the type of staff we have.

The Los Angeles County General Hospital is a 3,000-bed acute medical and surgical hospital with a physician staff composed of the teaching faculty of two medical schools—the University of Southern California School of Medicine and the California College of Medicine of the University of California.

This hospital serves as the primary clinical facility for 311 medical students. It also has an intern staff of 225 and 336 resident physicians in training. There are 213 hospital-based physicians and 2,444 attending physicians; these physicians are all in private practice, supervising the care of the patients and instructing the students, interns, and residents. The hospital also has a school of nursing with an enrollment of 389 students. One of the primary purposes of this hospital is to train physicians and nurses.

A drug formulary system has been in effect at the Los Angeles County General Hospital since July 1964, and has had enthusiastic acceptance by the medical, nursing, and pharmacy staffs.

The formulary system depends on a competent, well-informed therapeutics committee. The committee, serving in an advisory capacity to the medical director, formulates all policies and procedures relating to drug use in the hospital. The therapeutics committee at the Los Angeles County General Hospital consists of physicians from medical administration and the departments of medicine, surgery, outpatient services, and clinical pharmacology; a pharmacologist, the chief hospital chemist, the chief hospital pharmacist, and the director of nursing.

I. Reasons for Adopting Formulary System

A. Need for "standard" familiar medications

Before the formulary system was adopted, more than 1,500 different drugs were stocked in the Los Angeles County General Hospital pharmacy. These were dispensed either by generic name or by brand name, depending upon the physician's order.

Because of the similarity of the names of some drugs with widely different activity—for example: disodium edathamil, used to lower blood calcium levels; and calcium disodium edathamil, used as an antidote for lead poisoning—and the confusion resulting from having the same drug ordered by generic name or by one of its several brand name—for example: generic name, tetracycline; brand names, Achromycin, Panmycin, Polycycline, Steclin, and Tetracyn—an accurate ready reference was needed by the hospital nursing staff to prevent errors in drug administration.

Senator NELSON. May I interrupt for a moment.

Dr. MCCARRON. Yes.

Senator NELSON. You mention on page 1 the similarity of the names of two drugs which have distinctly different uses. Do you have, from your experience, any examples of errors or confusion that has resulted from the multiplicity of brand names or names for any one drug?

Dr. MCCARRON, Yes, we do. This is one that I picked because a doctor ordered disodium edathamil and the nurse was unfamiliar with that drug; she went to the shelf and found calcium disodium edathamil, she thought he forgot to put the calcium before it. We had one episode where this particular drug was administered. If she has any question she can now go to the formulary and see that they are two distinctly different drugs.

We felt that this was very important. We also had instances where a doctor would stop Achromycin and give Tetracyn.

Senator NELSON. And do what?

Dr. MCCARRON. And give Tetracyn—the same thing by a different brand. He didn't know it. There was one hospital in the Los Angeles area that did bacteriological sensitivity studies to tetracycline and to Panmycin, and they were the same drug. The doctors were giving two different sensitivity tests, because somebody in the bacteriology department had gotten sensitivity discs for these two antibiotics, not realizing they were the same thing.

We try to teach our doctors a little better than that.

Because of recent advances in pharmacology, many potent therapeutic agents are available that require special knowledge for safe administration. The medical staff needed an authoritative guide to the selection of drugs, an understanding of their pharmacological properties, information regarding adverse effects and contraindications, and specific instructions regarding the policies and procedures for using these drugs at the Los Angeles County General Hospital.

Believing that the chance for error would be less if the entire staff became familiar with a limited number of medications, the therapeutics committee at the Los Angeles County General Hospital evaluated each of the 1,500 drugs in the pharmacy, and in consultation with the medical staff, selected 550 items to be included in the hospital formulary as "standard" hospital drugs.

Senator NELSON. These 550 made up your formulary; is that correct?

Dr. MCCARRON. Yes.

Senator NELSON. And the doctors are required to prescribe from the formulary?

Dr. MCCARRON. Yes.

Senator NELSON. Is your formulary all in generic terms?

Dr. MCCARRON. Yes. In our formulary the drugs are listed in alphabetical order by generic name. I have included a sample for you to see. It is exhibit D. We have the generic name at the top of the page, and that is how the drug is filed. We have brand names over at the side; in this case it was only one brand name, but the brand name is for identification purposes.

Then we have a cross index that lists the drugs by generic and brand name and refers a person to the proper page listed by generic name.

Senator NELSON. Then you give the known clinical effect of the drug, side effects and so on?

Dr. McCarron. Well, if you look at this particular one, you will find that there are many judgments in the write up that we include in our formulary. These are judgments made by the therapeutic committee.

For example, where it says "Use of this drug," we start right out by saying "The usefulness of this drug is limited by its toxicity." Then we describe the toxicity in detail, and we try to discourage the use of this drug. We ask them only to use it for short periods of time, and it tells them in what situations this might be detrimental.

Then we include in our formulary the scientific references so that they can look it up and get more detailed information if they are interested. But here is a concise summary.

Senator Nelson. I notice that at the top on the right, you have the generic name. Then you list brand name. In your formulary, do you list all of the brand names? Is there only one brand name for this?

Dr. McCarron. Yes, there is just one here that is commonly used. I am not sure if there is another one, but we would use all the common ones.

Senator Nelson. So if you had tetracycline, for example, you would list all of the brand names, also.

Dr. McCarron. Yes; that has eight or nine.

Senator Nelson. Thank you.

Dr. McCarron (reading).

B. Use of the drug formulary to protect the patient against errors in drug administration

Although most of the necessary prescribing information is available in the package insert which accompanies each drug, these are easily misplaced on a busy ward and are not available to the physicians in the outpatient clinic. The hospital drug formulary provides ready access to concise, pertinent information. It provides information regarding drug storage, mixing, and incompatibilities, as well as a cross-index of drug names, usual therapeutic range, maximum dose, and other information vitally needed to decrease errors and provide maximum protection for the patient.

Certain dangerous and rarely used drugs are available only to physicians who have experience in treating the condition for which the drug is used. For example, all chemotherapeutic agents used in the treatment of cancer are only released to members of the hermatology department and the cancer chemotherapy team. This restriction is clearly noted in the drug formulary.

C. Use of the formulary system by the pharmacy for inventory control in relation to cost saving and efficiency of operation

The annual drug budget at the Los Angeles County General Hospital is approximately $2 million. This is based on maintaining an inventory of about 550 drugs. If we were not operating on a formulary system, the inventory would be multiplied many times on some items and the total inventory would probably be doubled.

For example, the 1967 edition of the "Physicians' Desk Reference" lists 108 different brands of antihistamines. The Los Angeles County General Hospital Drug Formulary lists eight. If we carried each brand according to the physician's preference, we would be unable to accurately gage consumption and would lose our advantage in competitive bidding.

The drug purchasing system of the county of Los Angeles operates as follows:

1. The therapeutic committee evaluates the drug thoroughly and accepts it as a standard hospital item.
2. The chief pharmacist places the order and gives the purchasing department an estimate of consumption.
3. A drug specification committee writes the specifications for the drug.
4. Bids are accepted from all companies meeting the specifications.
5. The contract is awarded to the company with the lowest bid.

These contracts are usually for large quantities of a drug—a 3-month, a 6-month, or a 12-month supply.

Senator NELSON. How do you determine whether or not the company bidding can meet your specifications?

Dr. MCCARRON. Well, we have our own little internal system for this. First of all, we categorize companies by A, B, and C companies.

Senator NELSON. By what?

Dr. MCCARRON. We call them A companies, B companies, and C companies. These are our lists that we have made up from experience. We also have some companies that we have had trouble with, for one reason or another, that we do not accept bids from.

Either the labeling has been wrong, or we have consistently gotten into some type of problem, and we don't feel we can depend on that company, and we don't accept bids from them, they are informed of this.

Then, when the specifications are made, we select the things that we think are important, and later in my statement, I will give you a little example of this. Some drugs we buy only from A companies; other drugs aren't that critical, and we buy from whatever company makes it.

When the drug is delivered, we quarantine it in the pharmacy. We have a division in our purchasing department that does testing for us. There are certain standard tests that we do, such as tablet disintegration time, and we check the labeling, and we see that the drug doesn't deteriorate on the shelf or change color.

The specifications are different for each of these drugs. If they don't meet the specifications, then we return it to the company unused. We have quite an elaborate system to guarantee that the drugs we use in the hospital are effective drugs.

Senator NELSON. Do you basically test them to determine whether they meet USP standards?

Dr. MCCARRON. It depends. Some of them we actually analyze. If we are buying a drug from a company that we haven't dealt with before, and we feel it is an important drug, in our contract requirements we say that if we feel that the drug should be analyzed by an independent firm that we may have the right to do this, and the company pays for the analysis. We have done that on occasion.

Mr. GORDON. Dr. McCarron, you assume, as I understand it, that if the drug, when you test it, meets your standards, your specifications, it will do the job you expect it to do; is that correct?

Dr. MCCARRON. Yes.

Mr. GORDON. And you have never been disappointed in that, have you?

Dr. MCCARRON. Yes. I will get to that.

Mr. GORDON. All right.

Dr. MCCARRON. It takes approximately 3 months between the letting of the bid and the arrival of merchandise—except in emergency situations. I would like to emphasize here that at no point is the patient's welfare jeopardized. The hospital has a system of emergency drug ordering. Any physician may obtain any drug for a specific patient if he has an adequate reason why the standard medication is not suitable. A pharmacist is on call 24 hours a day to provide this service.

By controlling the number of items stocked in the pharmacy, an adequate flow of drugs can be maintained. All orders are placed when the inventory reaches a certain level, and the pharmacist has reasonable assurance that the drug will continue to be used. Before the formulary system was instituted, we had a significant problem in drug wastage. An item would be ordered for an individual physician; by the time the drug arrived, the physician may have decided to use something else, or he may have even left the hospital. Because the drugs were not thoroughly evaluated before the order was placed, some drugs were later found to be unsatisfactory or no longer popular and were not used.

The hospital has recently implemented a program for computer control of drugs. At the present time, the pharmacist, using a typewriter computer terminal and a code system, generates a computer record of the patient's therapy and a label by generic name for all prescriptions. This information is also used for inventory control.

I would like to insert here that we have had problems when our prescriptions were not labeled by generic name. A very good example of this is hydrochlorothiazide, which is a diuretic agent that is in wide use. This drug is made by three drug companies, Hydrodiuril for Merck, Oretic from Abbott, and Esidrix from Ciba.

Because of our system of bidding, and the size of our hospital, we may have three brands of this drug in the hospital at the same time. Patients go to various clinics, and there are several conditions in which the patient would have edema, for which this type of drug would be used. The doctor in the medical clinic would order Esidrix. I am not sure of these colors. I think Esidrix is yellow.

Then the patient would go to another clinic and the doctor there would see a little edema and would give her Oretic or hydrochlorothiazide. The patient might end up with three bottles labeled with different names of drugs that were of different colors. The patient obviously thinks they are three different drugs and takes all of them. We have had patients admitted to the hospital with low potassium levels and with digitalis intoxication and all kinds of things that result from the fact that they have taken an overdose of this medicine—hydrochlorothiazide.

Now, we are trying to obviate this: one, by using generic names and having our pharmacist print the generic name on the label, so that the patient can at least see that, although the tablet colors are different, and the sizes are different, the drug is the same drug.

We have also instituted a computer method, which isn't fully operational at this date. What we would like to do is have a computer record of all the medicine that has been dispensed, and present that to the doctor when the patient comes in to the clinic. The computer record would also include any adverse drug reactions that the patient has had

or any known allergies, so that every physician, every time the patient is seen, has a record of the drug therapy, and any complications to it.

Mr. GORDON. Dr. McCarron, you heard Dr. Cluff's statement before, did you not?

Dr. MCCARRON. Yes.

Mr. GORDON. Now, wouldn't you say that the example you just gave us about Esidrix, hydrocholorthiazide, and the other one, is a good example of how the use of brand names induces overmedication?

Dr. MCCARRON. Yes.

Mr. GORDON. Thank you.

Dr. MCCARRON. Well, these errors, and they are errors that shouldn't occur, are errors that do occur in a very large hospital where many doctors are taking care of a patient and a patient goes to various clinics.

We are trying to set up an administrative method to decrease that, but we have an added problem in that the names of the drug are not the same and the colors are not the same, and the patient gets confused. However, the patient could pick up some of these errors himself, if he knew what he was taking.

Senator NELSON. Is it also a problem of confusion to the physician?

Dr. MCCARRON. Yes.

Senator NELSON. Does he necessarily know all of the brand names?

Dr. MCCARRON. No; and the generic names have helped us tremendously this way.

The conversion to the new system was relatively easy because of the small number of items stocked in the pharmacy and the availability of the drug formulary. A pharmacist without prior training in computer techniques was able to type 500 labels in 1 day after 1 week's experience with the method. If the number of drugs available was not limited, a significant portion of her time would have been spent in nonproductive work inquiring the code name of the drug from the computer, with the hope that the computer had been programed for the item.

II. SELECTION OF DRUGS TO BE INCLUDED IN THE HOSPITAL FORMULARY

Requests to add a drug to the hospital formulary are submitted to the therapeutic committee by a staff physician with the approval of his department head. The therapeutic committee determines the acceptability of a drug on the basis of the following:

1. The drug should have specific pharmacological and beneficial actions.
2. The drug should have been adequately investigated, and well-documented clinical studies of the drug must be available.
3. The drug should have no serious untoward effects which would prohibit its use.
4. The cost of the drug must not be excessive as compared to the advantages over similar preparations.
5. If special packaging is involved, the committee evaluates whether the packaging constitutes enough of a saving in professional time and ease of administration to justify increased expense.
6. With few exceptions, all medications combining two or more active drugs in one dosage form are not acceptable. The hospital

staff strongly feels that active drugs should be prescribed in amounts calculated to best serve the patient's needs; if two drugs are necessary, each should be specifically prescribed. In our experience, set combinations of two or more drugs in one pill or capsule tended to make the physician think in terms of one or two tablets of the combination rather than the amount of each drug the patient actually required.

After the drug has been accepted as a formulary item a drug bulletin is prepared and sent to the entire medical, nursing, and pharmacy staffs. This drug bulletin is an evaluation of the drug with specific instructions for use. (See exhibit A: Sample drug bulletin.[1])

This shows the type of evaluation we give to a drug, the blue page. I would like to point out that this drug bulletin is sent to our staff members, and we have almost 2,500 doctors in private practice. They get these. We have requests from seven or eight of the private hospitals in the Los Angeles area, they get these and put them in their library. Physicians call us and ask to be put on our mailing list, so there is an active interest in achieving information about drugs.

Senator NELSON. How often do you publish the bulletin?

Dr. MCCARRON. About twice a month.

Senator NELSON. And is this just one drug?

Dr. MCCARRON. This happens to be one drug. What we try to do is, one drug bulletin a month describes in detail a new drug, and this isn't to——

Senator NELSON. A new drug?

Dr. MCCARRON. A new drug that we are adding to the formulary.

Senator NELSON. I see.

Dr. MCCARRON. The next drug bulletin is on adverse drug reactions, and in this we use the experience in our hospital. The Therapeutic Committee coordinates the adverse drug reactions, and the information that we receive from the FDA and other sources in medical literature, so that one bulletin describes a drug and the next one reports adverse reactions, especially ones that have occurred in the hospital.

This has pretty wide circulation.

A modification of the information contained in the drug bulletin is then prepared for the hospital formulary. The formulary page is then sent to the wards for insertion into the formulary. (See exhibit B: Sample page from Los Angeles County General Hospital Formulary.[2])

III. USE OF GENERIC NAMES

It is the policy at the Los Angeles County General Hospital to stock and dispense drugs only under their generic or official names. The attending staff has agreed to prescribe by generic or official name and has approved of the dispensing of a drug by its generic name even when the prescription is written with a proprietary or patented name.

The prescriptions used at this hospital are printed as follows: "RX— or USP, NF, NND, or generic equivalent." (See "Exhibit C: Los Angeles County General Hospital Prescription Form." [3])

All drugs are purchased by generic name on a bid basis, with some exceptions. Certain critical drugs are specifically designated by manu-

[1] See p. 595.
[2] See p. 596.
[3] See p. 598.

facturer. Example: Spinal anesthetics are purchased by brand name; the brand is changed only on the recommendations of the anesthesia department.

On occasion, noncritical drugs are also specified by manufacturer because of previous experience in obtaining ineffective drugs when generic equivalents were used.

Mr. GORDON. May I interrupt at this point? In these cases, did you attempt—I mean, did the hospital attempt—to determine whether those ineffective generic drugs, in fact, met the USP or national formulary standards?

Dr. MCCARRON. Yes. I will give you an example of that. We bought generic thyroid hormone. The USP standards for thyroid hormone are based on the iodine content which should have a relation to the hormone content. We started using drugs that had met our specifications. Of course, we had no way of doing biological assays on this.

After this generic thyroid hormone was in use in the clinic, the physician in charge of our thyroid clinic came in and told us there was something wrong with the medicine. People who had been well-controlled on two grains of thyroid a day were now taking three, four or five grains and were slipping out of control.

On the basis of this, and he had at least 30 cases to show us, we pulled all the generic thyroid out, and we substituted it with the Armour brand thyroid.

After we started using Armour, these patients went back to their two grain dose and we therefore said that we did not want to take any chance like this again. We know that Armour works, and we know that we have no way of evaluating the other preparations of thyroid and that the iodine is not an accurate evaluation. Therefore, we have specified only Armour brand thyroid.

This has not been a significant problem; the hospital purchases less than 50 drugs by brand name, and most of these are low-use items. But I would like to say that some of these things that we buy by brand name are mainly used in critical situations. The cardiac glycosides, which are used for treating a patient with a severe condition where his life is threatened are very important, especially if you are giving this medication intravenously. We want to have standard medicines that the doctors are familiar with, and we just buy them from one company so that he always knows what he is giving.

IV. VALUE OF MANUFACTURING CERTAIN ITEMS AT THE LOS ANGELES COUNTY GENERAL HOSPITAL

The pharmacy at the Los Angeles County General Hospital manufactures many items for use within the hospital. This is not a commercial business. The manufacturing division was established to decrease the cost of pharmaceutical supplies, to provide better service, and to aid the physician in the initiation of new treatment programs.

Eighty-five percent of the intravenous fluids used at the Los Angeles County General Hospital are manufactured by the hospital pharmacy; 15 percent—or that amount used by the pediatric division—is purchased from commercial vendors on a bid basis because pediatric solutions are needed in small sizes and requires special bottles.

The pharmacy also prepares many medications in multiple dose vials and manufactures certain liquid preparations, detergents, ointments, and creams. The types of items manufactured by the hospital pharmacy are listed in exhibit D. (See exhibit D: Items Manufactured by the Los Angeles County General Hospital Pharmacy.[4])

Many ointments and creams are formulated by the hospital staff and are not available commercially. Other ointments are very expensive and are available only in small containers, such as 5-gram, or 15-gram tubes—these items are prepared by the pharmacy and packaged in amounts usually ordered by the physicians.

When new treatment programs are initiated, the pharmaceutical materials specified by the staff are often unavailable commercially; 0.5 percent silver nitrate solution was recently found to be very beneficial in the treatment of burns. Our burn service requires 200 gallons of this solution per week. The pharmacy prepared this because there was no other way of doing it; when the solution became commercially available, we continued to manufacture it because of cost saving. Another example of this service to the physicians was in the peritoneal dialysis program for renal failure. The chief pharmacist formulated the necessary solutions and manufactured them.

It is estimated that $1,130,000 is saved annually by our manufacturing division.

Senator NELSON. As I recall it, in the first part of your statement you stated that you spend $2 million a year on drugs?

Dr. MCCARRON. Yes.

Senator NELSON. And you calculate then, if you were not manufacturing that you would be spending $3 million?

Dr. MCCARRON. Yes; definitely. And we can show that just by multiplying the cost of what we make by the retail cost, or rather the wholesale cost.

SUMMARY

In summary, the drug formulary system at the Los Angeles County General Hospital provides the staff with standard, familiar medications and enough information to use the drugs intelligently. It has improved the teaching of physicians and nurses and thus affords an added degree of protection for the patients.

It has eliminated from the drug supply at the hospital those items with little or no therapeutic effectiveness, has substituted some toxic agents with less toxic ones, has replaced some very expensive items with less costly ones, and has allowed the pharmacy to maintain a manageable inventory.

The manufacturing division of the pharmacy improves service to the patients and the staff and has contributed to the overall saving in the hospital drug budget.

Senator NELSON. I notice, Doctor, referring back now to your formulary, that this is a representative excerpt?

Dr. MCCARRON. This is a printed front and back of one page. I had it Xeroxed. The formulary sheet is a half-sized page. You can see that this would be the formulary, printed front and back.

[4] See p. 598.

Senator NELSON. What resources do you use in addition to your own physicians, for determining side effects?

Dr. MCCARRON. Well, we have a system for this. First, as I mentioned, we have an adverse drug reporting program for adverse side effects that we have observed ourselves.

We keep a file on every drug that is in the formulary, and many of them that aren't. We subscribe to the Medical Letter, Clinalert, and there are many publications like these besides the medical journals that give us information on drug effects.

We get information from the manufacturers. We get as many reprints as we can find, and then we subscribe to certain journals. One of my jobs is to go through all these journals and look for all the drug material.

This is then filed in the drug file, and we do this for all formulary drugs and for a drug that we think may be coming up for deliberation. We assemble these things. Whenever something is being written up in medical literature pertaining to drugs we make sure that we accumulate this information.

Then, when it comes time to evaluate the drug for the therapeutic committee we have the necessary information. All of the members of the committee have similar systems, and we spend a lot of our time going through the medical literature, and this formulary page is the compilation of that information.

This is not all of the things, by any means, but these are the significant things that we quote in the formulary write up.

Senator NELSON. As I remember the early part of your statement, there were some 2,700 attending physicians, privately practicing physicians?

Dr. MCCARRON. 2,400 physicians who are in private practice, and you see, we do this work for them. They don't have enough time to go through the medical literature, but we do, and we abstract it for them, and we give them either the formulary sheet or the drug bulletin, and they accept this as an authoritative guide to their drug usage.

Senator NELSON. Are the private physicians who are not on the permanent and full-time staff of the hospital required to prescribe from the formulary for their patients who are in the hospital?

Dr. MCCARRON. The attending physicians do not have patients in the hospital. The system in our hospital is that the patients are assigned to a resident supervised by a full-time staff member, who is a member of the faculty of the medical school. The attending physicians come in to help with the therapy, and they suggest things, but we all use the same formulary.

Senator NELSON. I don't understand the function of the 2,400 attending physicians.

Dr. MCCARRON. They come into supervise the care of the patients on the ward.

Senator NELSON. Are they their patients?

Dr. MCCARRON. No; they are not their patients.

Senator NELSON. The hospital hires them?

Dr. MCCARRON. No; they come voluntarily. An attending man in practice comes to the hospital to help in the teaching of the residents and interns. All of these attending physicians are on the clinical faculty of the medical school. They come in. They operate on the patients. They do tests. They do whatever has to be done, in an advisory capacity.

Senator NELSON. This is all donated services?

Dr. MCCARRON. Yes.

Senator NELSON. But this formulary is available to all of the 2,400 physicians; is that correct?

Dr. MCCARRON. Oh, yes; and many of them have asked for personal copies. They take them home or use them in their offices.

Senator NELSON. Do you get requests for your formulary from physicians who are not on the staff and not attending physicians, but simply private physicians?

Dr. MCCARRON. We have had requests for our formulary from all parts of the country, to the point where we are having it printed next year, and we will probably sell it.

Mr. GORDON. I have several questions, Senator.

On page 12, in discussing your formulary, you say that "it has eliminated from the drug supply" the cost of "those items with little or no therapeutic effectiveness."

Can you give us some specific examples on that?

Dr. MCCARRON. Yes; I think meprobamate is a good example. We took meprobamate out of the formulary. It was a very commonly used tranquilizer and it was used as a muscle relaxant. We found no good scientific evidence that this drug did either. It had mainly a placebo effect, and we felt we were spending too much money buying meprobamate, that we had cheaper placebos, and we just took it out. Now, when we do that, we write a drug bulletin and explain to the staff what the scientific evidence is behind this decision.

Mr. GORDON. That is one of them.

Do you have a couple more, offhand?

Dr. MCCARRON. I can't think of—yes, I can think of many things. We had an ointment, Allantoin Ointment, that had been in the pharmacy forever, and the physicians in the hospital had gotten used to using it. They did not know what it was, really, because nobody had ever evaluated it. But they used it for burns. It turned out that Allantoin is a chemical that is found in the urine of maggots and maggots were found to clean wounds during World War I. Somebody discovered that the Allantoin in the maggot urine was also present in the urine of horses and dogs, and then they extracted it and chemically synthesized it, and put this into an ointment base. We started using it as an ointment for the treatment of wounds, and obviously, this had little if any therapeutic effectiveness. There are many other drugs that were much better.

Mr. GORDON. On what basis did the doctors use this in the first place?

Dr. MCCARRON. Well, for something like that, it had been in the hospital for years. It had started out when we did not have a formulary system, and people applied this to wounds. It had gotten to the point, and this is one of the things that we try to overcome, that instead of knowing what you are doing and what the drug is, you learn from somebody else that this is good for this condition.

Mr. GORDON. Are there any figures available which show how great the savings are as a result of adopting a formulary system? I don't think I have it here. Maybe I missed it, but I can't seem to find it.

Dr. MCCARRON. Now, that is very hard to say. We can give you examples on individual items.

Mr. GORDON. That would be fine, if you could.

Dr. McCarron. We now buy hydrochlorothiazide on a bid basis. Previously, we had chlorothiazide, Diuril, which is only made by one manufacturer, as the standard diuretic in the hospital. Chlorothiazide was the first thiazide diuretic out, and it became popular with the physicians. We deleted chlorothiazide from the formulary when hydrochlorothiazide came out because hydrochlorothiazide, we thought, had a little advantage over chlorothiazide, but mainly, it was made by three companies, and we had a competitive advantage, so we took out the chlorothiazide and accepted bids on hydrochlorothiazide.

Both of these drugs at the beginning were $5.50 a hundred.

Mr. Gordon. All three of them?

Dr. McCarron. The hydrochlorothiazide, yes, from three manufacturers, and the chlorothiazide were the same price. The first bid that we got came in at about $5.50 a hundred. The next time, the bid came in at about $3.80 or $3.60. The next time it was down to about $2.70 a hundred, and we finally got this drug down to about $1.20 per 100. However, the retail price of the drug has not changed, using the "Red Book Guide to Pharmacy Prices."

So that by having three companies bid against one another for the large business in the county hospital, we were able to effect a true saving, and that item happens to be used in all, or practically all, of the departments in the hospital.

Mr. Gordon. But here is a case where you can have competition among different trade names; is that correct?

Dr. McCarron. Yes. We ask for hydrochlorothiazide. It happens that this drug is made by three major companies, and we had no qualms about accepting the drug from either one of the three.

Mr. Gordon. In selecting drugs for inclusion in the formulary for the Los Angeles County Hospital, 950 drugs previously stocked were eliminated from the hospital inventory. How about the 550 remaining drugs? Do they cover all types of illnesses for which a patient may be hospitalized?

Dr. McCarron. Yes.

Mr. Gordon. And would it be fair to say, then, that many of the drug products on the market are duplicative?

Dr. McCarron. I am sorry, we didn't just eliminate duplicates.

Mr. Gordon. Duplicates, as well as useless drugs?

Dr. McCarron. Well, many drugs are a little bit different, and you can't say they are therapeutically equivalent, but they are used for treating the same condition.

Mr. Gordon. Yes.

Dr. McCarron. And we can pick a particular drug. Say there are 10 drugs available for treating this particular condition, and they each may vary a little bit, so they are really not duplicates. But we can pick three or four of those to start.

Mr. Gordon. The variations were not sufficient to keep them in the formulary?

Dr. McCarron. That is right.

Mr. Gordon. They were not meaningful variations; is that correct?

Dr. McCarron. That is right.

Mr. Gordon. Do all of the 2,400 attending physicians prescribe generically?

Dr. McCarron. As I said before, the orders are written by the residents.

Mr. Gordon. I see, and they prescribe generically?

Dr. McCarron. Yes.

Mr. Coughlin. Dr. McCarron, I notice on page 5 of your statement you enumerate the system followed in the purchase of drugs, and No. 3, you say, "A Drug Specification Committee writes the specifications for the drugs."

I am curious to know whether these are chemical specifications only, or are branded or trade-name drugs included, listed, if a therapeutic difference has been noted by the committee?

Dr. McCarron. Yes. The specifications are written by the committee and they use the generic name unless there is a reason for not using the generic name, but most of the specifications are chemical. Some of them have to do with labeling also, and packaging.

In certain cases, if we want to limit the drug to one manufacturer, we must justify this to the Drug Specification Committee. The Therapeutic Committee sends in a statement saying why we will not accept anything but this particular drug.

Mr. Coughlin. Is this predicated upon your own independent testing?

Dr. McCarron. It is usually because of experience we have had with the drug.

Mr. Coughlin. I am interested in a quotation which appears on page 10 of your statement, doctor. I quote:

> On occasion, non-critical drugs are also specified by manufacturer because of previous experience in obtaining ineffective drugs when generic equivalents were used.

I notice that you alluded to the thyroid hormone during your testimony as an example of this. I was wondering if you have any other examples or if you know of other drugs that fall in that category?

Dr. McCarron. Well, I have a list here of all the drugs we buy by specified manufacturer. I am not sure what all the reasons were for this, but I can tell you some of them.

Under antibiotics, for parenteral use, we specify chloramphenicol from Parke, Davis. We found when you added the generic equivalent for chloramphenicol to water the drug clumped and did not go into solution so obviously the patient wasn't going to get the right amount of drug. We just said we don't want to have this happen. We haven't had any trouble like this using Parke, Davis' brand, so we buy Chloromycetin.

Mr. Coughlin. May I ask you, Doctor, whether the generic brand satisfies the requirements of the U.S. Pharmacopeia?

Dr. McCarron. It apparently did, or we wouldn't have accepted it in the pharmacy at all.

Mr. Gordon. Excuse me, doctor.

Concerning chloramphenicol, when was this that you are talking about, what was the date?

Dr. McCarron. June 8, 1967. That is when this last list came out.

Mr. Gordon. The patent just came off.

Dr. McCarron. The chloramphenicol patent just came off.

Mr. Gordon. That is a dangerous drug anyhow, isn't it, doctor?

Dr. McCarron. Yes, and we have restrictions on it. But it has therapeutic usefulness in certain conditions.

Mr. Coughlin. And you use it?

Dr. McCarron. Oh, yes.

The corticosteroids for parenteral use we also specify by brand. This is mainly because the patients who need these drugs need them in a hurry for emergency conditions, and we want to use drugs that we have had experience with and know are effective, and we do not want any variation.

For cardiac glycosides we have six that we specify by brand. Tensilon, which is a drug used to make the muscles tense up again after a patient has received a muscle relaxant during surgery, is another very important drug that we buy only by brand name.

Some of our estrogenic substances were found not to be effective. Again, these are hormones, and we have a very difficult time with hormones. Even if they meet the standards that have been laid down, sometimes they don't have biological activity. So we have specified certain hormone substances by brand names.

We also had some problem with heparin. We bought generic heparin, and the patients were not anticoagulated as they had been before. There were variations in the dose required, so we standardized on the liquaemin heparin. There are several other drugs listed here, vasopressors, glaucoma agents, demercarium, and all of our spinal anaesthetic agents.

Mr. Coughlin. Will you make that list available for the record, with the permission of Senator Nelson?

Dr. McCarron. Yes.[5]

Mr. Coughlin. One final question with respect to this general discussion.

Does your hospital accept any brand of oral antidiabetic product?

Dr. McCarron. Any brands?

Mr. Coughlin. Any brand. On a generic basis, or do you purchase by brand name?

Dr. McCarron. Well, we specify chlorpropamide tolbutamide acetohexamide, and as I understand it there is only one company that makes each of these drugs.

Mr. Coughlin. Thank you, Senator Nelson.

Senator Nelson. Did I understand that out of your formulary of some 550 drugs that less than 50 are ordered by brand name?

Dr. McCarron. That is right. There are 43, and I have the list here.

Senator Nelson. Forty-three?

Dr. McCarron. Yes.

Senator Nelson. And the other 500 are generic?

Dr. McCarron. Generic.

Senator Nelson. Doctor, I want to thank you very much for your very valuable testimony. We are very pleased that you inserted an example from your formulary. This has been very instructive and useful for the committee.

We appreciate your taking the time to come here.

Dr. McCarron. Thank you.

(The supplemental information submitted by Dr. McCarron follows:)

[5] See p. 599.

EXHIBIT A

DRUG BULLETIN: COUNTY OF LOS ANGELES, DEPARTMENT OF HOSPITALS

[No. 50, Los Angeles County General Hospital Therapeutics Committee, May 25, 1967]

FUROSEMIDE (LASIX, HOECHST CO.)

Furosemide, a monosulfamylanthanilic acid derivative, is a non-thiazide diuretic quite similar in potency and mode of action to ethacrynic aid. In maximally effective doses, furosemide is probably 8 to 10 times as potent as thiazides in increasing the excretion of sodium (1). In most cases potassium excretion is slight in relation to the natriuretic effect. Because of its mode of action, there is a strong tendency toward fluid and electrolyte disturbances, especially hypovolemia, hypokalemia, and hypochloremic alkalosis. In contrast to mercurial diuretics which lose effectiveness when alkalosis appears, furosemide—like ethacrynic acid—continues to be effective and may augment the electrolyte disturbance. To provide a safe diuresis, rapid decrease in plasma volume must be avoided, alkalosis must be prevented, and potassium balance must be maintained.

Action of furosemide: The biochemical basis of action is not known. Furosemide probably inhibits the reabsorption of sodium and water in the proximal tubules and the loop of henle and may also have some effect on the distal tubule. Sodium reabsorption may be decreased by as much as 30% (2). During maximal diuresis with furosemide, urine output may reach ⅓ of the glomerular filtration rate (3). Chloride is also excreted in large amounts and bicarbonate is retained; this may lead to hypochloremic alkalosis (4). The amount of potassium loss is variable, but is usually more marked in patients with cirrhosis of the liver.

Effect of furosemide with other drugs

Furosemide has an effect similar to thiazides in lowering blood pressure and potentiates the hypotensive effect of antihypertensive agents. It decreases the arterial responsiveness to pressor amines and enhances the effect of tubocurarine.

Maximal diuresis with thiazides can be enhanced by the administration of furosemide, but maximal diuresis with furosemide is not altered by adding thiazides. Robson concluded that there was no advantage in combining thiazides with furosemide (3). However, the administration of spironolactone with furosemide in patients where there is danger of hypokalemia seems to be of benefit.

Use of furosemide

Because of its potency, this drug should be used with caution. Furosemide is particularly useful when an agent with greater diuretic effectiveness than the thiazides is needed for patients with refractory endema. Furosemide is effective in the presence of depressed glomerular filtration, acidosis, alkalosis, and hypoalbuminemia (5). This drug has been used successfully in patients with renal insufficiency and the nephrotic syndrome (5, 6) but should not be used when the patient is anuric.

When used in the management of ascites due to cirrhosis of the liver, special care must be taken to avoid rapid fluid depletion and electrolyte disturbances.

If excessive diuresis is avoided, furosemide may be used for the treatment of acute pulmonary edema.

Outpatients may be treated with furosemide, usually on an intermittent schedule, but the patient should be followed closely and electrolyte disturbances should be anticipated.

Contraindications to the use of furosemide: The safety of furosemide *in pregnancy* has not been determined. The drug is not recommended for cirrhotic patients *in hepatic coma* or those *with severe electrolyte disturbances* until the basic condition is improved or corrected. Furosemide is contraindicated *in anuria.* It is not recommended for the treatment of hypertension. Until further evidence of its safety is obtained, it is not recommended *for children.* Since furosemide enhances the effect of tubocurarine, great care should be exercised in administering curare-like drugs to patients receiving furosemide. NOTE.—It is advisable to discontinue furosemide therapy for one week prior to surgery if possible.

Untoward Effects of Furosemide

Adverse effects related to the drug's potency include rapid massive diuresis, hypokalemia, hyponatremia, and hypochloremic alkalosis. Excessive diuresis may result in hypovolemia and shock which may lead to arterial thromboses—particularly in elderly patients. Sometimes a marked fall in plasma volume results in decreased renal function—this is a result of the potent diuresis rather than a toxic effect of furosemide.

Electrolyte disturbances may be manifested as lethargy, weakness, dizziness, leg cramps, anorexia, vomiting, and/or mental disturbances (2). Hypokalemia may be a special problem in patients with cirrhosis of the liver and may precipitate hepatic encephalopathy. Cardiac patients being treated with digitalis may develop arrhythmias if hypokalemia occurs. Some patients may complain of epigastric discomfort when therapy with furosemide is started; this may disappear with continued treatment or may necessitate stopping the medication.

Skin rash, paresthesias, blurring of vision, pruritus, postural hypotension, and diarrhea may also occur. Hyperurecemia (6) and acute gouty attacks (2,6) have been reported. Hyperglycemia may also complicate treatment with furosemide (4). One case of thrombocytopenia and several of leukopenia have been reported in patients taking this drug.

Absorption and Excretion of Furosemide: Furosemide is well absorbed from the GI tract. About 40% of the drug is excreted in the stool, 10% in the urine, and small amounts in the bile and milk (6).

Timing of Therapeutic Effect With Furosemide

After oral administration, diuresis begins within 1 hour and lasts for 3 to 5 hours. Maximal effectiveness, if this is desired, can be obtained by giving the drug every 4 to 6 hours. In most instances, 1 dose per day is sufficient.

After I.V. administration, the drug acts within about 5 to 30 minutes and lasts from 1½ to 4 hours. (NOTE: an I.V. preparation is being tested and is not yet available commercially.)

Dosage and Administration of Furosemide: Furosemide is given orally. The patient should be carefully followed and excessive weight loss should be avoided.

Usual Adult Dose: Use the smallest effective dose. Begin with one dose of 40 to 80 mg in the morning. If the diuretic response over the next 4 to 5 hours is inadequate, a second dose of 40 to 80 mg can be given 6 to 8 hours after the first dose.

For More Resistant Cases: Up to 300 mg daily may be given.

For Maintenance Therapy: The dosage should be adjusted according to the patient's requirements for continued diuresis and his serum electrolyte levels. 40 to 80 mg every other day may be safe and adequate.

Children's Dose: At this time furosemide is not recommended for children.

How Supplied: Tablets 40 mg.

Approx. Retail Cost: About $8.40 for 100 tablets.

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2. Stokes & Nunn, *Brit, M. J.*, 910, Oct., 1964
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4. Hutcheson, et al., *Arch. Int. Med.*, 115: 542, May, 1965
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EXHIBIT B

[Page from the Los Angeles County General Hospital Formulary]

PHENYLBUTAZONE
(GENERIC NAME)

Brand name: Butazolidin (Geigy)

Category: Analgesic; antipyretic

Description: Phenylbutazone is a potent analgesic and antipyretic drug. Like aminopyrine, from which it is derived, phenylbutazone may be toxic to the bone marrow and may cause severe and even fatal reactions.

Action: The mechanism of action is unknown. In addition to its analgesic and antipyretic effects, the drug may act on the renal tubules to inhibit the reabsorption of urate and to increase the reabsorption of sodium.

Use: The usefulness of this drug is limited by its toxicity. Phenylbutazone is not recommended for prolonged administration, but it has some usefulness when given for very short periods (2 or 3 days) in the treatment of acute musculoskeletal disorders such as gout or bursitis.

Untoward effects: In 1955, Mauer (1) found *22 deaths* due to this drug in the literature and added a case of his own. Since then other deaths have been recorded. Fifty serious complications and *18 deaths* were reported in the United Kingdom during a 20-month period in 1964–1965.

Incidence of adverse reactions with this drug is 40%. In general, untoward effects are more apt to occur with high dosage or prolonged administration. However, death has occurred from small doses and short-term therapy. *The most frequent reactions are* nausea, edema, rash, epigastric pain, vertigo, and stomatitis. *The most serious* are reactivation of peptic ulcer—sometimes with severe hemorrhage, agranulocytosis, thrombocytopenia, aplastic anemia, exfoliative dermatitis, C.N.S. stimulation or depression—occasionally with psychosis or visual hallucinations, hypertension, and toxic hepatitis. In addition, *acute renal failure* has been reported in a healthy man on the sixth day of treatment for back pain (2). This complication has also been noted before (3, 4). *"Allergic granulomas"* may occur. Rash, fever, lymphadenopathy, and hepatosplenomegaly were reported after 200mg daily for six weeks; biopsy showed "sarcoid-like" granulomas which disappeared in four month after the drug was stopped (5). Another patient had rash and generalized lymphadenopathy on three separate occasions when the drug was given—after taking it for six weeks, for a few days, and after only one tablet (6). Another patient had painful swelling of parotid and submaxillary glands on two occasions after taking phenylbutazone (7). It is suggested that "allergic grandulomas" may also occur in the heart.

In 1957, two fatal cases of phenylbutazone-induced *cardiac complications* were reported—one with pericardial effusion and interstitial myocarditis; the other with multiple focal perivascular granuloma (8). A woman who had taken the drug for one week developed pericarditis and recovered (9). One patient developed phenylbutazone skin rash and died; at autopsy, extensive perivascular granuloma-like lesions were found in the heart (10).

Phenylbutazone depresses the bone marrow in some patients and causes leukemoid reactions in others. In 1960, Bean (11) reported six cases of *leukemia in patients who had taken this drug* and suggested a cause and effect relationship—which has not been proved although many additional cases have been reported. The only statistical study comes from Western Australia where eight of 55 patients with acute leukemia had taken phenylbutazone. Since rheumatoid arthritis may be associated with leukemia, Innis (13) cautioned against incriminating phenylbutazone until the incidence of leukemia in rheumatoid arthritis treated with and without phenylbutazone was studied. However, cases of leukemia in non-rheumatoid patients are of interest, along with cases who developed sensitivity reactions to phenylbutazone followed in a short time by the onset of leukemia (14, 15, 16, 17).

Timing of Therapeutic Effect: The pain of acute gout is usually relieved within 24 hours after phenylbutazone administration, but joint swelling usually does not subside for 3 or 4 days. The drug is slowly excreted over a 7–10 day period.

Dosage & Administration: The smallest effective dose should be used for the shortest amount of time possible. The patient should be closely followed for signs of toxicity. The drug is given orally.

Adult Dose: 600 to 800 mg daily in 3 or 4 divided doses for 2 or 3 days. Maintenance therapy is not recommended.

How Supplied: Tablets: 100 mg

Approx. Retail Cost: About $10.00 for 100 tablets (100 mg).

Special drug request forms must accompany orders for this drug because of toxicity.

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17. Thorpe, *Brit. Med. J.*, 1 :1707, 1964.

EXHIBIT C.—*Los Angeles County General Hospital Prescription Form*

LOS ANGELES COUNTY
GENERAL HOSPITAL
1200 N. State, Los Angeles, Calif. 90033

Ward or Clinic ADMITTING ROOM

℞ No.

P.F. # _____

Name _____
Surname First Name

Address _____
Number Street

_____
City State

℞ (or USP, NF, NND, or Generic Equivalent.)

Date _____ _____ M.D.

CHECK: Non-Rep ☐. Rep: XI ☐. X2 ☐. X3 ☐. Reg. No. _____

76P574---543---2-64

EXHIBIT D.—*Items manufactured by the Los Angeles County Hospital Pharmacy*

Category and sample items	Annual production	Estimated annual savings
Intravenous solutions (1 liter size) 5 percent dextrose in water, 5 percent dextrose in saline, 5 percent dextrose in ½ normal saline, normal saline, and multiple electrolyte solution.	500,000 liters	$130,000
Multiple-dose vials (15 cc., 30 cc., and 60 cc. sizes) Aminophylline for injection, calcium salt solutions, distilled water for injection, epinephrine solution, normal saline for injection, procaine solution, Vitamins for injection, and 50 percent dextrose solution.	140,000 units	
Liquid preparations Antiseptics, disinfectants, detergents, laboratory reagents, cough syrups, potassium supplements, and silver nitrate solutions.	100,000 gallons	500,000
Ointments and creams Ammoniated mercury ointments, coal tar ointments, hydrophilic petrolatum, lanolin and cold cream, triamcinolone ointments, and sulfur ointments.	11,000 pounds	500,000
Total yearly savings		1,130,000

LOS ANGELES COUNTY GENERAL HOSPITAL, JUNE 8, 1967

List of drugs to be restricted to specific vendors (when listed), to "A" class company (if printed in italic), or to previously acceptable vendors (if marked with asterisk). Any other vendor for these items must be cleared by the Drug Specifications Committee and by the service most involved and/or the Therapeutic Committee of the Hospital ordering. This list was developed by the Los Angeles County General Hospital Therapeutics Committee for the protection of this hospital and the guidance of the County Drug-Purchasing Agent, and may be periodically revised.

Antibiotics for Parenteral Use:
- *Chloramphenicol*
- Penicillin*
- *Polymyxin B*
- Streptomycin*
- *Tetracycline*

Corticosteroids for Parenteral Use:
- Cortisone*
- Hydrocortisone*
- Hydrocortisone Acetate*
- *Hydrocortisone Sod. Succinate*
- *Hydrocortisone 21 Phosphate*
- *Prednisolone*
- *Triamcinolone*
- *ACTH*

Cardiac Glycosides:
- *Deslanoside*
- *Digitalis* & the Davies Rose Co.
- *Digitoxin Tablets*
- *Digoxin Tablets* & Fougera & H. & Co.
- *Digitoxin Injectable* & Fougera
- *Digoxin Injectable* & Premo & Vitarine
- *Edrophonium* (Tensilon, Ciba)
- *Epinephrine* 1:100 1cc

Estrogens:
- *Estrogenic substance,* conjugated injection (Premarin)
- *Estrogenic substance,* conjugated tablets (Premarin)
- Diethyl Stilbestrol*
- *Heparin*
- *Isoproterenol Parenteral*
- Oxytocin (Syntocinon, Sandoz, or Pitocin, P.D. *only*)
- *Pentylenetetrazol*
- *Picrotoxin*
- *Procainamide*
- *Quinidine* Injection

Spinal Anesthetics:
- *Dibucaine* (Nubercaine)
- *Procaine* (Novocaine)
- *Lidocaine* (Xylocaine)
- *Tetracine* (Pontocaine)
- Succinyl Choline (Amectine, B&W *only*)
- Thyroid (Armour brand *only*)
- *d-Tubocurarine*

Vasopressors:
- *Levarterenol*
- *Mephentermine*
- Meteraminol (Armine, MSD or Pressonex, Winthrop *only*)
- *Methoxamine*
- *Phenylephrine* Parenteral
- *Warfarin Parenteral*
- *Warfarin Tablets*

Glaucoma Agents:
- *Demercarium Br.* (Humorsol, MSD)
- *Echothiophate Iodine* (Phospholine Iodine)
- *Isoflurophate* (Floropryl, MSD)

Diagnostic agents and kits are not to be changed from item ordered unless cleared by the hospital or physician.

Senator NELSON. The next hearing of the subcommittee will be on July 24, 1967, at 10 a.m., in this room.

(Whereupon, at 12:35 p.m., the subcommittee adjourned, to reconvene at 10 a.m., Monday, July 24, 1967.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

MONDAY, JULY 24, 1967

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

The subcommittee met, pursuant to adjournment, at 10:05 a.m., in room 318, Old Senate Office Building, Senator Gaylord P. Nelson (chairman of the subcommittee) presiding.

Present: Senators Nelson and Javits.

Also present: Benjamin Gordon, staff economist; Daniel T. Coughlin, minority counsel; Susan H. Hewman, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator NELSON. The Subcommittee on Monopoly of the Small Business Committee will open its hearings this morning. Our first witness is Mr. Harold W. H. Burrows, president of Parke, Davis & Co.

I understand, Mr. Burrows, that Mr. Kenneth McGregor, vice president and general attorney, is accompanying you.

STATEMENT OF HAROLD W. H. BURROWS, PRESIDENT, PARKE, DAVIS & CO., DETROIT, MICH.; ACCOMPANIED BY KENNETH D. McGREGOR, VICE PRESIDENT AND GENERAL ATTORNEY

Mr. BURROWS. Yes, sir.

Senator NELSON. Mr. Burrows, we appreciate very much your taking the time to come here this morning and appear before the Monopoly Subcommittee. You may present your statement in any way you see fit, either by reading it or extemporaneously.

Mr. BURROWS. Senator, would you prefer that I read the statement?

Senator NELSON. However you prefer to present it. It is a short statement, and perhaps you would prefer to read it. If it does occur to me to ask questions during the course of your presentation I assume you have no objection.

Mr. BURROWS. No.

Senator NELSON. The committee is happy to have you as representative of one of the distinguished drug companies in this country. Despite what you may have read in some of the journals and trade magazines, we are not antidrug companies. We think the druggists and drug manufacturers have made a great contribution to medicine and the health and welfare of the people of this country, and your company is among the leading ones in the drug manufacturing and invention field. You have made a great contribution to the health of the country, and we are sure your company will continue to do so.

This committee is interested in some matters that we think are of public concern, but that doesn't make the committee antimedicine or antidrug company or antianything else. It is conceivable we may have some differences in our interpretation of the practices and in various aspects of the field, but they certainly would be honest differences of opinion, and we are very pleased to have you come here and make your contribution. It will be of value to the committee and to the Congress and to the country.

Mr. BURROWS. Thank you very much, Senator Nelson. I appreciate those comments. I also might take this occasion to express my appreciation of the manner in which I was invited. I thought perhaps I might get a letter saying "laying aside all your excuses and the like, appear." Instead I received a very courteous letter embodying very fine use of the King's English. Other committees who have occasion in the future to invite witnesses might well take the text of your invitation as an example.

Senator NELSON. I might say, Mr. Burrows, that we appreciate your courtesy and willingness to postpone your appearance. At the time we had asked for 10 days advance on your statement, and I know that it was impossible to give us 10 days, and we appreciate your willingness to set another date.

Some questions have been raised in the trade about why I asked for 10 days. The answer is very simple. We have a staff of one economist and one fine young lady researcher, and with my busy schedule it is necessary for me to read all the testimony in advance if I am to attempt to ask any questions whatsoever. Therefore, I have to have 10 days if I am going to go through the testimony and familiarize myself with it so that I can attempt to ask some questions that would be of value. That is the reason for the request that we have 10 days advance, and we appreciate your courtesy in complying with our request.

Mr. BURROWS. Shall I proceed with my statement?

Senator NELSON. Yes.

Mr. BURROWS. As the committee is well aware, prednisone is a steroid compound used primarily in the field of arthritis. It has been generally available in the market since about the middle 1950's.

In 1956 Parke-Davis decided to add a prednisone product to our list of products under the Parke-Davis label. When we made that decision, several of our major competitors already were selling this compound and it seemed probable that it would be a standard pharmaceutical item that would continue to be prescribed by physicians for a long time. At that time we had a major interest and program in steroid research and development and we felt it important to be represented in this apparently growing field. "Paracort" is the name under which we offered our brand of prednisone for sale beginning in 1957.

When we introduced the product, we did not expect to become a major factor in the prednisone market; however, as a minimum, we wanted to have it available as a standard item in our line. During the first 2 years we made an earnest effort to establish our product in the market and actively promoted Paracort to the medical profession.

For the next sentence in the formal statement I would like to add the words "United States" after the first word so as to read: "Our United

States sales in those early years achieved an annual volume in the range of $225,000 but subsequently steadily declined."

Senator NELSON. May I interrupt, Mr. Burrows? Was that mainly on the retail market?

Mr. BURROWS. It was to all classes of trade with which we did business at the time. I don't believe that I have with me a breakdown of the sales volume by classes of trade at that time, but most of our sales then were directly to the retail trade.

Senator NELSON. Directly to the retail trade?

Mr. BURROWS. That would be our normal channel of distribution.

Senator NELSON. Is $225,000 the maximum you reached in total sales?

Mr. BURROWS. That was the maximum amount that we received. It was not the total at list prices. It was the total of our selling prices to whoever our customer happened to be, the retailer, the wholesaler, or whoever.

Senator NELSON. But is this the maximum that you reached in sales?

Mr. BURROWS. Yes, it was the maximum.

Senator NELSON. Would it be feasible for you to furnish the committee what amount of this was the retail market—when I say retail market I mean your wholesalers who sell to the retailers—versus to Defense Supply Agency or hospitals directly.

Mr. BURROWS. I believe we can get you that information, but I do not have it with me today.

Senator NELSON. The committee would appreciate it if you would supply it to us.

Mr. BURROWS. Thank you. We will submit that information.[1]

Mr. GORDON. What are your total worldwide sales of this product?

Mr. BURROWS. In the first year of introduction, we had additional sales outside the United States of $35,000, and the second year additional sales outside the United States of $156,000.

Mr. GORDON. That was the most foreign sales you ever had.

Mr. BURROWS. Yes.

Mr. GORDON. Can you give us any idea as to why the sales steadily declined?

Mr. BURROWS. As I noted previously in my statement, several of our competitors already were on the market before we entered the market, and that gave them quite a competitive advantage inasmuch as we could not claim for our product attributes which were superior to the products already on the market. The first one on the market with an effective drug has quite a competitive advantage.

I will continue with the reading of my statement. One of the contributing factors in the decline during this period of time was the fact that other manufacturers with significant research programs in this field were able to introduce newer and improved steroid compounds for use in treating similar conditions. As a result, we concluded that our potential for prednisone sales was on the decline and we lost active interest in the product.

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[1] The information requested by Senator Nelson was subsequently supplied. Parke, Davis states, "that on the basis of the best available estimates approximately $145,000 of the total 1957 sales were made to the retail trade either directly or through wholesalers."

Parke, Davis is still very interested in making an original contribution in the field of arthritis and related diseases. We have continued with our own research work and we have expended substantial sums of money for this purpose.

It has been estimated that in the year 1966 the industry sold about $4 million of prednisone in the United States. Parke-Davis sold only $29,465 of this drug in that year in the United States, representing less than 1 percent of that market.

Senator NELSON. May I ask a question at this point? As I understood you a moment ago, the major portion of your sales were into the retail trade. Does the fact that your sales declined relate to the question of how or by what name the doctor prescribes the drug?

Mr. BURROWS. You mean insofar as the retail trade is concerned?

Senator NELSON. Yes.

Mr. BURROWS. The chances are that the doctor who prescribes the original compound put out by the first house on the market with that compound found it to be effective and satisfactory. It did what was claimed for it and there was no reason why the doctor should change. Presumably he kept on with the first product that he found to be safe and effective.

Senator NELSON. So this is the question of familiarity to the prescribing physician in the competition for the prescription of various brand names of prednisone.

Mr. BURROWS. That certainly is a factor.

Senator NELSON. Did your company consider reduction in the price to the retail trade to meet the competition?

Mr. BURROWS Apparently we did not. As I am about to say in a following part of my text, I doubt that we can justify carrying this item for sale to the retail trade, because we are such an insignificant factor in this field. I think that we probably didn't do the best job that we might have done in monitoring our catalog. I really am surprised that it continues to be listed there considering the small volume of sales that we have. But sales departments are inclined to be sort of product "string savers," and once an item gets into the catalog, it can be difficult to persuade them to remove it.

Senator NELSON. But originally, as I understand it from your statement, you made a genuine effort to sell your product at the retail trade level.

Mr. BURROWS. That is right.

Senator NELSON. You did achieve a level of somewhere around whatever portion of $225,000 is within the retail trade field.

Mr. BURROWS. That is right.

Senator NELSON. And then decided at some stage that you couldn't meet the competition with the more established drug Meticorten?

Mr. BURROWS. I wouldn't want to identify any one drug. But whatever the competition was, we weren't making any headway against it despite the fact that we spent reasonable amounts of money for advertising and promotion.

Prednisone sales represented only an insignificant fraction of our $138,700,000 sales in the United States during 1966. We do not now advertise the drug or promote it in any way to doctors or pharmacies, regarding it largely as an accommodation item. In fact, with our very low volume of present sales, I doubt if we can justify continuing to carry it in our catalog.

Our catalog net price to the retailer for 100 5-milligram tablets is $17.88. This is higher than the prices listed by many of the more than 70 other companies in this highly competitive business.

Senator NELSON. You mean 70 other companies that are producing prednisone?

Mr. BURROWS. Either producing or selling.

But since we make no effort to sell the product through retail channels our catalog price has no real significance or importance. Further, in recent years we have not actively promoted our product to physicians, and sales by us to retail drugstores have been practically nonexistent. The few sales of any consequence we do make are to hospitals and institutions on the basis of bids which we have submitted as a result of requests for quotations sent to us by such as city, county, State, and Federal agencies. In 1966 our average sales price of prednisone to such institutions in the United States was $1.36 per 100 tablets. This compares with the prednisone prices of various other suppliers which were cited in earlier testimony given to this committee ranging from 46 cents to $2.09 per 100.

You have asked for our costs and I am obliged to say that because of the very small amount of business we have done, it is not practical to determine our costs with any great degree of accuracy. We buy the basic raw material and then subject it to a number of quality and production tests and controls in processing it into final form for distribution.

Senator NELSON. From whom do you buy the basic material?

Mr. BURROWS. At the present time I believe we are buying from Upjohn. In the past we have bought from Roussel and Schering of Germany, and at the present time we are buying from Upjohn.

As best we can figure, the bare manufacturing cost of this item in 1966, including the purchase price of the raw material, was about 50 cents out of the average selling price of $1.36, or 37 percent of the selling price. This does not include any allocation for such as research, general overhead, handling, distribution, inventory carrying costs, and administrative expenses.

Senator NELSON. When you say research, did you do any research on prednisone?

Mr. BURROWS. Possibly. I think we did very little work on prednisone per se but we have done quite a lot of research on steroids in general. By about the time that prednisone was introduced, I think we had filed some 60 U.S. patent applications in the steroid field.

Senator NELSON. This price of $1.36 per 100 is the average sales price to hospitals and other sources on a competitive bid basis?

Mr. BURROWS. That is right; but it includes whatever minimal business we did at the retail level, which was practically nothing.

Senator NELSON. These bids to hospitals and other institutions were submitted on a generic or a brand-name basis?

Mr. BURROWS. They probably were requested on a brand-name basis?

Mr. MCGREGOR. Entirely.

Mr. BURROWS. We would submit our response to the bids with our product name Paracort, but it is quite conceivable that the requests for bids were on the basis of the generic name, prednisone.

Senator NELSON. Is it not correct that what you manufacture is prednisone and the name you give to your generic prednisone is your brand name of Paracort?

Mr. BURROWS. That is right.

Senator NELSON. Is there any difference, so far as you know, between your brand name, if it meets the USP standards, and any other prednisone that meets USP standards?

Mr. BURROWS. I don't know of any significant difference. On the positive side, however, I do know something about the drug that Parke, Davis manufactures, and I do know something about the quality controls that we introduce during the steps of manufacture that we are responsible for.

I can speak for Parke, Davis quality, but I don't think I am in a position to speak for the quality of other manufacturers. By that I don't mean to imply that other manufacturers have some lesser standards or lesser accomplishments of quality than does Parke, Davis. I only am capable of speaking for our own controls.

Senator NELSON. You are familiar with the Medical Letter which was published June 2 of this year, in which it reports on tests of 22 prednisones. Your company's product was among the 22 that was tested. Are you familiar with that?

Mr. BURROWS. Somebody handed me a copy of that Medical Letter just as I left Detroit, and I have read it.

Senator NELSON. In the Medical Letter it states that all of the 22 brand or generic prednisones that were tested met the USP standards, and yours was among those that met USP standards.

If drugs meet USP standards, doesn't that mean that those that do are, according to USP anyway, equivalent drugs?

Mr. BURROWS. They are equivalent in terms of those standards. Again, I am not a scientist, but I understand that the results in individual patients for drugs that meet USP standards may not necessarily be identical results. Even in this Medical Letter you will see a recitation on page 2, and I don't know what significance this has, of variations in the percentage of cortisone found in the various prednisone drugs of other manufacturers. The variations are all within the limits of the standards, but you will note that to the extent of the variations apparently all the drugs are not identical.

Senator NELSON. No; it isn't possible, I suppose, for any two drugs to be identical or even any two tablets out of the same batch to be identical, if we use the word "identical" in the strictest sense of the word.

The representative of the USP who testified here said that they established the highest standards in the world for drugs. Based upon their careful studies, they set limits within which there may be variations, and the variations may not exceed these limits and comply with USP standards.

As they stated to us, their standards are the highest in the world, and they set a variation tolerance which is narrow enough so that, in their judgment, all drugs that meet the standards are equivalent. As you will notice, and as I am sure you know, the USP standards are set as a consequence of the deliberations of very distinguished pharmacologists, pharmacists, clinical physicians, the representatives of the drug industry.

Mr. BURROWS. That is right.

Senator NELSON. And it may very well be that Parke, Davis has a representative on the council that establishes the USP standards.

Now I read to you from page 42 of the Medical Letter of June 2, 1967, and under the title "Prices" the Letter states:

The great price spread among tablets purchased from different pharmaceutical companies suggest the desirability of prescribing by generic name and specifying, at least for patients of limited means, that the prescription be filled with low priced prednisone tablets.

On page 41, it states:

None of the variations are outside Pharmacopeia limits—

That is of the 22 drugs they tested—

None of the variations are outside Pharmacopeia limits or of sufficient magnitude to have an adverse effect in the treatment of conditions requiring the use of corticosteroids. This disintegration test measures, only disintegration and not the rate of dissolution or physiological availability. There is nothing however, either in the reports of the clinical trials or in the experience of Medical Letter consultants to suggest that variations in formulations are causing any problems in the treatment of patients.

Do you have any evidence that would refute that statement?

Mr. BURROWS. On this product?

Senator NELSON. Yes.

Mr. BURROWS. No.

Senator NELSON. Are you aware of any clinical evidence from any source in medical literature or any source from the scientists within your company that would indicate there is any difference in the therapeutic efficacy or therapeutic equivalency of any of these 22 prednisone products that have been tested by the Medical Letter?

Mr. BURROWS. No, I am not aware of any such differences. But let me state again that I am not a scientist or a technician, and I am only in a position to stand behind the products that Parke, Davis makes and sells. We want to have our name associated with whatever we sell so that the doctor will continue to have the choice of prescribing a Parke, Davis product as such, be it a generic product or be it a specialty product with a brand name that includes directly or indirectly a reference to the Parke, Davis standards of quality that we have built into our drugs for so long.

By that statement let me say again that I am not intending to reflect on the quality capabilities or quality accomplishments of any other manufacturer. But we are in the business of advancing Parke, Davis as a company, advancing our products, and hopefully finding new products which we can introduce. That has been our business for 100 years. We have done it by building and maintaining a reputation for the name of Parke, Davis that the medical profession can rely on. They can rely on other names also. But we want the doctor and the pharmacist and the public to feel that they can rely on the Parke, Davis name and it is for this reason that we want to have our name associated with the products which we sell.

Senator NELSON. I think that the public and the medical profession certainly can rely upon the quality of the products that the drug companies produce, though all companies as you know may from time to time produce a product that represents a failure in quality control, as is inevitable. My question is aimed at the problem that is highlighted here by the Medical Letter.

Mr. BURROWS. I am not in a position to refute anything that is in the Medical Letter. I know of no evidence to the contrary.

Senator NELSON. Thank you. Go ahead. I think you were on the last sentence, page 4.

Mr. BURROWS. Actually, we may not in fact have achieved any profit on the small volume of prednisone sales which we made.

Senator NELSON. In the selling of the product at $1.36 for 100 tablets, I assume that whoever is responsible for setting the sales price intended at least that the product would make a profit and not a loss; is that not correct?

Mr. BURROWS. That would be their hope, but it doesn't necessarily follow that they are good accountants.

Senator NELSON. Do you have any evidence to submit to the committee that in selling at $1.36 for 100 tables, that the company did in fact sustain a loss in the production of and sale of this item?

Mr. BURROWS. I don't think that I could prove that the company actually incurred a loss. However, as an exercise, if we prorated our unallocated expenses in the United States such as our general and administrative expenses; our selling expenses and I will leave out advertising from the selling expense group because we did no advertising on this product; our excess of actual production costs over standard costs; a percentage factor for research; and if we add these prorations to our 50-cent base standard cost of manufacturing, we come out about even-steven. These added charges also would include the royalties paid on the product sold, cash discounts allowed on sales and the like that were involved in this particular product.

Senator NELSON. Do I understand you to say that if you took into consideration all factors of cost——

Mr. BURROWS. As we incurred them in the United States and related them to this average U.S. selling price of $1.36.

Senator NELSON. That you think you would have about broken even, is that correct?

Mr. BURROWS. About broken even. Obviously, we are not in the business of breaking even.

Senator NELSON. I assume, would this be correct, that part of the factor in your breaking even was the fact that your volume was not very large? Would it change, in other words, if your volume were $1 million worth of sales at $1.36 instead of $29,000 of sales?

Mr. BURROWS. That is a hypothetical situation which we haven't experienced, and I don't think I would like to speculate on what might happen if we had sales of $1 million.

In the first place, if you are going to sell at that level, you certainly are going to have to do some advertising, which was not involved in our product. The larger your inventory investment, the greater your risk of obsolescence and the like. The larger your production processing, the greater your risk of production hazards, which as they occur have to be written off. So, not having experienced a capacity or a volume in the range of $1 million or more, I would not like to speculate on what might have happened if we had been in that fortunate position.

Senator NELSON. So that it is clear in my mind, I understand you to have said in your statement that you paid 50 cents for the raw material; is that correct?

Mr. BURROWS. No. Fifty cents is the basic standard cost.

Senator NELSON. The manufacturing cost.

Mr. BURROWS. The standard cost including the raw material was 50 cents a 100.

Senator NELSON. And that with a sales price of $1.36 a 100, your best judgment is that you about break even on that.

Senator JAVITS. Would the Senator yield?

Senator NELSON. Yes.

Senator JAVITS. Give us a description. You get the raw material? What does that mean? What is the raw material?

Mr. BURROWS. The raw material is prednisone.

Senator JAVITS. Is it a powder or a tablet or what? I think we ought to have some concept of what happens. I mean is the raw material the very same tablet you put in a bottle and sell for $1.36 or is it something else? What is the processing that it goes through, et cetera?

Mr. BURROWS. There is a certain amount of processing involved to the raw material after we get it. We have to make it into tablets, among other things.

Senator JAVITS. Is that the only processing?

Mr. BURROWS. I think there is additional processing.

Senator JAVITS. How can we find that out? I think those are important points. We ought to know just what goes on here.

Mr. BURROWS. I will be glad to send you an outline of the steps that are involved in our production of Paracort.

Senator JAVITS. Can you tell us now?

Mr. BURROWS. I don't have the information with me.

Senator JAVITS. Senator Nelson, may I request that the next witness, Mr. Conzen, perhaps by being given notice, may try to find out exactly what steps are followed. What is the raw material, what do they do with it, et cetera?

Senator NELSON. Maybe the competition doesn't want to furnish that information.

Senator JAVITS. If they don't they can say so. We have the liberty to ask questions. They have the liberty not to answer them. Thank you, Senator.

Senator NELSON. Included in this price of $1.36 a hundred, is also the royalty that Parke, Davis pays to the Schering Co.?

Mr. BURROWS. The royalty is included in the factors that I proposed to recognize in my previous exercise as an addition to the 50-cents manufacturing cost.

Senator NELSON. And that royalty is——

Mr. BURROWS. The royalty is based on the selling price, our realized selling price, so that if, on the average, we realized $1.36, the royalty would be based on $1.36.

Senator NELSON. Is that 6 percent?

Mr. BURROWS. Six percent; yes.

Senator NELSON. Do you have at hand the amount that you have paid to Schering based on that 6-percent royalty?

Mr. BURROWS On Paracort through 1966 we paid to Schering, $48,004. This is on U.S. sales. On international sales to Scherico Limited, a Switzerland-based company, which I understand is a subsidiary of Schering, $20,972. In addition, for the period from November 14, 1956, to June 30, 1959, we paid some $2,733 to Upjohn.

Senator NELSON. What was the last figure you gave?

Mr. BURROWS. $2,733 to Upjohn for the period from the latter part of 1956 through the middle of 1959.

Senator NELSON. Go ahead.

Mr. BURROWS. In summary, our U.S. catalog price has no real significance because sales are virtually nonexistent to or through the retail drug trade. Further, our average sale price of $1.36 per 100 tablets in the United States during 1966 is competitive with other suppliers in this country and also is lower than our prices for the same product abroad.

Senator JAVITS. Senator Nelson, may I ask one question?

Senator NELSON. Sure.

Senator JAVITS. I must say that I am very puzzled by this last statement, Mr. Burrows. Why would you publish this catalog price if it is so completely misleading and misleading in such a manner as to be harmful to you? The drug industry complains that they are being crucified by exaggerated reports of what they charge as compared with the nongeneric price, and yet you yourself by printing this catalog and making this offer to the retail druggist, I don't want to speak a conclusion. You say it for me. Why do you do it?

Mr. BURROWS. I wish I knew.

Senator JAVITS. Well, are you going to continue to do it?

Mr. BURROWS. We are going to have a little session on the subject with our sales people. As I said initially, I doubt that we can justify carrying this product when we sell less than $30,000 a year, and practically none to the retail drug trade.

Senator JAVITS. Well, people are often their own worst enemies, and, as I have said many times before, it is high time that we had all the facts in toto. This is one evidence that all the facts may do you the most good, though many in your business started out by thinking they do you the most harm, in terms of cleaning up your own situation.

It seems to me really beyond belief that you torture yourself with this kind of standard, which you don't observe yourself.

Thank you, Senator Nelson.

Senator NELSON. I understand you buy the prednisone compound from Upjohn.

Mr. BURROWS. Yes, at the present time.

Senator NELSON. Do you manufacture——

Mr. BURROWS. This is the bulk chemical.

Senator NELSON. Yes. Do you manufacture, does your company manufacture and sell any bulk chemicals to other companies?

Mr. BURROWS. The prednisone bulk chemical?

Senator NELSON. Of any drug.

Mr. BURROWS. As a finished drug I can't think of any we sell in bulk. We sell some intermediate chemical compounds in bulk to other companies.

Senator NELSON. Is this a bulk chemical compound that is not in tablet form, that requires final processing by another company?

Mr. BURROWS. I can't think of any compounds of the same category as prednisone would be.

Senator NELSON. No, I mean of any category, any drug.

Mr. BURROWS. I can't think of any drug that we sell in bulk in any quantity.

Senator NELSON. In addition to the prednisone that you buy in bulk from Upjohn, do you purchase any bulk compounds manufactured by other drug companies for the purpose of processing into tablet or other form for sale?

Mr. BURROWS. We purchase a steroid in bulk from Syntex to which we add another compound. I am not in a position to identify the other compound which is added but I can get that information if it is important to the committee. We process and sell the end product as Norlestrin.

Senator NELSON. What you purchase is the compound and then you add the excipients.

Mr. BURROWS. Right. It is more than an excipient. It is another active ingredient.

Senator JAVITS. I just asked Senator Nelson what an excipient is.

Senator NELSON. Neutrals, nonactive ingredients.

Mr. BURROWS. Nonactive ingredients.

Senator NELSON. Syntex, is that a Mexican corporation?

Mr. BURROWS. I think it is organized in Mexico and has an American affiliate or subsidiary. Its manufacturing facility for this particular compound is in Mexico.

Senator NELSON. Do you buy this steroid compound under its generic name, or do they have a brand name?

Mr. BURROWS. No, we buy it under the generic name and sell the end product under our own brand name.

Senator JAVITS. Mr. Burrows, I must say I am very bothered about this catalog business as far as the retail druggist is concerned, and may I tell you why? Perhaps you could help us.

This very morning it is widely advertised that the retail druggists in New York City are allegedly going to refuse to fill medicaid prescriptions for the city of New York on the ground that the city is insisting that they be filled in generic terms. Now, doesn't the maintenance of what you say is, for practical purposes, a fictitious catalog price enormously complicate our problems in that regard—in giving an air of unrealism to everything, including the practices of the retail merchant?

Here you say, "Our U.S. catalog price has no real significance because sales are virtually nonexistent to or through the retail drug trade." Yet with this catalog price I suppose there are a few sales really being victimized. It gives a completely false impression to the whole business, with your catalog 20 times your actual average sales price, as disclosed on page 4. As a merchandising proposition, isn't this bound to cause us tremendous difficulty with the retail druggist unless it is corrected throughout the whole pharmaceutical industry?

Mr. BURROWS. I don't think it is as simple as that. First, I think the doctor, if he elects to prescribe a Parke, Davis product, should have the right to prescribe a Parke, Davis product. I don't find fault with the price of $17.88 per 100 tablets at which this item is included in our catalog. I find fault with the fact that we leave it in the catalog when this is not the kind of business that we should be pursuing.

We made an attempt at that business. We didn't succeed. We should have directed our attention to other more promising fields, and let this one drop. That should have been our alternative, and I think that it would have been prudent on our part if we had taken the product out of our list entirely. That we neglected to do, and it is the neglect

that bothers me rather than the price. We never expect to be able to compete with drug houses that for their own good and sufficient reasons have elected not to be research oriented, and there are a number of them. Obviously, if you have no research program, you can afford to sell at a smaller margin of profit than can a strongly research-oriented company such as Parke, Davis. Our sales policy has to be such as, hopefully, to produce an economic climate in which we will be inspired and encouraged to spend money for research.

Somebody has to spend money for research, if the health and well being of this country and of the world is going to be advanced. I think that the ethical pharmaceutical industry, including Parke, Davis, has made a significant contribution in that field, and we hope to continue to do so.

If by way of advocating so-called "low" prices we are going to discourage the research-oriented pharmaceutical manufacturers from continuing to pursue research for new and improved products, then the health and well being of this country and of other countries in the world are going to suffer, unless there is a substitute for such research.

Perhaps some people might advocate the Government as a substitute. For myself, I would prefer to place reliance on private enterprise supplemented by whatever may be appropriate for the Government to do in this field.

Senator JAVITS. Mr. Burrows, I too would prefer to place the emphasis on private enterprise, which I think is more productive, but I think private enterprise must also meet public interest standards. That is the purpose of our hearing, and I am very pleased that you are cooperating, as are the other witnesses.

I would like to ask you this question because I think it is very pertinent. First let me make a correction: I used the figure of 20 times $1.36. That is increase. I gather that it is somewhere in the area of 10 to 12 times, because your listed price is $17.88. I correct that.

I would like to ask you this question. Based upon the practices of your industry, is it, in your judgment, necessary to price an item at 10 or 12 times the price at which it is sold to the categories of city, county, State and Federal agencies, in sales to the retail druggist in order to deal with the manifold cost, including reasonable profit problems? It seems to me that would be way, way out of line. But you tell us. Is it, in your judgment, legitimate and honorable business to charge 10 or 12 times the city, State, county and Federal agencies price to the retail druggist? Is it necessary, in terms of your business?

Mr. BURROWS. It is necessary to charge somebody. Let me put your question somewhat in reverse. If Parke, Davis, for our 1966 year, had reduced our prices by 20½ percent, we would not have made any money. So on a worldwide average of all that we make and sell, and despite this item of 10 times or 12 times which you have mentioned, and taking everything that we do as a whole, had we realized 20½ percent less than we did realize, we would make no money. That is the maximum margin that we are talking about, assuming that we maintain our present level of research expense and the like.

Senator JAVITS. Mr. Burrows, if I may—I apologize for interrupting, sir, but I would like to pinpoint the question of the internal structural difference between the sale to the governmental agencies and the sale to the retail druggist. It seems to me that, even accepting your

explanation, the internal structural difference seems unduly lopsided to the retail druggist.

Is it essential in the structure of your business that there be this lopsided relationship? Isn't the retail druggist, and, therefore, the retail buyer, being asked to pay far too much of these costs, and an equitable share not being assessed, as it were, upon other buyers, to wit, city, county, State and Federal agencies? That is my question.

Mr. BURROWS. I don't know that I can provide an answer for that. I have to assume that we used our best judgments under the circumstances when we made those bids. It is conceivable that for one reason or another we wanted the Parke, Davis label represented in these institutions. We knew from previous experience and previous bids what the bid prices were liable to be, and if we wanted to have our name represented in the institutions by our product, we knew that we would have to bid at or near the past prices in order to accomplish that end.

Senator JAVITS. Senator Nelson, I have an urgent summons to the Education Subcommittee. May I ask the Chair's indulgence to excuse me. May I ask also if the Chair would be kind enough to give me notice before the next witness is through, so I may come back and ask some questions.

Senator NELSON. Thank you, Senator. I want to pursue a couple of questions raised by Senator Javits of New York. As to your observations about the necessity for making certain charges and making a certain profit in order to carry on research, isn't that whole question settled by the fact that under our law, if you discover a product, you have an exclusive patent for 17 years, and may charge any price that the manufacturer of the new product wishes to charge, and isn't it sufficient to make the necessary profit to do the research in that 17-year period?

Mr. BURROWS. I don't know that I could speculate on that. By whatever fair means we can, we at Parke, Davis want to, as I say, create that atmosphere and climate in which we are encouraged to continue to do research and encouraged to earn profits that will justify an extensive and we hope effective research program.

After a patent has expired, anyone who has the competence to make an item can come in and sell in competition, and it is normal to expect that the price structure would, by the very nature of that competition, be adjusted downward.

Senator NELSON. Well, I still want to get at the question that we build into the law a 17-year exclusive right to the discoverer of a new drug. He may charge whatever price he wishes. He may license or not license anybody else. He may charge a royalty. And then once the 17 years have gone by, his drug is well established in the retail market, and I am sure you are aware that there are a number of drugs on the market on which the patent has run out, and yet the original owner of the patent is charging a price far higher than the competition, but the competition can't get on to the market because the prescribing physician is only familiar with the drug he has been prescribing for 17 years.

Mr. BURROWS. I think you use your own best business judgment as to what you do under those circumstances, and act accordingly.

Senator NELSON. Isn't it really the fact that when the drug companies bid on an offer from the Defense Supply Agency or the city

of New York, or a large hospital, that they are bidding on a generic solicitation, and they are bidding in competition? That accounts for the fact that in every single case that we can find, the brand-name companies will bid far lower in that competition, sometimes a 10th, a 20th or a 30th of what they charge the retail druggist, because it is competitive, and the fact is that on the retail market where the brand is established, there is no competition, no serious competition. Therefore the American free competitive system is not working on the retail market. For example, Schering can charge $17.90 on the retail drug market when there are drugs available at a fraction of that price, because the prescribing physician is prescribing that well-known drug. I do not want to select out Schering. This is true of any number of drugs that have been called to the attention of the druggist. Now, what is your observation about competition against a standard brand name? For example, your attempt to establish Paracort versus the competition in the retail trade which you failed to do.

Mr. BURROWS. The competition was very fortunate, and as I say the company that is there with a sound drug first has a competitive advantage. That is what most of us are looking for, something that gives us a competitive advantage and contributes to our capability to expand and do better and provide better.

Senator NELSON. Would you explain to me why is an established name in the retail market able to sell at the much higher price than the competition, but yet as soon as that established brand name is bid to the Defense Supply Agency, it goes down in an attempt to meet the competition of all the rest, and come in at a much lower price? Why doesn't that occur on the retail market?

Mr. BURROWS. I think it does occur on the retail market with prescription drugs providing the physician is prepared to substitute another drug, a non-brand-name drug, for example, for a brand-name drug.

Senator NELSON. What I am trying to get at is why does the physician prescribe the high cost prednisone, for example, when the best evidence we can find is that there are a large number of competing prednisones which the Medical Letter says are equivalent, and recommends be prescribed generically. Why doesn't the physician prescribe those?

Mr. BURROWS. I am not a physician and I am not sure that I should be providing a physician's answer, but I imagine that he prescribes the drug in which he has confidence, and he probably is not inclined to cut and fit and experiment.

Senator NELSON. What is most puzzling in any case, however, is that in looking at the list of drugs in the Medical Letter, there is included a low priced prednisone that meets Pharmacopeia standards. It is as pure as the leading drugs on the market, practically the same percentage of impurities. It sells for 61 cents a hundred to the pharmacies, and the highest priced one—Parke, Davis is listed as $17.88 but I guess that has been settled, you sell at an average of $1.36—is listed at $17.90. Why would a physician prescribe a drug costing $17.90 a hundred to his patient, when there is one available at 61 cents a hundred, which the Medical Letter, the most respected source of information according to the physicians' testimony before this committee, is available at 61 cents? Can you explain that?

Mr. BURROWS. I cannot explain it, except I am sure that the physician is doing what he thinks is in the best interests of his patient, all things considered, including the reputation of the company that supplies the drug that he is prescribing.

Senator NELSON. Is the individual practicing physician better prepared to judge the therapeutic value and quality of the drug than the Medical Letter which does scientific research and has the advice and consultation of distinguished pharmacists, pharmacologists, clinical physicians and all of this information? Is he really better prepared to make that decision than the Medical Letter?

Mr. BURROWS. I think you will have to give to the physician the final responsibility for his patient, and he cannot and should not be expected to pass the buck for his responsibility to the Medical Letter or to any other source, and again I am not reflecting on the Medical Letter. The Medical Letter in absolute terms may be entirely accurate and correct, but in the last analysis, it is the physician that has to decide what he thinks is in the best interests of his patient.

Senator NELSON. Nobody is suggesting, as has been reported in some of the literature, that somebody is going to take away the physician's right. I think what is questioned very seriously by the facts in the Medical Letter is the physician's judgment.

U.S. Vitamin Corp. is a very distinguished drug company in this country, isn't it?

Mr. BURROWS. It certainly is.

Senator NELSON. And it meets USP standards, selling prednisone at $2.50 a hundred. On what basis would any physician make a judgment that his patient ought to pay $17.90? What is the basis for making the judgment?

Mr. BURROWS. Again I should not be speaking for the physician, but physicians apparently feel that the product at $17.90 for their particular patients is worth the difference. Otherwise they would not prescribe it.

Senator NELSON. Isn't it really a fact that we are facing the same problem that Parke, Davis had in trying to get into the retail market but failed to do so? In your statement you said you tried vigorously for 2 years, and you could not meet the competition. Now, your product in your judgment is as good as any one of the other prednisones on the market, isn't it?

Mr. BURROWS. Yes.

Senator NELSON. You testified earlier that you were not aware of any information indicating that there was greater therapeutic value to any other drug than your own?

Mr. BURROWS. That is right.

Senator NELSON. Therefore on what basis does that individual physician make his judgment?

Mr. BURROWS. I would suggest that among your witnesses you will have some individual physicians here, and that they would be in a better position to answer than I would.

Senator NELSON. We have, of course, had some very distinguished physicians, pharmacologists, who say that the ordinary physician does not have any basis for making such a judgment, that he does not have the necessary information. I think this is what we are getting at, that the advertising and the promotion on the retail market is what deter-

mines what the physician finally prescribes. Of the 22 prednisones available here the doctor prescribes one that cost $17.90 because that is the one that has been advertised successfully to him. The doctor is really unaware that the Medical Letter has said that all 22 are equivalent and that he ought to prescribe generically, particularly for his impecunious patients. I guess that means if they are rich it really does not make any difference if they pay a higher price, but doesn't it suggest to you that it is the advertising to the doctor that determines what he is going to prescribe, and not the quality of the drug, when you have a case right here of 22 drugs of equal quality? This is the puzzling thing that the committee is trying to get at. The smokescreen is repeatedly thrown up in the literature that these drugs aren't equivalent. The fact of the matter is, if you look at the Medical Letter, you will find that the highest priced drugs here are not the purest. There are some that are not selling on the retail market very much although they are pure. You keep saying that purity is a factor. The fact is that they are within USP limits and whichever one you use really does not make any difference clinically. This is the issue that the committee is trying to get at and trying to get an explanation, without, if I may say so, very much success. Would you as a physician, if you read the Medical Letter and looked at their assertions about this, would you order the highest-priced one for your patient, unless you had some clinical evidence that one was better than the other?

Mr. BURROWS. That is a speculative question. I am not a physician, and I don't know what I would do if I were a physician other than to do what I thought was best for my patient, and if I thought, all things considered, that a drug at $17.90 a 100 was the best thing for my patient, that is what I would prescribe.

Senator NELSON. I am sure you would, and so would I and so would anybody else. The real question here is that the——

Mr. BURROWS. I think possibly too that I would keep in mind as a physician and as someone that was interested in the future developments in the health care field—that I would be mindful of whether the company whose drugs I was prescribing, assuming other things being equal, was likely to contribute in the future something new and improved over what was available to me now versus another company which had elected not to indulge in that phase of the drug business.

Senator NELSON. Yes, but of the companies listed here—some I assume produce only generically—perhaps do not do any research. But Merck, one of the great corporations in the country, is listed here and is selling 100 tablets for $2.20. Would you say that there would be any doubt in your mind as a physician about the quality of the product of Merck?

Mr. BURROWS. No, I would have no reservations about Merck as being a research-oriented house, certainly.

Senator NELSON. U.S. Vitamin Corp is selling prednisone at $2.50. That is a research-oriented corporation, isn't it?

Mr. BURROWS. I presume it is.

Senator NELSON. There is the very distinguished company Upjohn which puts out Deltasone. That is one of the two drugs with the lowest amount of impurities in it and is selling for $2.25 a 100. They are research-oriented are they not?

Mr. BURROWS. Very much so.

Senator NELSON. So I still do not get the explanation of why the doctor would be requiring his patients to spend $17.90 or some other price, $8.70, or $17.88, when well-known corporations are producing the same drug which meets USP standards at much lower prices. There is no difference in therapeutic value, as far as we can find out. I still don't understand why a physician would prescribe the highest-priced one. On what basis does he make his judgment, is what I am trying to get at.

Mr. BURROWS. I do not think I am capable of answering that other than what I already have said.

Senator NELSON. All these prices that I have been reciting, Mr. Burrows, are prices to the druggist. They do not involve the retail price or the markup that he charges, just for clarification of the record.

Would you think it would be of any value to establish a national compendium of drugs? I assume it would have to be done in cooperation with the industry, the medical profession, and other advisers, but that it would have to be done largely, I am assuming, by the Federal Government. Do you think it would be of value to establish a national compendium in which the drugs are all listed by their generic names, brand names, and with all of the known clinical information recited alongside them? A physician would open up the national compendium, and find there all the drugs, their side effects, and the companies that manufacture them. This, of course, would also involve testing by FDA, and also involve putting in the known clinical information? Do you think this type of a national compendium would be of value to the country as a whole?

Mr. BURROWS. I think it would as long as the doctor is still allowed his prerogative of prescribing the particular drug of the particular manufacturer that he thinks best, and providing that we, as a manufacturer, are not stopped from attempting to advance and advocate our particular line of products. Those are the ones we know about. Those are the ones that we are in business to make and sell, and those are our potentials for corporate progress for the future.

Senator NELSON. I want to be sure that I was understood.

I was saying national compendium, not formulary. I am not suggesting that you have a formulary from which a physician must prescribe. I am simply saying you list the drugs in a national compendium with the pertinent information and the manufacturer as informational matter to the medical profession, the teaching hospitals and the practicing physician. That will be all that is intended, and it should not interfere with the private operations of the drug companies. That is my question.

Mr. BURROWS. I can see nothing wrong with having facts on such an important subject as drugs and health available for reference by people who have occasion to use and benefit from such information.

Senator NELSON. Thank you.

Mr. GORDON. I would like to clarify a couple of points. Do you sell any prednisone at all today at the price of $17.88, any at all?

Mr. BURROWS. I think during 1966 we sold 117 bottles of 100 tablets each.

Mr. GORDON. But at one time you did sell at $17.88; is that correct?

Mr. BURROWS. That is right.

Mr. GORDON. Now, I just want to clarify another point and that is this: When you sold it at $17.88, it was the same drug as the drug you are selling for $1.36 at present; am I correct there?

Mr. BURROWS. That is correct.

Mr. GORDON. So there is absolutely no difference in quality, efficacy or purity or anything else?

Mr. BURROWS. There might be some difference and some small saving if you sell in bottles of 1,000, for example, inasmuch as the price per 100 tablets in a container of 1,000 would be less than the cost per 100 tablets in a container of 100.

Mr. GORDON. But the difference between $1.36 and $17.88 would not be accounted for by this?

Mr. BURROWS. Oh, no.

Mr. GORDON. I just want to make sure of that.

Mr. BURROWS. No.

Mr. GORDON. And you also stated, if I recall correctly, that your prednisone, as far as you know, is just as pure, safe, and efficacious as anyone else's; is that correct?

Mr. BURROWS. I don't know anything against our prednisone, and I do not know anything against any other prednisone.

Mr. GORDON. Now, you stated that $1.36 is your average competitive price. Can you give us the range of prices at which you sell the product, the high and the low?

Mr. BURROWS. Certainly the high would be not more than $17.88.

Mr. GORDON. Yes.

Mr. BURROWS. As for the low, I do not know if I can cite that price. No, I am sorry, I do not have the low information.

Mr. GORDON. But the $1.36 is not your price but merely an average price?

Mr. BURROWS. That is right. It is the average that we realized during the year 1966 on our sales to all customers.

Mr. GORDON. In fact, the chances are you may not have sold any at $1.36 but some at lower prices and some at higher prices?

Mr. BURROWS. That is right.

Mr. GORDON. Now, this $1.36, as you told Senator Nelson, includes a 6-percent royalty to Schering. When did you start paying this royalty?

Mr. BURROWS. I am informed that the first payment was made in 1958 on 1957 sales. I think probably at that time it was at a tentative 5-percent rate which rate was to prevail until and unless Schering received the patent on the product, which it did in 1964.

Mr. GORDON. This is my next question. Since Schering got its patent on May 26, 1964, can you please tell the subcommittee, then, why you paid royalties to Schering for about 6½ to 7 years before it received a patent?

Mr. BURROWS. May I ask my associate, Mr. McGregor, to comment on that.

Mr. MCGREGOR. As Mr. Burrows has said, we decided in 1956 to enter this market with a product under our own brand name. There was a patent interference then pending in which a number of research-oriented houses were involved. We felt it desirable to try, if we were going to enter the market, to get a solid position in furtherance of which we negotiated licenses with the firms that were involved in that interference.

Mr. GORDON. Are you paying royalty or did you pay royalties to Syntex? They were included in the patent interference, were they not?

Mr. MCGREGOR. We had a license agreement with Syntex on this product also.

Mr. GORDON. And you paid royalties to them?

Mr. MCGREGOR. No; we did not. We knew or we believed that Schering was the inventor of the product. We knew that they were the first on the market with it. It was our opinion, after getting all the patent information we could, that Schering had the best chance of success.

Mr. GORDON. Of course, if they did not succeed, you would have been out on the royalty payments?

Mr. MCGREGOR. Yes.

Mr. GORDON. Up until that time?

Mr. MCGREGOR. Yes.

Mr. GORDON. Now, is it customary in industry to pay royalties on an unissued patent?

Mr. MCGREGOR. It is not unusual.

Mr. GORDON. You have done this on other occasions?

Mr. BURROWS. We have done it, and reciprocally, both ways. We have had people pay us on patents as well.

Mr. GORDON. Not on patents.

Mr. MCGREGOR. On applications.

Mr. GORDON. On applications only?

Mr. MCGREGOR. Yes.

Mr. GORDON. Now; is this because you feel that if you do not pay the royalty, you may not get a license afterward?

Mr. MCGREGOR. Of course.

Mr. GORDON. Were any conditions imposed upon you by the license that you eventually got?

Mr. MCGREGOR. What do you mean by conditions?

Mr. GORDON. For example, am I correct that you were not allowed to manufacture the bulk material? You could manufacture only the finished material?

Mr. MCGREGOR. I am not aware of any such condition. I haven't examined the license agreement with that specific thought in mind.

Mr. GORDON. But you could have manufactured the bulk material if you desired to do so?

Mr. MCGREGOR. I don't know, Mr. Gordon. I would have to look that up and tell you later.

Mr. GORDON. Would you please supply the license to the committee.

Mr. MCGREGOR. I would be glad to. It already is in the Kefauver record and I assumed you had looked at it.

Mr. GORDON. I did but I was just wondering if there is a newer one.

Mr. MCGREGOR. No, there isn't.

Mr. GORDON. Well, that one did impose a condition that you could not sell the bulk, or manufacture the bulk.

Mr. MCGREGOR. I see. That is quite possible.

Mr. GORDON. I don't know if Senator Nelson has already asked this question, but do you manufacture for other companies?

Mr. BURROWS. You mean do we do contract manufacturing for other companies?

Mr. GORDON. Yes.

Mr. BURROWS. No. We used to but we have gotten out of that field.

Mr. GORDON. Do other companies do contract manufacturing for you?

Mr. BURROWS. Yes, R. P. Scherer Corp. makes some of the products which we sell in the United States as soft gelatine capsules. We have other manufacturers that put some of our products in special kinds of containers or dispensers. By and large, however, apart from the Norlestrin item from Syntex that I spoke of previously, we do most of our own manufacturing.

Mr. GORDON. Coming back once again to licensing, when you secured your license and started producing the finished form of prednisone, did you establish a price similar to Schering's? Was it exactly the same price, $17.90?

Mr. BURROWS. I think the two prices were within pennies of each other, and I imagine there were other prices in the same range, but I am not sure.

Mr. GORDON. Do you have any other examples showing a great difference in the price of your drugs when sold under a generic name or when sold under a brand name? For example, what I had in mind was some material submitted to us by the city of New York to whom you sold Benadryl, 1,000, 50-milligram tablets for $15.63 under its trade name and $3 under the generic name. Here is the material submitted to us by the Purchase Department of New York City.

Mr. BURROWS. I am not familiar with this particular transaction. As you will recall, Mr. Gordon, we came prepared to discuss the subject of prednisone, as had been requested. If there are other drugs that Parke, Davis makes in which this committee has an interest, we would be very glad to give those the same research as we have given the prednisone subject.

Mr. GORDON. My point here is that regardless of the price at which you sell the product, whether at $3 or $15.63, they are both of high quality?

Mr. BURROWS. You can assume that for sure.

Mr. GORDON. So, really, price is not the criterion?

Mr. BURROWS. That is right.

Mr. GORDON. Is prednisone the kind of a drug used for short or long periods of time?

Mr. BURROWS. I understand that it could be used for a long period of time in certain types of arthritis, but I am not a medical man and I wouldn't want anyone to start taking it on my say-so.

Senator NELSON. I just have one more question. There is some question raised from time to time about the adequacy of the inspection of the testing of drugs, the adequacy of the inspection of plants. One of the problems as you are aware, is that there is a very large number of manufacturers, some quite small. Would you consider it in the public interest if the Food and Drug Administration had continuous inspection of all drug manufacturing plants in this country?

Mr. BURROWS. Senator, what do you mean by "continuous"?

Senator NELSON. Well, perhaps, I am raising too general a question. I am not familiar enough to make a comparison, and I realize it is probably difficult. As you know some drugs do get onto the market that do not meet appropriate or proper standards. In the meat industry, for example, for all meat moving in interstate commerce, there

is in the plant at all times a Federal inspector. I realize that is an entirely different problem. It is no doubt much simpler, but do you think it would be in the public interest to broaden the nature of the inspection testing of drugs?

Mr. BURROWS. It well might be. In our own case, being prejudiced, we wouldn't think it was necessary, but if it was felt that that would add to the assurance of quality in drugs that are made available to the public, on that basis, I can see nothing wrong with it. We are as you know subject to periodic inspection at the election of the Food and Drug Administration and other agencies of the Government.

Senator NELSON. As a practical matter, how often does the Food and Drug Administration inspect your plant?

Mr. BURROWS. I don't have that information, but I could get it for you if you wish. As far as I know the inspections are unannounced with no such advance notice as "come 3 weeks from now we are going to be there, so you can tidy up." We try to operate so that we do not have to do any tidying up. We hope we always are reasonably tidy.

Senator NELSON. Would you mind submitting to the committee the number of inspections that have been done by FDA, say in the last 2 or 3 years, so we can have some idea?

Mr. BURROWS. Yes, sir.[2]

Senator NELSON. I don't have any more questions.

Mr. Burrows, we thank you very much and your general counsel for taking the time to come over here today, and we appreciate very much your contributions to these hearings.

Mr. BURROWS. Thank you very much.

Senator NELSON. We will have a 5-minute recess and then we will resume.

(Short recess.)

Senator NELSON. The hearing will resume. Our next witness is Mr. W. H. Conzen, president of Schering Corp. Did you have somebody you wish to have with you?

STATEMENT OF W. H. CONZEN, PRESIDENT, SCHERING CORP., BLOOMFIELD, N.J.; ACCOMPANIED BY DR. DONALD R. LONGMAN, VICE PRESIDENT; AND IRVING H. JUROW, VICE PRESIDENT AND GENERAL COUNSEL

Mr. CONZEN. Yes, Senator Nelson, I have Mr. Jurow and Dr. Longman with me. Mr. Jurow is our general counsel. Dr. Longman is our vice president for domestic operations.

Senator NELSON. Will you give their names to the reporter so the record will be clear as to who is appearing. Mr. Conzen, we are very pleased to have you appear here as president of the Schering Corp. I know that we will find your testimony very helpful to the committee record.

You may proceed to present your testimony in any way you see fit. If you don't object, I may interrupt from time to time with a question. If you prefer, I can always wait until you get through. Do you have any objection to questions during the course of your presentation?

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[2] At the time of going to press, this information was not available.

Mr. CONZEN. No, sir.

Senator NELSON. Why don't you go ahead and proceed in your own fashion.

Mr. CONZEN. Thank you, sir. And in the interest of time, instead of reading my entire statement, which will be part of the record, I will summarize certain sections.

Senator Nelson and members of the subcommittee, I am W. H. Conzen, president of Schering Corp. Schering is an international pharmaceutical company serving the medical profession throughout the free world. Its administrative and research headquarters are in Bloomfield, N.J.; its manufacturing facilities are in New Jersey, Wisconsin, and a number of foreign countries.

I am accompanied by two of my associates. May I introduce them: Dr. D. R. Longman, our vice president for domestic operations, and Mr. I. H. Jurow our vice president and general counsel.

We are here in response to your invitation of June 12 to appear and to answer your subcommittee's inquiry concerning the price of our product Meticorten. It is our purpose to cooperate fully so that you may hear all sides and reach a fair evaluation of the criticisms of prescription drug prices that have been made here.

In your letter to me, you asked that I discuss pricing policies and practices of our brand of prednisone. You said that "striking differences in prices of prednisone among various manufacturers" had been referred to in recent testimony before your subcommittee.

During these hearings there have been frequent references to the price of Schering's Meticorten tablets and comparisons of that price with the prices charged for so-called "generic" prednisone tablets. Obviously, the reference to "striking differences * * * among * * * manufacturers" pertains to these comparisons in the testimony.

However, so that there is no misunderstanding as to precisely what is being discussed, I believe a few words of explanation are in order as to what prednisone is, what Meticorten is, and how significant they are in the pharmaceutical field.

Prednisone is the official, or established, name of a chemical substance which was discovered by Schering research scientists in 1954. It is what is known in chemistry as a steroid, more specifically, a corticosteroid. We have developed and marketed a number of pharmaceutical products which contain prednisone and its sister compound prednisolone—14 to be exact. These products provide a variety of pharmaceutical dosage forms, many of which are offered in several package sizes. In addition to plain tablets, there are injectables, creams and ointments for dermatological use, ophthalmic preparations, and a number of combination products.

Meticorten is Schering's brand name for tablets formulated with prednisone as the active ingredient; it is a typical example of what many people have chosen to call "miracle drugs." It is used by people of all ages for the treatment of a variety of short- and long-term medical problems such as allergies, asthma, arthritis, skin and eye inflammations. Elderly people with chronic arthritis represent a relatively small portion of its users.

Prednisone, in addition to being the official name for the chemical compound, is also the so-called "generic" name for pharmaceutical products made available by many generic distributors, which contain, as the active ingredient, this particular chemical substance.

Before I address myself to your specific question, I think it would be helpful if I explained for the subcommittee some of the magnitudes involved to establish the relative significance of what we are discussing.

In the first place, the domestic ethical pharmaceutical industry is estimated to have a volume of about $3 billion at the manufacturers' level. The term "ethical pharmaceuticals" as used here refers to those products which are promoted only to the medical and allied professions, and available through pharmacies. The sales volume of all corticosteroid tablets totals approximately $40 million; this not only includes prednisone, but all other corticosteroid tablets. The estimated volume of prednisone tablets is $3 million. Consequently, this product represents one-tenth of 1 percent of this country's total ethical pharmaceutical market.

Senator NELSON. Would you tell me, sir, what percentage of the total amount of prednisone sold in this country is sold by your corporation?

Mr. CONZEN. This I was going to read in the next paragraph, but to answer your specific question, our total sale of prednisone tablets in this country is approximately $1 million.

Senator NELSON. In this country. Now, you have sales overseas.

Mr. CONZEN. Yes. They are less than that.

Senator NELSON. Do you know what amounts?

Mr. CONZEN. Approximately three-quarters of a million dollars, I would estimate.

Senator NELSON. Three-quarters of a million dollars?

Mr. CONZEN. Dollars.

Senator NELSON. Sales by your company?

Mr. CONZEN. Our brand name, Meticorten, yes.

Senator NELSON. And do you know what the rest of the industry in this country sells overseas?

Mr. CONZEN. No, I don't know that.

Senator NELSON. What percentage of your sales in this country are in the retail drug market, that is either to the wholesaler or directly to the druggist for the retail trade?

Mr. CONZEN. By far the largest portion of our business in Meticorten tablets is to the wholesale and retail trade.

Senator NELSON. When you say, by far the largest percentage, can you give me some rough estimate of what percentage?

Mr. CONZEN. I can give you a rough estimate. I would say it would be about 80 percent or more. Perhaps 88 percent, my colleague tells me, is more accurate.

Senator NELSON. About 88 percent?

Mr. CONZEN. Yes.

Senator NELSON. Is this retail?

Mr. CONZEN. And wholesale trade.

Senator NELSON. And wholesale trade. What is the total wholesale-retail trade in this country, do you know, of the $3 million total sold here?

Mr. CONZEN. At the rate of 88 percent, it would be over $2½ million.

Senator NELSON. As I understand your testimony, the Schering Corp. sells about one-third of the total sales in this country, $1 million. Of this, the Schering Corp. sells about 88 percent to the wholesale-retail trade market.

Mr. CONZEN. Yes.

Senator NELSON. Now, of the balance of the $2 million that are not sold by Schering, how much of that is sold in the retail-wholesale market?

Mr. CONZEN. I am sorry, I don't have that information, Senator Nelson.

Senator NELSON. Is that available in the drug literature?

Dr. LONGMAN. It could be obtained. We don't have it.

Mr. CONZEN. I don't know whether there is such a market survey available.

Senator NELSON. All right, thank you.

Mr. CONZEN. Second, within the pharmaceutical industry, Schering is about 16th in size, with a domestic ethical sales volume of some $65 million. Of that total, Meticorten tablets represent less than $1 million.

In other words, Meticorten tablets amount to only about 2½ percent of the total corticosteroid tablet market. The relative importance of Meticorten volume, both in terms of the consumer's drug bill and with respect to Schering, is certainly not large.

Nevertheless, those who require this medication have every reason to ask why Meticorten tablets should cost more than products which contain the same active substance available from other companies at much lower prices.

The answer lies in the basic difference in the nature of the functions and services performed by Schering Corp. in our economy, as contrasted with those performed by distributors of generic prednisone. Schering Corp. and the generic distributor operate in such different ways as to be engaged in totally different businesses.

I am not, however, going to discuss the merits of the so-called generic products and the so-called brand-name products and the question of therapeutic equivalence. There is a considerable difference of opinion in the scientific community on that subject. The study now going on under Government auspices, hopefully, will throw light on this question.

Let me explain what I mean by "different kinds of businesses."

Schering Corp. is fully equipped and fully staffed with highly skilled research scientists to discover and to develop new drugs, to produce them under the most rigid standards of good manufacturing procedures and quality control, to disseminate promptly throughout the scientific and professional world full and complete information about such new drug discoveries, to make available a wide range of dosage forms to meet all physician needs, to market them widely in all parts of the free world, and to continue to service its discoveries for the medical profession.

These are the characteristics of our company; it is research-oriented, it manufactures products of the highest quality, it markets its products worldwide, and it is devoted to total service to the medical profession for the benefit of its patients. Implicit, however, in this succient statement is a host of detail, activity, and responsibility.

Senator Nelson, in my statement, which you have, I have gone into some detail as to what we did and what Schering actually did in connection with the discovery and marketing of Meticorten. In the interests of time I will not read it; I will merely summarize.

I refer there to our continuous search for new compounds, to the one success out of the many, many thousands of tries, to the extensive

laboratory and animal testing, the extensive and critical clinical testing in human beings, the development of safe and effective pharmaceutical formulations, of sound manufacturing procedures, of precise specifications and standards, the preparation of voluminous records and reports for Government approval, which as you know, Senator Nelson, takes many, many years to obtain, the critical quality control activities, the preparation of labeling and informational material for the profession, the activities of our detail men in bringing all this information to the profession, the preparation of symposia, films, brochures, et cetera, all this not only in the United States but throughout the world, and, of course, the marketing and distribution of the product, its many dosage forms, and its variations on a worldwide continuous basis.

Senator NELSON. If I may interrupt, you referred a moment ago to research in the field. Did any other of the drug companies do research in prednisone, in the development of it?

Mr. CONZEN. I am not aware of any research that has been going on in prednisone in recent years, except in our own company. We continue to search for new indications in this field with our drug Meticorten. We supply the medical profession, clinical investigators, and approved——

Senator NELSON. Are you talking about the clinical research?

Mr. CONZEN. Clinical research which is still going on today with Meticorten in different strengths, for instance, in such fields as leukemia. I understand that we are the only company which continues to do research with Meticorten, or for that matter, with prednisone.

Senator NELSON. You are familiar with the research that has been done by the National Institutes of Health with prednisone, are you not?

Mr. CONZEN. They were originally working with prednisone when we discovered it; yes, sir, if my memory serves me right.

Senator NELSON. Is it not correct that the first clinical experiments done with prednisone were done by the National Institutes of Health?

Mr. CONZEN. Yes; I understand this is correct, with material provided free by Schering Corp.

Senator NELSON. Just for the record, NIH informs us that intramural research expenditures related to prednisone and prednisolone, fiscal years 1953 through 1965, amounted to $2,114,000.

Mr. CONZEN. I am not familiar——

Senator NELSON. Excuse me, let me correct the record. In the years 1953 through 1967, NIH informs us, they spent a total of $2,114,000 in intramural research on prednisone and prednisolone. Were you aware of that?

Mr. CONZEN. No. I find it somewhat difficult to believe, because prednisone and prednisolone were only discovered in 1954. Moreover, I don't know whether this figure may include research done with other corticosteroids.

Senator NELSON. Unless they misinformed us, which is possible, the information they gave us was that research on prednisone and prednisolone in 1953 amounted to $15,000, 1954, $68,000, and increasing progressively to fiscal 1967 when they will spend $552,000 in research in this field.

In 1966 they spent $409,000. Anyway, that totals $2,114,000 and I would ask that listing identified at the top as "Estimated NIH intra-

mural research expenditures" be printed in the record at the conclusion of your testimony.[1]

They also submitted to us expenditures by NIH in extramural research grant obligations. This involved 639 grants from the period 1953 through 1967. These grants were not, I understand, exclusively to do research in prednisone and prednisolone, but in each of these 639 grants, research was done on prednisone and prednisolone, and that totaled $14,384,144. I ask that this table entitled "NIH Extramural Research Grant Obligations" be printed at the conclusion of your testimony.[2]

You are aware that they are engaged in this kind of research?

Mr. CONZEN. In this general field, yes, as far as I know.

All supplies of prednisone and prednisolone were made free of charge to the Institute. In other words, there are no sales involved. This is part of our contribution to the research program.

Senator NELSON. Thank you. Maybe at this point I ought to ask if you can give an estimate of how much the Schering Corp. is spending in research on prednisone?

Mr. CONZEN. I can't give you a dollar figure, but I can give you some figures which may be of interest and help to you and your subcommittee. As far as Meticorten is concerned, there are 1,979 published clinical papers available to date.

Senator NELSON. Published what?

Mr. CONZEN. Clinical papers, attesting to the efficacy and therapeutic value of Meticorten in human medicine.

Senator NELSON. Are these clinical studies in the strictest sense of the word, or are they in the nature of testimonials?

Mr. CONZEN. They are strictly clinical work published in reputable medical journals and available. I could make available to you a bibliography, if you would be interested.

Senator NELSON. Were these in the United States?

Mr. CONZEN. These are all in which our product was involved, both here and abroad.

Senator NELSON. Do you know how many were in the United States?

Mr. CONZEN. I don't have that figure with me, but I could let you have it.

Senator NELSON. These are papers that have been written on clinical studies of prednisone.

Mr. CONZEN. On Meticorten, Schering's particular brand of prednisone.

Senator NELSON. Were these clinical tests done at the request of Schering Corp.?

Mr. CONZEN. Either sponsored by us or done spontaneously, in which cases, as a rule, we make these supplies available free of charge.

Senator NELSON. Were these done by independent clinical investigators?

Mr. CONZEN. Yes, sir; entirely.

Senator NELSON. Were any of these test double-blind tests measuring the clinical efficacy and therapeutic equivalency of Meticorten versus any other prednisone?

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[1] See p. 656.
[2] See p. 656.

Mr. CONZEN. I can't answer this question. I can find out. Probably there are such studies in these numbers.

Senator NELSON. I would appreciate it, for the record, if you would advise us, when you have the chance to check it, whether any of these were double-blind clinical tests evaluating the therapeutic comparative value of Meticorten versus any other prednisone, and if they are, the committee would appreciate it if you would send us copies of those double-blind clinical tests.

Mr. CONZEN. Yes, sir.

(The information referred to, subsequently received, follows:)

SCHERING CORP.,
Bloomfield, N.J., August 15, 1967.

HON. GAYLORD NELSON,
U.S. Senate,
Washington, D.C.

DEAR SENATOR NELSON: In the course of his appearance before your Monopoly Subcommittee on July 24, Mr. Conzen referred to the fact that there were, to date, some 1,979 published clinical papers on Meticorten, and he was interrogated by you as to how many covered clinical work in the United States, as distinguished from abroad. Mr. Conzen replied that he did not have the information with him, and that he would furnish it (Tr. pp. 1033–4).

He also was asked whether any of these included "double-blind" tests; again he offered to obtain this information for you (Ibid).

Additionally, you inquired as to our "nonprescription" sales totals in the United States; Mr. Conzen agreed to supply that figures (Tr. p. 1042).

Finally, in the course of the discussion concerning the marketing of prednisone overseas you expressed interest in ascertaining whether "competing foreign-produced prednisone" was being marketed in Switzerland; it was indicated that this information could be made available.

Responsive to the foregoing, we submit the following information:

(1) Of the total number of publications to which reference was made, namely 1,979, our review indicates that 1,416 were in the United States and 563 were outside the United States.

(2) Four publications appear to have consisted of "double-blind" studies:

a. Smyth, Charley J. A method of drug evaluation in rheumatoid arthritis: results with phenylbutazone, oxyphenylbutazone, cortisone and prednisone, *Ann. N.Y. Acad. Sc.* 86:292–306, March 30, 1960.

b. Spilka, Conrad J. The place of corticosteroids and antihistamines in oral surgery. *Oral Surg.* 14:1034–42, Sept. 1961.

c. Combined Rheumatic Fever Study Group. A comparison of short-term intensive prednisone and acetylsalicylic acid therapy in the treatment of acute rheumatic fever. *New England J. Med.* 272:63–70, Jan. 14, 1965.

d. Dordick, Jack R. and Gluck, Edward J. Preliminary clinical trials with prednisone (Meticorten) in rheumatic diseases. *J.A.M.A.* 158:166–70, May 21, 1955.

Six publications appear to have been "controlled," although not "double-blind," studies:

a. Hutchison, J. L. and Burgen, A. S. V. Infusion of non-autologous plasma. Effects of chlorpheniramine, prednisolone and adrenaline. *Brit. M.J.* 2: 904–8, Oct. 12, 1963.

b. Bollet, Alfred J., et al. Treatment of systemic lupus erythematosus with prednisone and prednisolone. *J.A.M.A.* 159: 1501–7, Dec. 15, 1955.

c. Bunim, Joseph J., et al. Studies on metacortandralone and metacortandracin in rheumatoid arthritis. *J.A.M.A.* 157: 311–18, Jan. 22, 1955.

d. Calkins, Evan, et al. Comparison of the metabolic effects of prednisone and cortisone. *Ann Rheumat. Dis.* 14: 419, Dec., 1955.

e. Bosch, Samuel J., et al. Prolonged use of prednisone in rheumatoid arthritis and disseminated lupus erythematosus. *Medicina panam.* 11: 258–62, Sept. 15, 1958.

f. Sicuteri, F. and Ficini, M. Effects of prednisone on the symptomatology and histamine cranialgic sensitivity in medical cephalea. *Minerva med.* 46: 1744–48, Dec. 12, 1955.

As Mr. Conzen stated in his testimony, we are not aware of any "double-blind" studies comparing Meticorten with other brands of prednisone. However, the

three studies to which he referred, the results of which appeared in the publications furnished with my letter of July 28, were comparative studies involving different brands of prednisone.

(3) Of our total 1966 sales of $131 million (as reflected in our Annual Report), $65 million represented domestic "ethical" sales, $49 million represented all foreign sales, and $17 million represented domestic proprietary sales.

(4) We have been advised that in Switzerland the substantial portion of the market for prednisone/prednisolone tablets is covered by some 13 companies; of these 10 are Swiss companies, marketing locally manufactured products, and three are non-Swiss companies. Of the 13, five market under brand names, seven market under "generic" designation, and one Swiss company markets both a brand name and a "generic" designation prednisone and prednisolone.

We appreciate the opportunity to submit this information for inclusion in the record.

Very truly yours,

IRVING H. JUROW,
Vice President and General Counsel.

Senator NELSON. To go back to the question on the amount spent, do you have any idea how much you have spent that is attributable to research?

Mr. CONZEN. I am afraid not, because we have an overall research budget this year of over $12 million. Now, this is broken down into various areas of research, such as cardiovascular diseases and inflammatory diseases.

Now, this would fall more into the area of inflammatory diseases, and another area, allergies and related indications. There we research on many compounds, most of which never see the marketplace.

A few will finally be of sufficient value to the medical profession to warrant intensive clinical studies, and finally an application—a new drug application—and after that has been granted it appears on the market. So, we have many compounds which fall under this general area of research, and to break it down to any specific compound would be very arbitrary and possibly misleading.

Senator NELSON. What do you include in your $12 million of annual expense for research? What I am trying to get at here is, do you include only laboratory research, or do you include the distribution of samples of drugs and responses from the institutions, their observations about them? What do you call research?

Mr. CONZEN. This term research, as I used it, encompasses, first of all, the laboratory work and chemistry and microbiology to synthesize or discover new compounds, to put them through biological screens to determine whether there is some biological activity which would be of interest and importance to the medical profession.

It includes pharmacology in animals. It includes extensive toxicological studies before the drug can be given to man on an experimental basis. It includes pharmaceutical development to develop a form or dosage form or vehicle in which the active drug can be safely and effectively administered. It includes the production of the initial quantities which go both into animals and into men.

Senator NELSON. What do you mean the initial quantities?

Mr. CONZEN. Of the active drug and the preparation of the product form which is given to animals first and later on when it is considered safe to go into clinical pharmacology, to give it to man whether in the form of injection or in the form of an implantation or a tablet or an ointment or whatever it may be.

It includes the setting up of clinical studies which will determine whether there is sufficient material available to satisfy the Food and Drug Administration for us to apply to the FDA for approval of a new drug application, and these samples or trial quantities during this initial phase are included in research. However, once the drug has been introduced on the market, whatever samples are then being distributed do not fall under research unless they are for indications which have not yet been approved and are still in the experimental stage.

Senator NELSON. So you either do the laboratory research and the research on animals yourself or you contract it out; is that correct?

Mr. CONZEN. Most of it is done by ourselves; yes.

Senator NELSON. Then after you are satisfied that it has some therapeutic efficacy so far as animals are concerned, the next stage is to test it on human beings?

Mr. CONZEN. There is one step in between, and that is toxicology, to satisfy the Food and Drug Administration and ourselves that the side effects or the toxic effects do not endanger the patient, or that the side effects outweigh possibly the beneficial effects of a new drug.

Senator NELSON. And if this drug gets the approval of FDA, then you are authorized to test its efficacy on human beings?

Mr. CONZEN. Well, this is not exactly so. We file an investigational new drug application with the Food and Drug Administration, and in the absence of any notification to the contrary, we are authorized to proceed with clinical trials.

Senator NELSON. These clinical trials include sending samples to specific physicians to test; is that correct?

Mr. CONZEN. They are special studies set up under regulations of our Government, and the investigators have to file very strict protocols and procedures, and we again have to comply with very strict regulations as to what we send, how we send it, and to whom.

Senator NELSON. And then you also do clinical testing by arrangement with teaching hospitals and that sort of thing?

Mr. CONZEN. Yes, sir.

Senator NELSON. Then what you are saying is that to this point all the steps you described are chargeable to research.

Mr. CONZEN. Yes, sir.

Senator NELSON. Beyond that, your distribution to physicians, once a drug is approved, is not chargeable to research.

Mr. CONZEN. Unless it is a new, not yet approved indication which still falls into the realm of experimental research work. For instance, I mentioned leukemia. This is not an approved indication in the high doses in which experiments are being conducted, and this would still be chargeable to research; but in the approved indications, the material which we sell, and the amount of money which we spend would appear in our financial statements under selling expenses, including samples.

Senator NELSON. So, no aspect of the market promotion is chargeable against research?

Mr. CONZEN. That is correct.

Senator NELSON. A few moments ago you said it was not possible to break down the amount spent by your corporation on research on prednisolone or prednisone. It isn't possible then for your corporation

to do a cost accounting, so to speak, of the costs that went into the development of prednisone, so that you can price in accordance with the cost of your development?

Mr. CONZEN. I don't think so, because the clinical staff and the laboratories are used for all drugs, whether they are in research or continuing research, and we can't intelligently allocate all these expenses to a specific drug.

Senator NELSON. I understand.

Mr. GORDON. May I interrupt for just a moment? Can we say that NIH was the first to introduce prednisone into clinical medicine?

Mr. CONZEN. I wouldn't say that, no. As far as I remember, the first clinical paper was published under the auspices of NIH using Schering's prednisone, namely Meticorten.

Mr. GORDON. I have here excerpts from hearings on drug safety before a subcommittee of the House Committee on Government Operations. NIH stated that the first clinical studies of these new steroids were conducted on patients with rheumatoid arthritis in the National Institute for Arthritis and Metabolic Diseases. The results were encouraging and so on and so forth, and NIH reported these findings to the scientific community in November 1954.

Mr. CONZEN. Yes, sir.

Mr. GORDON. Now, wouldn't you say that the report of these findings by NIH was really the introduction of prednisone to the scientific community?

Mr. CONZEN. I would say the introduction to the scientific community was made by Schering Corp. when it made the product available to NIH.

Mr. GORDON. I mean the medical community, clinical medicine.

Mr. CONZEN. As far as the clinical findings are concerned, this would be correct as to this particular work.

Mr. GORDON. Now, isn't it also true that in getting a new drug application, you depended to a considerable extent on work done by or for the National Institutes of Health?

Mr. CONZEN. Only for one part of the new drug application, because the new drug application has to satisfy the Government that the manufacturing procedures and processes are sound, that the toxicology is good, that you observe the usual standards of manufacture and quality control, and they would also undoubtedly expect clinical trials beyond those from one source.

Mr. GORDON. Did you mention efficacy? Efficacy has to be proven, too, does it not?

Mr. CONZEN. Yes, efficacy and safety.

Mr. GORDON. And you used the work done at NIH?

Mr. CONZEN. Oh, yes.

Mr. GORDON. As part of your contribution.

Mr. CONZEN. Absolutely.

Mr. GORDON. To the FDA.

Mr. CONZEN. Yes.

Mr. GORDON. And you are not trying to claim, as I see it, that Schering alone was responsible for the research and development of prednisone?

Mr. CONZEN. I would say that we were alone responsible for the discovery of the drug and the development of the drug, but that we

did not have our own clinical facilities within the company, and we had to go outside to have the therapeutic value of the drug and different indications proved outside. As a matter of fact, we have studied 45 disease indications with Meticorten.

Senator NELSON. If I may go back a moment, I neglected to ask you on page 3, where you state that the domestic ethical drug sales volume of Schering Corp. is $65 million, what your sales amounted to outside of the United States?

Mr. CONZEN. Our sales abroad last year were approximately $46 million, if I remember correctly. The balance between these two figures; namely, 65 and the 40 odd million in foreign sales, refers to domestic sales in other than prescription products. Those are lay products, those are products which can be sold without a prescription, and they also refer to products in the animal health field.

Senator NELSON. Do I understand you to state that your sales outside the United States in ethical drugs are $46 million?

Mr. CONZEN. No; the foreign sales also include sales of nonprescription products.

Senator NELSON. I see. It's a total of $46 million?

Mr. CONZEN. That is correct, sir.

Senator NELSON. Then so that the record is clear, what are your nonprescription sales totals in the United States, over and above the $65 million?

Mr. CONZEN. I don't have the exact figure with me, but I will be glad to supply it. I would estimate these to be in the neighborhood of between $20 and $25 million.[3]

Senator NELSON. Does the $65 million figure in domestic ethical sales include royalties received?

Mr. CONZEN. No.

Senator NELSON. What are the royalties received on domestic sales?

Mr. CONZEN. The royalties received by the corporation are stated under other revenues. As far as Meticorten is concerned, at a royalty rate of 6 percent and estimated sales by licensees of approximately $2 million per annum, it would amount to about $120,000 per year.

Senator NELSON. As I understand it, your total royalties on domestic sales of prednisone or Meticorten are what?

Mr. CONZEN. On prednisone tablets, approximately $120,000 per annum, I estimate.

Senator NELSON. These are royalties paid by companies that are producing prednisone?

Mr. CONZEN. That sell prednisone as tablet preparations licensed by us in the United States.

Senator NELSON. But they are not selling it under the name Meticorten. They may be selling it under their own brand name or they may sell it generically, is that correct?

Mr. CONZEN. Yes, sir. If I can continue, what follows is an oversimplified and only a partial list of what Schering does, and must do, to fulfill its role in today's complex and highly competitive world of medicinal products. Moreover, it is what Schering actually did for prednisone.

In the first place, we must search constantly and continuously for new and better compounds which may be formulated into new and

[3] See p. 627.

better medicines. The industry's average, as you know, is one success for every 6,000 probes. We must investigate each promising new compound in a series of costly, time-consuming steps: first in the laboratories and then in animal testing, to determine the usefulness, and more importantly, to insure the safety, of any such compounds for testing in human beings. We must then develop pharmaceutical formulations so that the useful compound can be made available as a medicine in a variety of dosage forms. Additionally, we must develop manufacturing procedures, often novel and frequently complex; we must learn how to make, initially, limited quantities for release to a limited number of doctors for clinical investigation of the compound's effectiveness and safety in human patients; and later, if successful, larger quantities for marketing throughout the world. These investigations on the part of clinical investigators must be carefully supervised and monitored, the results meticulously correlated and analyzed, and a host of detailed information accumulated, which would take much too long here to catalog.

Suffice it to say that the research work that has to be done in connection with the investigation of a new and promising medicine, in view of the elaborate and strict rules and regulations of the Food and Drug Administration in our country—and similar requirements abroad—is costly, time-consuming, and involves a myriad of details. All this takes a number of years—nowadays usually from 5 to 8 years. In the meantime, considerable additional investigation proceeds, more data are developed, more reports prepared and filed with the FDA.

Other areas of our company's operations are involved:

Our engineers must learn how to make the new drug in large quantities for commercial use—both economically and accurately.

Quality control scientists must develop standards, design tests to validate them, so that up to 24 different factors contributing to the safety and effectiveness of a single tablet or capsule or vial of injectable liquid can be guaranteed.

A marketing organization must be established and continually maintained to assure that the product will be speedily available throughout the United States and the free world.

Scientific and clinical documentation about all aspects of the new drug must be carefully created and produced by us and then cleared by the FDA in Washington.

Our representatives—or detail men—receive a thorough, in-depth course of training so that they are fully knowledgeable concerning every aspect of the new drug—its usefulness, its limitations, in advantages, its "problem points"—in short, they must be thoroughly briefed to be able to provide full information and to answer the questions about the new drug which the physician might ask.

Our detail men must then call on those doctors who might possibly use the new drug in their practice, brief them fully on the drug's properties and recommended uses, and provide them with samples so that they can become acquainted with the drug. These personal calls on physicians, hospitals, and pharmacies must be supplemented with further information in medical journals, in direct-mail literature, in brochures and the like—all of which must be consistent with FDA requirements.

I could easily devote more time to explain to you the wide scope of the activities that actually did go into our discovery, development, and marketing of prednisone. I could, for example, refer to the symposia on prednisone which we sponsored for the scientific and medical community, the brochures we prepared, the films we created and distributed, the host of things we did to make this new and dramatically useful product known to the physician and available to his patients throughout the world.

How completely different is the business carried on by the large majority of the distributors of generic prednisone.

For the most part, they are essentially distribution operations; in fact, many of them have the finished product manufactured for them. These companies do not develop new drugs. They do not have the scientific staffs nor the facilities to develop them. They do no animal testing or clinical investigation. Usually generic distributors do not work for years to gain Government approval.

They do not introduce new drugs. They lack the personnel and skill necessary to communicate to doctors all that needs to be communicated to them about the indications for the drug, the dosage regimen, the methods of application, the side effects and precautions, and so on. They cannot answer questions about the drug's use in individual cases or provide other services to the doctor. They do not supply samples liberally to provide special formulations of the drug to use in treatment of eyes, ears or other organs, or special strengths for treatment of children, the elderly or other groups. These markets are usually too small and specialized. They limit quality control activities to legal requirements. They do not, in short, encounter the major burden of costs necessary to develop and launch a new drug successfully and prove its worth.

Without these activities, generic distributors contribute little to medical progress.

On the other hand, after someone else has developed a drug and after someone else has incurred the costs of introducing it properly, so that it gains widespread usage, they are able to copy it as soon as copying is legal. When the active ingredient is well known and highly regarded, they take advantage of this to sell it cheaply, in quantity, and frequently on a mail order basis. They concentrate on the one or two forms in widest use and on types of users easiest to reach. Sometimes such companies concentrate on Government bids only and operate in such a way as to minimize investment in facilities and personnel. Their entire business is built upon the pioneering work of others. Their appeal is based solely on their contention that their cheaper versions have the same active ingredient.

In fact, this is what happened in the marketing of prednisone.

When all is said and done, it was Schering's research which discovered prednisone, Schering's development which gave that product to the world and to the medical community, Schering's marketing and distribution which made it known and used throughout the world, Schering's activities which broadened its usefulness, and Schering's licensing which made it available from so many dstributors. Without all this, there would not be today any generic prednisone at all.

We at Schering are proud of our discovery of prednisone; it represented a real breakthrough. Indeed, every corticosteroid tablet prepa-

ration introduced since the discovery of prednisone embodies the unique principle that characterizes the prednisone molecule and that distinguishes it from cortisone and hydrocortisone. Prednisone blazed a new trail in anti-inflammatory steroid therapy.

Moreover, as the discoverer of prednisone, we are even today involved in servicing that compound, continuing research with it, in seeking to broaden its application and to expand the line of prednisone products. As the discoverer of prednisone, we carry, and must assume, the responsibility of continuing research not only with respect to that product, but with derivatives of it. At this point, some 12 years after we first introduced prednisone, we continue to supply clinical investigators with experimental forms of prednisone for further exploration of its potentials. These things, costly as they are, are not performed in any way by any of the generic distributors of prednisone.

To achieve our objectives, to maintain the kind of organization we are—research, development, Government clearance, worldwide marketing, total service to the physician and the trade-all this far exceeds to cost of operating a generic enterprise which ordinarily requires bare manufacturing cost and nominal sales expense. Many of our costs apply to failures, as well as successes, but only the successes are copied.

The "striking differences" in price you referred to are the inevitable consequence of these contrasts. In my judgment, they are fully justified. At generic-level prices, we cannot have new discoveries. At generic-level prices we will stifle research and the development of new medicines, and soon we will have neither the new drugs nor the generics.

If we were to attempt to compete at the same price level as the generic distributors, we would have to eliminate a large proportion of the activities and services which I have described as characteristics of our company. We would have to limit our activity to simple manufacture and distribution of drugs discovered, proven, and established by others—and they do—and one important source of new drugs for the treatment of sickness will have been removed from this country. I do not believe this would be in the public interest—certainly it would not advance medical science nor contribute to further development of higher health standards.

You also asked me to discuss our pricing policy with respect to prednisone. Let me answer that by giving you some of our guidelines in pricing—the highlights of the criteria we consider in establishing, and subsequently in reviewing, the prices for Schering products.

The ultimate responsibility for pricing policy at Schering rests with me as president. Pricing decisions and approvals, in each marketing division, must be in accordance with procedures and practices which I approve.

Schering prices are established at a level which covers our research budgets, including the cost of both our successes and our failures, the cost of materials and of efficient manufacture at reasonably attainable volumes, the cost of quality control under the highest standards, the cost of efficient marketing, including that of communicating product facts and benefits, the administrative cost of operating the company, and the taxes payable to national, regional or local governments. The cost of the active substance is a small portion of total costs.

Our pricing should also provide an average, long-run corporate-wide, after-tax return on stockholders' equity at a rate at least equal to that of the pharmaceutical industry as a whole, since we require earnings to support continued corporate growth and to compensate investors for the use of their capital.

All of this is evaluated against a background of the high risk involved in bringing a new pharmaceutical to market.

We consider the expected response, based on analysis of value of the product to the user, as compared with the value and price of alternatives he may have. We attempt to forecast the attainable sales volume for the product at various possible price levels, and at various times during the expected product life cycle. We give thought to the significance of the product with respect to our entire product line and its effects, if any, on the prices, sales, and profit margin of our other products. And, finally, we consider the magnitude of the investment required and the degree of risk we undertake.

These are broad principles—and like all broad principles, there are exceptions. We make exceptions under certain circumstances; for example, where economies in production or marketing are attainable in serving certain types of customers and where making a product available at a special price is expected to result in increased long-term usage.

There are also situations where we believe we have an obligation to provide vital drugs in rare and unusual conditions, even though they must be provided at a loss.

In pricing Meticorten and in our periodic review of its price, we have sought to apply these principles. Throughout the entire period that we have been marketing Meticorten, prednisone has been generally available to the public from a number of sources, and for the last 8 years, at a wide range of prices, so that the carrying out of our business judgment in this respect has in no way been in conflict with the public interest, but in fact, has served to advance it by enabling us to continue the creative development of the compound itself, and of succeeding therapies.

Many physicians prescribe Meticorten, knowing that prednisone is available at lower prices. We thing there is sound reason for their doing so. We think Meticorten is the best product—the one fully proven in patients and the most carefully prepared and controlled. Their experience has confirmed this. They continue to prefer Meticorten for their patients, despite its higher price. We think they are right.

Schering Corp.'s annual report for 1966 indicates that the application of this pricing policy has not resulted in excessive profits. Over the past 5 years, Schering has averaged a return on investment which is slightly below the median for the industry, and certainly not out of line with the risks and competitive situation with which it is faced.

We have on a number of occasions considered reducing the price of Meticorten tablets and have consistently arrived at the conclusion that this would not be sound business economics, given the nature and scope of the services the medical profession and the public expect from us. As I indicated earlier, the volume of Meticorten tablets and the sales of Meticorten tablets are such that any substantial reduction in he price to meet the generic price level would simply mean that we diminish our capacity to provide these services.

If Schering is to discharge successfully its responsibilities and achieve its objectives in our society, if it is to be the source of breakthroughs in the future, if, as I am persuaded, the community expects it to discover, to test, to produce, to market, and to service the new, high-quality, safe and effective medicines of the future—and to continue to make available those on the present scene—and to do all this in active and aggressive competition with companies like itself, then it must have the resources to take all the risks implicit in these activities and to attract the scientific manpower that is necessary to do that job successfully.

I believe that the large majority of our society expects this of us and is prepared to accept, and does accept, the fact that the economics of these circumstances demand that our prices be substantially higher than the prices which the generic distributors charge. To them the community does not look for, and from them it does not expect, these necessary services and activities. From them the community expects and receives only price-oriented distribution.

That is why our price for Meticorten is what it is, and why the generic distributor's price is what it is, and in my judgment these striking differences are justified by the contrasts I have attempted to put before you here today.

Nevertheless, I should not leave you with the impression that we are unaware or unmindful of the continued critical attacks in these hearings and in the press. Even though we regard our position as sound, for the reasons I have outlined, we have always reviewed our judgments in the light of the challenge of criticism; we plan to continue to do so.

We are not callous to the difficulties which our older citizens face because, due to their limited, fixed incomes, and often chronic illnesses, medical costs, including drugs, are high. Because of their limited incomes and greater needs, the difficulty they face in keeping pace with our inflationary economy is augmented. They need to be helped, and governmental and voluntary programs are doing just that. Moreover, under our present economic system and structure, we must look to the continued development of these programs to provide the help that is needed.

It will serve our society poorly if, in seeking to resolve these difficulties, we limit the ability of our creative pharmaceutical industry to serve the professions and the public through the discovery of new drugs.

Thank you, Senator Nelson.

Senator NELSON. Thank you very much, Mr. Conzen. You were here this morning, I assume?

Mr. CONZEN. Yes, sir.

Senator NELSON. You heard the testimony of Mr. Burrows of Parke, Davis. I would like to repeat to you a couple of questions that I asked Mr. Burrows at that time. I will be referring to the Medical Letter. On page 14 of your testimony you state that you think Meticorten is the best product, and I am sure as the president of Schering Corp. and knowing its operation you believe that. You state it is the one fully proven in patients and the most carefully prepared and controlled. You feel that doctors' experience has confirmed this and they continue to prefer Meticorten for their patients despite its higher prices and "we think they are right."

Now, I refer to the Medical Letter of June 2, 1967. As you know, the Medical Letter is a very highly esteemed professional publication. A number of witnesses, pharmacologists, physicians, medical spokesmen have referred to it as a very reputable high-quality publication. The Medical Letter asked the Fitelson Lab in New York to test 22 brands of prednisone, some generic and some brand name products. In the Medical Letter, on page 41, they state that none of the variations of the 22 products tested are outside of Pharmacopeia limits or are of sufficient magnitude to have an adverse effect in the treatment of conditions requiring the use of corticosteroids:

> The disintegration test measures only rate of disintegration and not rate of dissolution or rate of physiological availability. There is nothing, however, either in the report of the clinical trials or in the experience of Medical Letter consultants to suggest that variations in formulation are causing any problems in the treatment of patients.

Then on page 42 the Letter continues under the heading "Prices":

> The great price spread among tablets purchased from different pharmaceutical companies suggests the desirability of prescribing by generic name and specifying at least for patients of limited means that the prescription be filled with low-priced prednisone tablets.

You state on page 14 that you think yours is the best product. Now, have you any clinical evidence to demonstrate that your product priced at $17.90 a 100 is a better product than Upjohn's Deltasone priced at $2.25 a 100?

Mr. CONZEN. Available clinical testing still does not allow us to say just how much the drug products of one manufacturer differ from those of another. The clinical evidence does indicate that current quality control testing cannot guarantee that two supposedly identical drug products deliver the same amount of drug chemical at the same rate to the patient.

There are three medical papers which have reported experience in patients treated with two prednisone products. In each instance one product was effective, the other failed.

Senator NELSON. May I interrupt a moment. Were these double blind tests?

Mr. CONZEN. I cannot answer that.

Senator NELSON. Do you know the names of the products? Would you name them?

Mr. CONZEN. The names of the products were not disclosed in the studies. I refer to the Journal of Pharmaceutical Sciences, volume 52, page 605, in 1963, by Drs. Campagna, Cureton, Merigian, and Nelson; and the other one by Drs. Levy, Hall, and Nelson in the American Journal of Hospital Pharmacy, volume 21, page 402, published in 1964, which established these data. I will be glad to make copies of these publications available to the subcommittee.

Senator NELSON. We have those studies. Unless my memory is incorrect, Dr. Feldmann, Director of the National Formulary, said they were not double-blind tests.

Mr. CONZEN. I cannot, from personal knowledge, state whether these were double-blind studies or not.

Senator NELSON. If my memory is correct, he also said that they were testimonials and not scientific clinical studies.

Mr. CONZEN. These studies by these scientists state that they provide additional evidence to previously published work suggesting that the

USP distintegration time test should be reevaluated as a method to predict correctly physiological availability in vivo.

Senator NELSON. What I am getting at is that the Medical Letter stated that from their consultants, pharmacologists, clinical physicians, they can find no differences or variations in formulations that are causing any problems in the treatment of patients. They advise that the doctor prescribe generically especially for the patients of limited means. What I am asking is does the Schering Corp. have any double-blind clinical test to prove that the therapeutic efficacy of its prednisone is better than any other one of the 22 prednisones listed in the Medical Letter?

Mr. CONZEN. No, sir.

Senator NELSON. Is there any evidence at all that it is better than Upjohn's Deltasone in terms of its therapeutic efficacy?

Mr. CONZEN. We have no such comparative clinical studies.

Senator NELSON. Then looking at the test, as a matter of fact, Upjohn's is a purer drug than Schering's. Upjohn has only a trace of foreign bodies in it, that is cortisone. Schering's has five-tenths of 1 percent. So if you are using the question of purity, Upjohn's at $2.25 a 100, if that is as important as many drug companies insist, is a better drug in that respect than Schering's. And then Merck's has zero cortisone in it. Schering's has five-tenths of 1 percent. On the basis of purity then, Merck's prednisone, selling at $2.20 a 100, is of higher quality than Schering's selling at $17.90. Although I do not think that is a fair argument, the drug companies use it consistently by saying that they do more refining and produce a higher quality product. These are USP standards, and USP says the variations listed here really do not make any difference. If the drug companies are going to stand on the proposition that they do more work than some other company and get more purity, and that USP standards are not high enough, then Schering's drug is not as high a quality as the two drugs listed here, so far as purity is concerned. There are two with only a trace, and there are several, five that have the same amount of impurity, cortisone, in them. What is your observation about that?

Mr. CONZEN. My observation on this is that, in my opinion, the acid test as to the value of the quality of a product lies when the physician treats his patient, and how this drug acts and is effective in the patient himself. These physical or analytical tests in the laboratory are not the only criteria by which equivalency should be judged.

Senator NELSON. If that is the case, I again ask what proof does Schering have that their drug is a better drug from a therapeutic standpoint than any one of the 22 drugs listed in the Medical Letter?

Mr. CONZEN. We have no proof that it is better, but we have abundant proof that it is the best documented drug on the market, through these thousands of independent clinical studies, and the fact that physicians continue to prescribe our drug.

Senator NELSON. The fact that a physician prescribes it does not make it a better drug, does it?

Mr. CONZEN. It means that he considers it, for his patient and this particular indication and case, the best he should prescribe.

Senator NELSON. What is your response to the Medical Letter's statement that there is nothing, however, "either in reports of clinical trials or experience of the Medical Letter consultants" who are better