

Mr. HARRISON. Let us take the claim that is made and is subsequently found to be inaccurate. From my own limited experience, what happens is that the FDA comes back and finds that a particular statement, one of many statements that is made, is inaccurate; or that a statement which should have been included was omitted. In other words, I do not believe that we are speaking about a complete fabrication. FDA may find that one of the contraindications is not noted in the ad.

I believe that we would find in most instances, or in all instances, that the fault found by the FDA is the failure to include a contraindication that should have been included, or perhaps a misstatement of one fact which is only one of the many facts that must be included in the advertisement. It is of a limited nature in that respect, and I wonder whether or not it would warrant the kind of communication you indicate is needed by way of advertising.

But going back to my own schooldays, Senator, I recall when we discussed advertising as such, we found that the best way to communicate, the most effective way, was on a person-to-person basis, and that as you went down the ladder, the next best way to communicate was by direct mail, because that went to everybody, and we assumed that everybody opened up their letters and read the communication. Down the line somewhere was the advertisement in a periodical or newspaper, which might or might not be seen by the individual.

Now, apparently, here, the Food and Drug Administration has communicated with every one of the physicians in the country by way of a "Dear Doctor" letter, or has required the company to communicate by way of a "Dear Doctor" letter. It seems to me, Senator, that a very effective mechanism has been established to provide that physician, even if he never saw the ad originally—which is probably the case in most instances—with the information that has been required. I do not think anybody can improve upon that situation unless we got on the phone and called all 300,000 doctors in the country.

Senator NELSON. I would say to that two things: one, I have had several doctors say they never bother to read them.

No. 2, that does not relieve the AMA of its responsibility to the profession. It would seem to me that AMA could be quite dramatic and effective in two ways: one, convey to the doctor that you had a brand name company advertising in your publication that lied to you, and they were required to reform their ad or cut it out; that they were required to write a letter to every doctor in America. That would take a little gloss off of what all the doctors are saying, that you cannot trust anything but the brand-name company.

Secondly, I do not know how the doctors are going to keep up with this reading two "Dear Doctor" letters a month, 29 over the past 2 years.

Dr. ANNIS. The mail is measured by inches on this, Senator.

Mr. HARRISON. The publications are measured by feet.

Dr. ANNIS. First-class letters are in that pile. And the publications are measured, as Mr. Harrison said, by the foot.

We have indicated that we are a fallible organization, as are those who review our advertising, and if there are necessary changes by virtue of the facts, these will be instituted.

Senator DOLE. How many persons, other than doctors, receive the journal? What is the total?

Mr. HARRISON. The circulation is in the neighborhood of 215,000, I believe. I have the exact figure here.

Senator DOLE. How many of those are doctors?

Dr. ANNIS. 212,000 are members.

Mr. HARRISON. Except for libraries, Senator, and other recipients of that nature, almost all the direct recipients are physicians.

Senator DOLE. If they have all gotten the letter, I do not know why you would need to run an ad in the journal, unless you get it twice.

Mr. HARRISON. They all receive the letter. Also, the other hundred thousand or so physicians who do not receive the journal also receive the letter.

Senator NELSON. I would submit that there is a moral obligation involved. If you run an ad that misleads and it is seriously misleading, as a number of these were, in the place where the ad occurred, you ought to, and are morally obligated to tell the doctor that the company that advertised in here was wrong. If that is not a moral obligation of the AMA, I do not think the AMA has one.

My heavens, Doctor, if I ran a publication in which the health of the people—

Dr. ANNIS. Senator, we are guided, as I have repeatedly told you, in the basic content by the regulations of the Food and Drug Administration. Many of these rules have emanated as a result of hearings, such as yours, in an effort to tighten up this situation. If we are going to castigate any organization because they occasionally make an error—because unless you are going to accuse them of deliberate falsification—even those who have testified before your committee as to the severity of the complications, and Dr. Dameshek is a good example, have recognized this. One of his earliest statements was that this drug is rare in its complications.

Senator NELSON. Which?

Dr. ANNIS. Chloramphenicol. He indicated that it is rare that it event has side effects and that its absorption in youngsters was and is great. So many pediatricians used it. It is the rare thing that does occur that is tragic. There is not any question about this. There is no argument about this. But the point is that even these men have not held that the drug, for example, should be abolished. It still has limited but nevertheless essential uses. For this reason, the manufacturers have a legitimate right for it to be advertised.

Do not forget, as I indicated this morning, there is no question in my mind that many of the physicians who have used this drug are among physicians, such as myself, who have learned to use and depend upon a few basic drugs in the past. If a drug that I used for 4, 5, 6, 8 or more years was consistently successful, was consistently giving me good results, and I never had a bad effect—and that could easily be in a drug that has had a bad effect in one in 20,000, or up to one in 200,000—I would continue to use it. I can easily see if a drug is pulled off the market, when it comes back, a physician could say, in effect, that the FDA is saying, "look, after we have looked into this, we find this is still a good drug, and once again we will allow it to be sold, and the advertising to be done."

And once again, it comes on the market, and the content of that copy is contained in the inserts, as prescribed by the Food and Drug Administration. I maintain that we have not been derelict because we have not read fine print or taken occasional exceptions.

When you get to this point, you run into disagreements between physicians. For example, the one who may have used the drug for years and who has never had a side effect, the other who, by virtue of scientific, laboratory and other facilities available, and greater exposure to literature, is well aware of them.

These are basically conflicts. There is no reason on the basis of a difference of opinion to castigate anyone or told them up as though, by virtue of this, they deliberately misled the profession.

They are still advertising a product that our Government's FDA admits is acceptable for manufacture, sale, and distribution. So if there are objections to certain of the facts that are contained in ads, the Food and Drug Administration has full authority at the present time to bring about any necessary changes. This is neither the responsibility nor the prerogative of the medical profession.

Senator DOLE. In other words, the FDA could require——

Dr. ANNIS. They could require, in big red letters on the front page, if they so desire, "This is a dangerous drug except under certain circumstances." Even its danger may be ignored because it is the only, or one of the only treatments available for certain conditions.

Anything they could put in there. All they have to do is do it by regulation, and they have the authority right now.

Senator DOLE. But instead, they require a letter, as I understand it.

Dr. ANNIS. No, they set up certain standards. Then, if the advertising that we receive and the rest of the drug advertisers receive, they put it in print, assuming it meets the basic requirements of the law. The FDA, after reading it, says to the manufacturer, "look, you have exceeded what we have allowed or, you have failed to comply with the law; you must send out a 'Dear Doctor' letter." And the FDA requires it to be in a special envelope.

I do not care how busy you are, these envelopes doctors have come to recognize and they read them. Because whether you prescribe these drugs or not, the drug may come to your attention and you want to know which ones are involved.

Senator NELSON. I repeat, Doctor, at the risk of being boring, that I am talking about the case where the ad was misleading. I will find an example or two here for you.

Dr. ANNIS. I am satisfied you could find these, Senator. You have indicated that.

Senator NELSON. When you carry an ad and it is educational; it is intended to convince the doctor of something.

Dr. ANNIS. Senator, here are six or seven publications. You see how thick they are. If you would pick them up, you would see how heavy they are.

I do not doubt that we have errors in there. But they are not errors of commission; they are not errors deliberately made. They are errors inherent in human beings, and by virtue of our desire to bring up to date knowledge in an obviously changing area of communication and knowledge. What appears to be true today experience will prove is not true 6 months from now, even in the use of other drugs.

Senator NELSON. I am not saying that it is an error of commission for the Journal not to notify its readers that false claims have been made in an ad in its Journal. It is an error of omission. All I am saying is, since doctors to a large extent do prescribe on information they get out of the ads, the Journal has the obligation immediately to cor-

rect that misleading ad in the same place, in the same way, something similar to the way in which the claim was made.

Do you not think so?

Dr. ANNIS. I would suggest that you give the Food and Drug Administration enough money to do the job for which they are authorized and which they are qualified to do.

Senator NELSON. What is your obligation in JAMA? You are a private, independent, publication in an area that has run a false and misleading ad that was paid for——

Dr. ANNIS. Not deliberately.

Senator NELSON. I did not say that.

Dr. ANNIS. May I ask how long Dr. Goddard said it required the Food and Drug Administration to review one ad for approval?

Senator NELSON. I do not recall.

Dr. ANNIS. I do not, either, but it was 11, 12, 13 days or more. I am talking about reviewing each ad on this basis.

Senator NELSON. No, I am not talking about that. I am talking about the case where you ran the ad, you did not know that they were making false claims. FDA discovers they were making false claims.

Dr. ANNIS. Maybe they do not know it.

Senator NELSON. We have seen enough of it, so we do not think there is any question of it. It happens all the time. They are leading toward getting wider use of the drug than the FDA thinks——

Dr. ANNIS. As an attorney you are better at this than I am, but if there is evidence that they are deliberately trying to get around the law, they should be called to task on.

Senator NELSON. They run a bronchoscope in one of your ads. If that is not fact, I do not know what it is. If that does not indicate that that is to be used for general use in that area, I do not know how any other person in the world would interpret that, "When it counts," and a bronchoscope.

Dr. ANNIS. No, they said, "When it counts, think of Chloromycetin."

Senator NELSON. You and I are sophisticated enough to know what it means.

Dr. ANNIS. I have told you I have never used it. But my point is that many physicians still feel, and have testified before your committee, that there are indications for it.

Senator NELSON. We know that. But it is being used 90 percent of the time, 90 to 95 percent, in nonindicated cases.

Dr. ANNIS. These are guesses, and the men who testified admitted this. I do not know what the figure is. If somebody else says 20 percent, I would say, could be. I do not know that, either.

But the essential point is to get the message. It would seem to me that this should be the main point of what you are driving at; that is, that more physicians get notice of the potential side effects of this drug so that they are critical in their appraisal of the need and justification for its use.

And again, I would agree with you—we are in total agreement. I believe the records will show that since you have started this investigation, many physicians have paid attention. In fact, I believe, according to Dr. Ley, there has been a decrease in the use of chloramphenicol to a considerable degree.

Senator NELSON. From about 41 or 42 million grams in 1967 to 17 or 18 million grams in 1968.

Dr. ANNIS. Then I would say we must be on some proper wavelengths; let us increase the speed with which we use them to accomplish an objective that both of us desire.

Senator NELSON. But I think a major share of the credit comes from what the committee did with it.

Dr. ANNIS. My point is we are not in disagreement with you.

Senator NELSON. But I still cannot quite get an answer to the point that I—apparently you do not think is important. You say the FDA can correct any of this.

Dr. ANNIS. They have troubles, too.

Senator NELSON. I think the FDA had some problems with the industry and with the medical profession.

Dr. ANNIS. They do.

Senator NELSON. I think that since Dr. Goddard and I hope in the future, the FDA has done a superb job compared with what has been done in the past. I would be sure that Dr. Ley and Dr. Goddard would say that they would do a lot better and will hope to and try to. But I would have quarrels with them about what they permit in ads.

Dr. ANNIS. And they have the same problems we do.

Senator NELSON. But you have no problem at all, it seems to me.

Dr. ANNIS. Oh, yes, we do.

Senator NELSON. In this respect: the company runs an ad and it is found to be false and misleading. I still have not got an answer to the question, why do you not feel as a custodian, a most important custodian, with a special relationship to the people as custodian of the health of the people of this country, why you do not feel a moral obligation to run a prominent story saying that the claim made in X issue on this drug was false and misleading, according to the FDA, and here is their language; this claim was made and it is not indicated for that.

Dr. ANNIS. Probably because there are some real sharp lawyers in this country that have arranged the laws in such a way that we had better be careful what we put in print, especially any indication of malicious intent.

Senator NELSON. You would just report the news.

Dr. ANNIS. Well, that is all right. To say that they have made an error, that is all right. A lot of people make errors. I do not know anybody who does not.

Senator NELSON. I did not say malicious intent.

Dr. ANNIS. But you said lied to them.

Senator NELSON. False and misleading.

Dr. ANNIS. That is lying to them.

Senator NELSON. I think I could use the language of the FDA, but I would go further than that, Doctor.

Since the responsibility of the profession to the American people is special, I think you could make an agreement, if that is what is worrying you, with any company that advertised, that you intend to run a story on any misleading advertising as found by the FDA, you intend to run it prominently. I do not think there is anybody, and if any manufacturer says, we would not advertise with you on that basis, that is about the time they ought to be kicked out of your pages.

I am saying you have a moral obligation.

Dr. ANNIS. We will take it under advisement.

Senator NELSON. I was asked whether it was intentional. I can only repeat what the FDA said. This is a July 8 memorandum of the FDA. Here are three ads that ran in JAMA on June 29, 1964.

Dr. ANNIS. Senator, we do not deny that we have ads that you have indicated. In retrospect, I can think of a lot of things that have been wrong in the past.

Senator NELSON. Let me just read here. You raised the question of whether there was ever any intent. I shall just read what was said. These are on Pree MT. This is just one, June 8 and June 29, 1964. This is a July 8 memorandum, 1964.

To the Bureau of Regulatory Compliance, Joseph F. Sadusk, Jr., M.D., Medical Director—

Through him from Robert S. McCleery, M.D., section on advertising and promotional labeling—

1. We believe the faults—

What happened here was that they ran two ads, the first two. When they got to contraindications, they printed in the ad, "None known." Then when they got the complaint, they ran one on the 29th and they did not put contraindications in at all. They left it blank. So they had "None known," and there were contraindications, and they knew it. Then on the third ad, they did not put in the contraindications.

Dr. ANNIS. Were they prosecuted by the FDA?

Senator NELSON. Counsel advises me that the company was prosecuted and found guilty.

1. We believe the faults of the ad and the attached mail pieces are significant and that we can help you support any action you deem advisable. We are deeply concerned that the action chosen might also have as a consequence the immediate cessation of this type of promotion which can mislead the reader into using the drug in a manner that could jeopardize the safety of his patients.

2. An interesting and disturbing event has occurred since our interest in the Pree MT ads began on June 9. (See attached copies of June 8 and June 22 issues of Modern Medicine and June 8 and June 29 issues of J.A.M.A.)

Note that the heading "Contraindications" has disappeared from the June 22 and the June 29 ads.

The June 29 ad was in JAMA.

This kind of change is very easy to accomplish technically. It could have been handled by a telephone call from the company or the agency to the printer. In a few minutes the printer could knock off the offending type, without the need to produce new plates. The only difference is that the J.A.M.A. printer was not an expert. As a consequence, he also damaged the type for the word "Dosage."

a. The fact of the change is an obvious admission by the company that it had been wrong.

That is leaving out the contraindications entirely.

b. The cynicism of the company is disclosed by its willingness to continue the ad and merely change an error of commission to one of omission.

c. Since Section 502(n) of the Act requires a true statement of contraindications, they have not really removed the basis of our complaint. Further, the other errors, pointed to in our June 10 memo, still stand.

d. The act of the J.A.M.A., re: the June 29 issue, raises an important point. Its Council on Advertising could be perhaps excused, on the basis of ignorance, in accepting the June 8 ad copy. However, their agreement to delete the line, "Contraindications: None Known," makes it appear that the Council became a knowledgeable participant in an act of omission contrary to law.

This is FDA speaking. Now, I suppose somebody in JAMA might have an argument to respond to that. But again, they run an ad that is important. They run one in June—

Dr. ANNIS. Whose letter was that, Senator?

Senator NELSON. It was a memorandum from Robert S. McCleery, M.D., section on advertising and promotion, to Joseph F. Sadusk, Jr., M.D., Medical Director/BM.

Mr. HARRISON. Dr. Sadusk, I now believe is with Parke, Davis & Co.

Senator NELSON. Yes, he is.

Mr. HARRISON. I have some statements here with respect to the promotion, or lack of overpromotion, of Chloromycetin. The point I make is he has made some references here as to whether he believes—

Senator NELSON. Whom is he with now?

Mr. HARRISON. Parke, Davis.

Senator NELSON. And who manufactures Chloromycetin?

Mr. HARRISON. Parke, Davis.

All I am saying is there are some other statements here.

Dr. ANNIS. I hear proper action was taken, Senator.

Senator NELSON. Yes, but again I raise the point that an ad has been run in JAMA in which it tells all about Pree MT, and then it runs nothing on contraindications. Again, a doctor reads that and looks and says, great ad. I think I will use that because there are no contraindications.

Now, it seems to me—

Dr. ANNIS. Your point is that we should have the same kind of check that FDA has.

Senator NELSON. No, my point is, I don't know what you ought to have in advance. In your brochure that you submitted today, you say that you require evidence of efficacy and various other things.

Dr. ANNIS. And satisfaction of the requirements of FDA.

Senator NELSON. We have a case or so that I will show you where there was not any evidence at all. But let us stick with this one. This is a case where they were found guilty by the FDA. They left out contraindications. A doctor relying upon your ad may be prescribing this and no doubt is prescribing it, and he says, it is great, there is no contraindications, but there are.

It seems to me that there is a moral obligation on the part of the AMA when something like this is done to report that ad was incorrect. And here is what the FDA has done about it. I do not understand how you can shirk that responsibility.

Dr. ANNIS. Senator, we are not shirking any responsibility. But I recall one trip up here a few years ago when our mutual friend, Senator Smathers, returned at noon from the White House where, as a representative of the southern Senate group, he had had breakfast. I recall, too, that he came in and he said, "Ed, you think you guys have problems. I just came from the President's, and you think that a President of the United States has unlimited power."

And he said, "But during most of breakfast this morning he was talking that he will give an order and, by the time it goes down through various people, nobody knows who makes the changes along the way, but ultimately, it comes out—if it comes out—totally different from what was intended."

I think he used the illustration that it is like somebody standing on the end of the line and passing a handful of salt or sugar, one to another. When it gets to the end of the line, nobody knows how much was lost or by whom, but there is not as much there.

The fact that you can find errors occasionally, omissions occasionally, yes, nobody would deny that these things occur in medicine, in the AMA, in all publications, or in Government. What I am saying is that these are contrary to our basic intent, to our aims, to our procedures, to what we try to do in bringing to the American physician, as best we can, constant and continuing exposure to new drugs which are essential to the armamentarium of medicine.

By the same token, because the Government has taken over an important role, and in this the FDA has had strong support from the medical profession. They have taken over this role and have assumed responsibility not only for safety and purity, but also for efficacy. We feel that they have helped us immeasurably.

Now, within the confines of our organization, the manner in which we operate—I am satisfied that you can pick instances where we have failed to live up to that which we desire.

I would plead guilty of failing to reach that goal in many instances. But this is not a failure because of the lack of desire or because of an unwillingness on our part to direct our efforts toward these things. If it requires a change in our policies or our procedures, we will do so. This is my point.

Senator NELSON. The issue I am raising here is not that complicated a question as the President and unlimited power.

Dr. ANNIS. It makes no difference. I bet you give orders in your office sometimes and they do not quite come out the way you intended them to.

Senator NELSON. If it were a policy issue and it happened 10 times in my office, I would have a new employee.

Dr. ANNIS. You are impatient. I do not know that we would last that long.

Senator NELSON. Well, there are about 10 ads here; that is the reason I use the figure 10.

But I still get to the point of the obligation of the American Medical Association. You do not have a policy at all. It is not a question of giving an order as a President might on something and all of a sudden it goes through a lot of hands and is not executed the way he liked. It is something I know happens.

Dr. ANNIS. But we have a policy—

Senator NELSON. There is no policy as to this.

Mr. HARRISON. What you are saying, Senator, in summation, I guess, is that when it is found that an advertisement carried by the American Medical Association publications—

Senator NELSON. Or any other.

Mr. HARRISON (continuing). Or any other, but of course ours would only be with our own publications. When it has been found to contain information which the FDA subsequently feels inappropriate and, after negotiations with the company to issue a "Dear Doctor" letter, AMA should again, with full prominence, say, "look, there was one point here that should have been included," or "something was omitted."

Perhaps there is some merit in saying that we could be doing something beyond that which we are doing. But we should recognize that these letters, again, go out to all physicians, that they were a complete statement as such. Having just engaged a bit in some community

politics, on a very local level, I have come to know that sometimes you give more notoriety than it had when it was read the first time.

I am not quite sure, Senator, that it would be appropriate, in all instances certainly, to place in large prominence full-page ads with respect to some omission or some mistake that was made in the ad, as subsequently determined by the FDA.

However, you have a point there and I think we can review our present policy with respect to that point, and see if we should be doing something more.

But I wish the committee would keep in mind that we are speaking here of perhaps an omission which may be only one statement among a number of statements that were included.

Perhaps it took the FDA a couple of weeks to review that ad. The manufacturer may have been required to come in and discuss the problem, and then reach an agreement as to what should be done with respect to the way the ad was worded, and how it was in conflict with the statement made in the package insert.

And after all this is done, finally, it is agreed, perhaps in this one instance, that a "Dear Doctor" letter should go out to the physicians across the country—all of that. Then the question is, should the AMA in a large-page ad also say, "there is one other statement that should have been made here!" We cannot see that, but perhaps something should be done and, again, we shall take this under consideration, perhaps to improve our communication on this point.

Senator NELSON. Well, this is part of the whole context in which these hearings have been conducted, part of it, about the tremendous influence of the drug industry in promoting the sale of drugs. It seems to me that the AMA's journal is not an ordinary publication, and that when a false claim is made that can and will mislead the doctor to improperly prescribe for his patients, there is a moral obligation of JAMA to say right off the bat—and if every medical publication did that every time it happened, you will see some more honest advertising.

But if every time something like that happens, the publishers who receive the ads say nothing about it, why should they reform?

Mr. HARRISON. I think they are seriously hurt by these "Dear Doctor" letters, seriously hurt, because here is a communication that, in effect, again goes to every single physician and which states that they have done something in error and done something improperly. And I think this seriously affects them.

So I think there is a very pertinent and powerful restraining influence here.

Senator NELSON. You are saying after all this discussion that you do not think that the American Medical Association has an obligation to correct misleading advertising in its journal. Is that the conclusion?

Mr. HARRISON. We are not saying that at all, Senator. I think I have made the point that certainly we will look at this again, but the question is whether you use a sledgehammer here to kill a flea. We would have to look at the particular statement that was made, the context in which it was made, the advertising, and I would say to you that on the basis of what has been related here and more recently through the committee, we would have to evaluate again the procedures involved and perhaps effect some change.

But to just make a comment that the American Medical Association has failed to do something in this respect when these "Dear Doctor" letters go out to all the physicians and when we do not run the ads again when we are aware of their defects—I think this is the point that is unfair.

Senator NELSON. I shall be glad to see the FDA do these things, but I quite frankly say if the doctor read that ad and believed it and misprescribed to his patient on account of it, and the journal had not run a correction, the journal has defaulted in its moral responsibility. That is my opinion.

I would just like to spend a minute to find another example or two here.

Senator DOLE. While the chairman is looking, I might ask a few questions.

Senator NELSON. Yes, of course.

Senator DOLE. Does the journal ever make any reference to these "Dear Doctor" letters? Do you ever rerun the letter or anything of that kind?

Dr. ANNIS. I was just asking Dr. Hayes. I know I have seen them, either in the journal or the AMA News, but I do not know if they are run as a regular procedure. I have had my attention called to an AMA News article after I had received the letter, so that I know that it has occurred on occasion.

I know, for example, and Dr. Hayes feels the same way, that there was a reminder in the AMA News following the "Dear Doctor" letter, on chloramphenicol. Whether or not it is the regular procedure, this is one of the matters that we will look into and will take up with our Council on Drugs.

Senator DOLE. I think the record probably is clear on how many ads have been run in a period of time, total ads, and how many have been in the category suggested by the chairman. Do you have the figures on how many total ads you may run in a year and how many have been "false and misleading"? Is that information available?

Mr. HARRISON. How many false and misleading?

Senator DOLE. Out of the total? Is it 5 percent, 1 percent?

Mr. HARRISON. The Senator has indicated some 10 ads which have been subsequently found to require corrections through a "Dear Doctor" letter, appeared in the AMA Journal, I believe he said over a period of a year.

Senator NELSON. Twenty-nine over a period of 23 months.

Mr. HARRISON. Of which 10 were with AMA publications?

Senator NELSON. And others, but 10 of the 29 did appear in the AMA Journal.

Mr. HARRISON. So that would be 10 advertisements, and I can tell you the number of pages that we have. It is such an insignificant number—that we are talking about something like one-thousandth of 1 percent for just the journal itself, and we have 10 specialty journals. The journal is published once a week. That would be 52 issues during the course of the year.

In a period of 2 years, we would have more than 100 issues. There are approximately 100 pages of advertising, somewhere in that area, in each issue. I do not know where that takes us, but the percentage is obviously small.

Senator DOLE. As a matter of practice, do you screen ads that come to you?

Mr. HARRISON. Yes, we have a department which evaluates drug advertising and it does so in accordance with the principles included in our testimony.

Senator DOLE. Yes, I read the principles here.

Dr. ANNIS. The screening is there, but when it comes to such things as the drug content, the pharmacology, the chemistry, the efficacy, the safety, these are matters that the Food and Drug Administration is responsible for. Essentially, if they meet the FDA requirements and our requirements—advertising critical of others, or pricewise, saying we are better than someone else's, and all of the other things that are there, plus the keeping of medical ethics, they are acceptable.

That is what we screen basically for, but the basic contents, since the FDA has been given that authority by the Congress and has assumed the authority and are doing a good job with a difficult chore, we leave this matter to them, because we do not have the mechanism or the means to go into these details.

Admittedly, out of either their screen or our screen, occasionally there are errors.

Senator DOLE. The FDA has made errors, too, I assume.

Dr. ANNIS. Well, yes. Everybody has. A good example is thalidomide, a safe drug. You could buy it over the counter in Europe. The main reason it was so popular was that one could not commit suicide with it. One could take a barrel of it and it would not kill.

But looking back, for a young woman in her first 6 or 7 weeks of pregnancy, it created problems. Researchers could not find them in test after test on animals. They only found it in a certain species of rabbits. You have a drug that is safe. Old people take it, young people take it, it has minimum toxicity.

People take it for sleeping. If they take too many, it will not kill them. Think what a great thing this was. They could even buy it over the counter in Europe. It was never used in this country, not because of the drug effect on the unborn child, but because it had peripheral side effects—numbness in the fingers and toes, a sort of tingling.

But the research group, Richardson-Merrill, continued its research on it. Then we began to hear of the trouble they were having in Europe with this drug. Then, as a result of what happened, they saw the danger. From then, you could set a clear course.

Chloramphenicol has not been the same, but similar. It is a drug that has not been widely used, a drug with an admitted broad spectrum, a drug that came along with other drugs at a time when we were looking for something extraordinary. So in the minds of many physicians, older physicians, particularly, of 15 or 20 years ago, here was a great tool.

Now even its severest critics—and we are among those—admitted that its side effects are rare. But when they occur, they can be tragic. But a man could have used it for 15, 20 years without any trouble. So when he hears that other people have had trouble, he says, "I have had no trouble."

Then the FDA took it off the market. Then, for a while, he could not get his favorite broad-spectrum antibiotic. Now, it is back on the market. He can get it again. And in the mind of this fellow, not one

who has kept up with things, but one who had been getting good service from a drug over a number of years, he begins to use it again.

I suspect that a number of users of this drug will fall into that category, where they have never had any trouble with it and it is the same old deal. It has long been a human saying, and it is dangerous in drugs, I will admit, but the saying is "When you have something that works well for you, do not be the first to jump to the new."

I suspect—I cannot prove it, but I suspect this from physicians with whom I have had discussions in the last year and where I have zeroed in on this drug. But over the years, I have pointed out the many side effects that have occurred in rare instances.

Now, what has happened is that our recognition of it and the safeguards that Senator Nelson is referring to have not yet, at least in his mind, caught up to today's knowledge. It is different today. We are more secure, more certain.

Even the references he made this morning about the National Research Council—even these final pronouncements that apparently, for the first time, indicate that there is no indication left for chloramphenicol—that other drugs do as well or are better and safer—even this is only a result of today.

So we have several years where apparently, it was a pretty good drug with minimal side effects. Then we began to see some side effects. Then we began to see an increasing number of serious side effects—not often, but when they occurred, very serious indeed.

Now, the record begins to lay out.

So as we look back over those years, the Senator is amazed. Why did you not do something sooner? Well, of course, if we had known about thalidomide—they were not researching defects in children, but researching something else. That is the way research has been made.

Some of these are just as dangerous as flights in space. We are so proud of what we have accomplished, and it has been tremendous, it has been exhilarating as a nation. But we lost three men.

These are the hazards that come with progress, as we move forward. In retrospect, we now fix it so that we will not lose them that way again. But we lost three men.

The same is true here. Now, we can ask: should we not have recognized this earlier? Perhaps. Perhaps the safeguards we build in now will make it possible for use to recognize other and similar potential tragedies in the future, before they occur.

These are some of the very real problems that are the practical problems of medicine. You have a disease, you have a condition that is difficult to deal with. Somebody comes along and says, here is an answer. You begin to use it and you say, "gee, this is great," Then all of a sudden, you realize that the side effects that go with it can be very serious indeed.

We have a number of drugs which solve many problems, but they produce deafness, total deafness. One of my good friends, one of the outstanding otolaryngologists in this country, has a patient I met one day. This man is totally deaf from a drug, dihydrostreptomycin, given to him for something else. As we look back, we are adding to our knowledge, and as we keep people alive who used to die, we find that the same drug that saved life produced deafness or inability to see.

Aralen—a great drug in the control of malaria, was found by acci-

dent to help arthritis. It was prescribed for arthritis only to find that, though it is great for arthritis, if it is taken over a period of time, it begins to affect your ability to see.

This is the progress of medicine.

If you look backward, you can find many errors that we have made. But they are not errors that have come because of failure on the part of our researchers, our scientists, our drug manufacturers, to whom we owe so much, or the physicians who use the drugs. These are the human failures.

Admittedly, criticism highlights our appraisal of these facts. If, from a hearing of this kind, some of the criticisms can redirect our efforts toward a closer scurting, toward a more effective scrutiny, I can assure you that this will be one of the side effects, at least, that will make our appearance a justifiable one and a good investment of time.

Senator DOLE. Thank you, Mr. Chairman.

I have to go to another meeting.

Senator NELSON. I would just like to say, Doctor, though, on this question of acquiring new knowledge about a drug, the indications for using chloramphenicol, have been quite limited, according to the testimony before the committee.

Dr. ANNIS. According to our publications. We agree with you, Senator.

Senator NELSON. For 15 years.

Dr. ANNIS. Correct.

Senator NELSON. And then along has come tetracyclines, and that reduced again its indications. But they have been quite limited. And the point here is that the profession was not successful in that 15 years.

I am not going to go through all that again. But let me refer to something.

The committee has a stack of letters. This is the kind of thing that is so dramatic and so important.

Dr. ANNIS. Our medical literature will have a bigger pile than that, Senator.

Senator NELSON (reading). "Our eight-and-a-half-year-old daughter, Judy Dianne, was given intermittent doses of Chloromycetin from August 1964"—that is recent—"through February 1966 for reasons varying from minor ear infections, respiratory infections, and an abscessed tooth."

Now, we have lots of them like this. Here is one from a doctor saying that just recently, "A lady came into my office"—this is a doctor from Florida—no; I beg your pardon, these are attorneys. I guess there will be a lawsuit. "A lady came into my office stating that this drug had been prescribed for her only child for acne."

Here is one for a common cold.

When I raised the issue with Dr. Goddard and others who have been here, that since the failure to convince the profession has been so complete, why should we not do as Dr. Dameshek recommended, and several others—I would have to check the record to be sure that was his recommendation. This was a year ago. But I believe he was the one who recommended that the FDA simply require that the drug be prescribed only in a hospital.

Dr. ANNIS. I think that was Dr. Dameshek.

Senator NELSON. Subsequently we have had others say the same thing.

Well, Dr. Goddard said he was "at wits' end" about what to do about this problem. I have a high respect for him and I think I know what his problem was. Dr. Goddard said that restricting its use to hospitals would be an interference with the doctors' practice of medicine.

Do you think that would be interference in a doctor's practice, if you have a case of this kind, where little kids like this are dying and 4 million people are getting it, and we have been unable to persuade the doctors. This is a way to guarantee that in most instances it would call the doctor's attention to the fact that it should be used only in a hospital. Besides, in any good general hospital, you have some expertise on the drug there.

Do you agree or disagree that that would be a good proposal?

Dr. ANNIS. Again, Senator, you will recall, as I said before, I am not speaking as a user nor a defender of the drug. But I do know that there are many physicians in this country of ours who practice many miles away from a hospital. One of the real problems is to get physicians to practice in rural areas, in sparsely populated areas, in areas far removed from medical centers and often far removed from hospitals. I suppose that some, at least, of the rather consistent users of the drug fall into that category. If it becomes necessary, if the circumstances justify it, if there are no other drugs, if we fail in our education along other lines, then this, too, would have to be, as with anything, have to be considered.

I would suggest, however, that even in some of the testimony that has been presented before this committee, there have been indications that one need not have taken chloramphenicol over a long period of time if one is sensitive to it. One dose in itself can set up the mechanism that ultimately results in the depression of bone marrow production, aplastic anemia, and death.

I would also suggest—and I recite these not as arguments but as reasons for a continued dialog in this particular area—that one of my good friends in Miami had his wife take their little girl to the hospital and request a shot of penicillin for an infection a couple of years ago. She went into the hospital to the outpatient department and requested it. The physician who was in attendance agreed that it was all right, and Andrea, the little girl, was given her injection of penicillin. She was dead within a few minutes; they were unable to resuscitate her.

So the mere fact that a patient is brought to a hospital for treatment or as an outpatient does not necessarily protect him. The theory is, of course, that if they are in a hospital, they are under better care, you can watch their blood count, do other things. If, however, we are dealing with hypersensitivity for any one of a number of reasons, being in a hospital would not protect.

I think, ultimately, the point arises that it is not a question of the location at which the drug is given, it is a question of trying to educate our doctors wherever they practice as to hazards, as to new knowledge, as to the fact that whatever their experience has been in the past, there are other drugs today that can satisfy their needs much more safely. I still say that the answer to this, like most areas in the field of medical practice, where human beings are dealing with human beings, we should improve one's education to as great an extent as possible.

But not forget that a physician may be dealing with people where

they are often far removed from medical centers, far removed from the ability to get the tests and everything necessary, and where his practice or experience over the years with various diseases has led him to use drugs which, in his mind, have saved lives.

That is the other angle to this that must not be overlooked.

If we want to concentrate on the few with dangerous side effects, including those ending in fatalities, we must also, in fair appraisal of any drug, not just this one that we are talking about, take a look at in how many instances is the evidence there that it saved lives, prolonged lives, terminated illnesses quickly, protecting against further complications?

I do not know all these answers, but I do think so far, in reviewing the record of many distinguished physicians who have testified before your committee, and I share their concern about this drug, I am not yet convinced, nor are some of your other witnesses of equal prominence yet convinced, that confining or restricting the use of the drug to a hospital will solve the problem we all want solved.

I am not opposed to it, but neither am I a proponent of it. I would want to hear more from others in circumstances where its use is dictated by conditions beyond those to which I personally have been exposed.

Senator NELSON. But here you have a case in which it is really catastrophic, if Dr. Dameshek and the rest are correct, that this drug is being widely misprescribed and that we have deaths like this. Now, I assume that the person who got the penicillin in a hospital got the penicillin for an indicated case.

Dr. ANNIS. I would hope so.

Senator NELSON. But here is a case where 90 percent, if it is 90 percent, are getting it for nonindicated cases, and the fact that you require it to be administered in a hospital immediately reduces that percentage.

Presumably there is somebody there who asks if this disease is serious enough for this and is there another drug that will do the job?

Also, is the organism susceptible to chloramphenicol? You would save quite a few lives that way.

I believe it was Dr. Dameshek and some of the others, too, who advocated this and said, if they are sick enough to have chloramphenicol, they ought to be in a hospital. But it seems to me that Dr. Goddard's answer that it interferes with the practice of medicine is hardly a justification in a case where the medicine is being practiced incorrectly.

Dr. ANNIS. I think Dr. Dameshek's exposure has been in a great medical hospital where we have up-to-date tools and many qualified people around. He works in a totally different environment than those to which I have reference, and I suspect to which Dr. Goddard has reference. But I did indicate, indirectly perhaps, that even the use of chloramphenicol in a hospital would not protect that person, wherein one exposure is adequate to set off the very dangerous and ultimately destructive mechanism. Again, I am merely quoting some of the testimony before this committee that it does not have to be prolonged administration in a certain percentage of people for one reason or another. A very small amount of the drug, just like a small amount of tetanus toxin—antitoxin, I should say—can be sufficient to result in a fatality. This is merely an area where I do not believe that we

have had sufficient discussion or have had an opportunity to hear from all parts of the profession as to the limitation of any therapeutic agent just to a hospital.

In my earlier years of practice, I did a little of what they used to call barehanded practice when I was in Wisconsin. I was out in the country many times. I have seen patients where, if it were a necessity to send them to a hospital, they would rather stay home and die.

I do not know, maybe people have changed since that time. However, I am not quite sure. I know of instances in the past couple of years, at least of two people who have died following automobile accidents in Miami because the family, the patient who was dying and the family, refused to allow the physicians to give blood transfusions, where there was massive hemorrhage as a result of the accident. It was impossible to treat the patient without blood, and there was refusal.

In one instance, the mother of two children died.

There are these tragedies. We can go on through tragedy after tragedy for the want of proper medication.

In another case, the giving of a drug under ideal circumstances results in fatality.

In a third, ignorance and unwillingness to allow modern trained physicians to use a therapeutic agent that could be life saving, results in a fatality.

All of these are merely examples of the constant problems that face physicians. But many of them face physicians who are far removed from a hospital or medical center. And there I would not attempt to come to a conclusion. I would be reluctant and hesitant to tie the hands of any physician with a therapeutic agent that might, under some circumstances, be the difference between his offering his patient an opportunity to survive a serious or perhaps fatal illness, or depriving him of any such treatment by virtue of there being no other tool available at that time in that situation, and the inability to get into a hospital.

I do not know, and I gather from other testimony that others are not yet persuaded, including Dr. Goddard.

Senator NELSON. But the National Academy of Sciences has indicated these drugs are for very limited cases, that, in fact, it should not be used until no other drug would work, and since we have tetracyclines and other drugs—the doctor would then try those first. If you compare what is happening all over this country with the widespread misuse of this drug compared with the limited number of rare cases for which it is indicated—well, the doctor would say “I cannot use chloramphenicol in this case for acne or hang-nail or sore throat or a nonspecific high fever.” He would say “I shall try out one of the other antibiotics” and I submit you would avoid this kind of tragedy. Then after a year or 2, I believe you would find the drug would be limited to the uses for which it is indicated—which is very small, according to all the experts we have heard.

Dr. ANNIS. I think the record is becoming increasingly clear, Senator. I do believe that as a result of the testimony of very distinguished people before your committee, you have enhanced the effort of the American Medical Association to spread this message.

I have indicated earlier that we intend to expand it, that our Council on Drugs has already indicated its willingness to meet with Dr. Ley and to cooperate and work with him in its behalf.

As Mr. Harrison indicated, Dr. Ley has agreed to an interview with AMA News, for the specific purpose of a full disclosure of the most up-to-date information on chloramphenicol and its side effects. All this has already been done in the sense of establishing the rapport, the agreement for cooperation.

The only reason that it has not been done as the moment is because of the many responsibilities on the shoulders of Dr. Ley. He has made a couple of appointments to meet which have had to be postponed. I anticipate that much of the desired effects indicated by the Senator today will be accomplished, and the message will be gotten through various channels to more and more physicians.

In so doing, perhaps we shall get it down to the rare usage of this or any other drug. Their use will be limited to occasions when all indications are that it and only it is the weapon of choice against the invader of infection.

Senator NELSON. Thank you, Doctor. As I said earlier, I had not expected that I would cover as small an amount of the material I wanted to explore, and I made some other commitments. I think probably it would be helpful if I jotted a note on some of the other areas that I would like to have you comment on whenever we can arrange a future date that is agreeable with you.

I think 4 hours—more than 4 hours—is enough time for 1 day, anyway. So if it is all right with you, I shall not pursue any of the other questions I have, and we will work out some future date that is convenient to both of us.

Dr. ANNIS. Fine. If you will indicate the areas, Senator, as we have attempted to do in this presentation today. I do hope that you will have an opportunity to review some of the exhibits and the other material that we have. I do want to leave with you one we are very proud of. As I indicated, with a little prompting, I do not know for how many years, but for 14 years, we have had these continuing educational courses for physicians.

In all of these, we are dealing with these and similar problems. But these reflect, and I will see that it is given to the Senator, the continuing effort of the medical profession. We want to cooperate in every way possible to inform you and your committee as to what we are doing, what we are trying to do, our willingness to cooperate, as Dr. Ley well knows, with the Food and Drug Administration.

If there are particular areas which were not covered in the presentation, we will be very happy to provide answers.

Senator NELSON. I have a number and I will jot them down in a letter to you.

I want to thank you very much. I read all the exhibits and all your testimony this weekend. I always try to read in advance, so your effort at least was not wasted on me.

Thank you very much for coming here today. We appreciate your taking time to do so. I realize it is an imposition on you with your busy practice, but it is a valuable contribution to the record.

Thank you.

Dr. ANNIS. Thank you, Senator.

Senator NELSON. The committee is recessed until next Tuesday, March 25, at 10 a.m.

(Whereupon, at 4 p.m. the hearing was recessed, to reconvene on Tuesday, March 25, 1969, at 10 a.m.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

TUESDAY, MARCH 25, 1969

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

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

Present: Senator Nelson.

Also present: Chester H. Smith, staff director and general counsel; Benjamin Gordon, staff economist; and Elaine C. Dye, clerical assistant.

Senator NELSON. Our witness this morning is Dr. Marvin Pollard, who is president of the American College of Physicians.

Dr. Pollard, we are very pleased to have you appear with us this morning. We appreciate your taking time from your busy schedule to come here and testify.

Did you submit some biographical data?

Dr. POLLARD. Yes, before.

Senator NELSON. The biographical data will be printed in the record prior to your statement. Your statement will be printed in the record in full.

You may proceed to present the statement in any fashion you desire. And if you wish to depart from it at any time to elaborate on anything you have said in your statement, feel free to do so. And I assume if we have some questions as we go along you don't object to being interrupted?

Dr. POLLARD. Not at all.

Senator NELSON. Go ahead.

(The biographical sketches follow:)

BIOGRAPHICAL SKETCH OF H. MARVIN POLLARD, M.D.

ACP PRESIDENT HEADS VAST TASK OF KEEPING INTERNIST INFORMED

PHILADELPHIA, PA.—How to help the internist remain stimulated and keep fully informed of the continuing changes in medical knowledge and practice is the job facing the American College of Physicians (ACP), its new president maintains.

H. Marvin Pollard, M.D., Ann Arbor, Mich., who has taken the lead in many new continuing education programs in the specialty field of internal medicine, was installed as President of the College in April and will serve until the College's 50th Annual Session in Chicago, April 20-25, 1969.

As President, Dr. Pollard will be taking an official part in a major, 35-year-old program for continuing education of internists—the annual ACP regional meetings at which leading research investigators, including internists, present scientific papers on clinical studies. Dr. Pollard will attend some of these meetings as both scientific participant and ACP official.

"The internist must realize his great responsibility in keeping himself thoroughly informed with medical progress," Dr. Pollard believes. "He must cope with the enormous amount of research information pouring out of the various institutions, as well as with the problems brought about by government-sponsored programs such as the Regional Medical Programs, Medicare and Medicaid, in addition to his concern over family practice and community health."

Dr. Pollard is Professor of Internal Medicine at the University of Michigan Medical School and Head of the Section of Gastroenterology at the University's Medical Center.

During the past decade, the 61-year-old internist has served five years as Chairman of the subspecialty Board of Gastroenterology; served as Secretary-General of a World Congress of Gastroenterology, and spent two years as chairman of the senior staff at the Medical Center's University Hospital.

Dr. Pollard helped organize the first postgraduate course sponsored by the ACP in South America a few years ago. In 1963 he was made chairman of the ACP International Medical Activities Committee, which has organized and presented five subsequent courses in various cities of South America. These courses are designed for the young teachers in medical schools as well as for practicing internists.

In this country, Dr. Pollard and his Section on Gastroenterology at the University of Michigan Medical Center have organized and held three postgraduate courses for the ACP on gastroenterology. These courses have been part of the ACP's on-going program of continuing education for internists, a program which provides 20 concentrated, formal postgraduate courses on different subjects during each academic year. The courses are held at medical centers throughout the country.

Dr. Pollard has been "a Michigan man" since the start of his medical career, having received his medical degree from the University of Michigan Medical School in 1931. A native of Lamar, Colo. (born, Dec. 7, 1906), he attended school there and took his premedical course at the University of Colorado.

Dr. Pollard rose through the medical school ranks to become professor of internal medicine, his present academic title, in 1951. He is certified to practice internal medicine by the American Board of Internal Medicine and to practice his subspecialty by the American Board of Gastroenterology.

Among organizations in which he holds memberships are the American Gastroenterological Association, the American Endoscopic Society, the American Federation for Clinical Research, the American Medical Association as well as its local and state medical societies, the American Association for Cancer Research, the American Association for the Study of Liver Diseases, the Central Society for Clinical Research and the Central Clinical Research Club.

He has published more than 100 articles on various subjects in internal medicine with special emphasis on gastroenterology.

Dr. Pollard is a Director-at-large (1966-68) of the American Cancer Society and Treasurer (since 1962) of the World Organization of Gastroenterology. Among offices he has held are President (1951-52) of the Washtenaw County Medical Society and President (1959-60) of the American Gastroenterological Association. He has also served the ACP as Governor for six years and as Regent for six years.

BIOGRAPHICAL SKETCH OF EDWARD C. ROSENOW, JR., M.D.

COLLEGE EXECUTIVE DIRECTOR KEEPS IN TOUCH WITH CLINICAL MEDICINE

PHILADELPHIA, PA.—The Executive Director of the American College of Physicians (ACP) is one of a special breed of administrative physicians—the M.D. executive who likes to keep in touch with clinical medicine.

Edward C. Rosenow, Jr., M.D., who practiced internal medicine for 17 years before becoming the ACP's Executive Director in 1960, holds the title of Adjunct Clinical Professor of Medicine at the University of Pennsylvania. Among projects by which he keeps in touch with the practice of medicine are teaching assignments on the University of Pennsylvania's services at Philadelphia General Hospital and Pennsylvania Hospital.

He serves his specialty also as a member of the Joint Commission on Accreditation of Hospitals, the AMA Residency Review Committee in Internal Medicine and as secretary of the Council of Medical Specialty Societies, all of which are involved in improving standards of medical practice. Dr. Rosenow is also on

the advisory committee for CARE-MEDICO, the international organization of medical services.

Playing such an active role in the many facets of his specialty has been a habit with the 58-year-old executive director since his graduation from Carleton College, Northfield, Minn. in 1931. He received his medical degree from Harvard Medical College in 1935 and went on to the Mayo Clinic where, from 1936-40, he fulfilled his residency requirements in internal medicine. His father, the late Edward Carl Rosenow, Sr., M.D., was a distinguished physician-bacteriologist on the original staff of the Clinic.

While at Mayo, Dr. Rosenow received a Master of Science in Medicine degree in 1939 from the University of Minnesota (Mayo Foundation). His formal education completed, Dr. Rosenow moved to Pasadena, Calif. in 1940 to begin his nearly two decades of private practice. During this time, he undertook many activities that provided excellent background for his position as Executive Director of the College.

He taught at the University of Southern California School of Medicine from 1940 to 1959, attaining the position of Clinical Professor of Medicine. He was also appointed to the same post at the University of California at Los Angeles and at the College of Medical Evangelists, both in 1958-59.

From 1951 to 1959, Dr. Rosenow was chairman of the Postgraduate Activities Committee of the California Medical Association and became Editor-in-Chief of *Audio Digest*, non-profit subsidiary of the association, in 1954.

In 1957, Dr. Rosenow retired from active practice to become Executive Director of the Los Angeles County Medical Association, a position he held until moving to the American College of Physicians.

Thus, Dr. Rosenow came to the ACP equipped with a well-rounded career of private practice, medical school teaching and medical society administration. In addition, he became acquainted with research medicine as President, from 1955 to 1959, of the Charles Cook Hastings Home in Pasadena, Calif., an institution for tuberculosis research.

Among other organizational offices he has held are presidencies of the Los Angeles County Medical Association, the Los Angeles Society of Internal Medicine, the Los Angeles County Heart Association, the Huntington Memorial Hospital Staff, Pasadena, Calif., the Alumni Association of the Mayo Graduate School, the American Medical Writers' Association and the Association of Medical and Allied Publications.

Currently, he serves as President of the Carleton College Alumni Association and of the Commission on Professional and Hospital Activities.

Dr. Rosenow is a Fellow of both the American College of Physicians and the College of Physicians of Philadelphia; a Diplomate of the American Board of Internal Medicine, and a member of the American Association of Medical Society Executives and the Professional Convention Management Association. He belongs to the Philadelphia County, Pennsylvania State and American Medical Associations.

His honorary memberships include the American Society of Internal Medicine, the Los Angeles County Medical Association, the American College of Chest Physicians, the Los Angeles Society of Internal Medicine and the American College of Gastroenterology.

Among honors and awards are an honorary degree of Doctor of Science granted in 1967 by Carleton College; the Distinguished Alumnus Award of the University of Minnesota, given in 1965 and the 15th Peter Bohan Lectureship of the University of Kansas School of Medicine, delivered to the 1966 graduating class.

He has written papers on blood groups in China, published in the *National Medical Journal of China*; "Extreme Cardiac Hypertrophy," published in *Minnesota Medicine*, "Calicification of Renal Pappillae," published in the *Journal of Urology* and "Septicemia," published in the *Proceedings of the Staff of Mayo Clinic*.

Dr. Rosenow, who resides in Philadelphia, is married and has two children. He is a member of St. Christopher's Episcopal Church in Gladwyn, Pa., the Merion Golf Club, the Racquet Club and the Faculty Club of the University of Pennsylvania.

STATEMENT OF DR. H. MARVIN POLLARD, PRESIDENT, AMERICAN COLLEGE OF PHYSICIANS; ACCOMPANIED BY DR. EDWARD C. ROSENOW, JR., EXECUTIVE DIRECTOR

Dr. POLLARD. I think to open with I will read this prepared statement word by word, and then we will proceed from there if there are any questions.

My name is Dr. H. Marvin Pollard, and I am the president of the American College of Physicians. I am also a professor of medicine at the University of Michigan School of Medicine. With me is Dr. Edward C. Rosenow, Jr., the executive director of the American College of Physicians. He holds a faculty appointment at the University of Pennsylvania School of Medicine as a clinical professor of medicine. The comments I wish to make are my own.

STATEMENT OF FACTS

The American College of Physicians is a corporation organized under the State laws of Delaware in 1915 for educational and scientific purposes and except under section 501(c)(3) of the Internal Revenue Code. The college has, at the present time, approximately 15,000 members throughout the United States and Canada, with a few members located in Mexico and the Central American countries. All of the members are specialists in internal medicine and allied specialties. The headquarters office is in Philadelphia, Pa.

The object of the college, as stated in its constitution, is to maintain an organization of qualified in the field is to maintain an organization of qualified physicians in the field of internal medicine and its allied specialties for the following purposes:

1. Maintaining and advancing the highest possible standards in medical education, medical practice, and research.
2. Preserving the history of perpetuating the best traditions of medicine and medical ethics.
3. Maintaining both the dignity of internal medicine and the efficiency of its function in relation to public welfare.

All of the educational activities of the college are open to nonmember physicians as well as members and all of the financial aid programs such as scholarships, fellowships, and residency loans are available only to nonmember. The ultimate beneficiary of all of these programs is the general public.

In order to carry out these functions, the college conducts numerous seminars and postgraduate courses. These are presented throughout the year and are held at various locations in the United States and Canada. There are numerous regional meetings during the year, conducted for the benefit of the college members and nonmember physicians. Once each year a large national scientific meeting is held, which lasts for 5 days, with four large scientific sessions going on simultaneously. The meeting last year, in Boston, in April of 1968, attracted 3,159 college members and 2,073 nonmember physicians.

The college publishes a monthly medical journal, called the *Annals of Internal Medicine* which contains scientific articles and reports of new developments of importance to its readers. This outstanding medical journal is distributed all over the United States and, in fact, all

over the world. In addition to college members, the journal is mailed to over 32,000 nonmember physicians, students, hospitals, and medical libraries.

Included in the journal are advertisements for pharmaceuticals, medical equipment, and medical textbooks. All advertisements are carefully screened by a special committee to insure that they are confined to products related to the care of patients by specialists in internal medicine or in allied specialties.

Senator NELSON. May I interrupt a moment.

Dr. POLLARD. Yes.

Senator NELSON. Do you have some established principle that the ad must conform to?

Dr. ROSENOW. Yes; Senator. You have there this folder that is in blue. That is the policy statement and the code for advertising that we use for our advertising. The committee consists of four members, physicians, who screen each ad that comes along. We establish general policies as to how they should be done. And briefly, that is our primary concern at the present time. It is somewhat easier than it used to be because of the requirement of Food and Drug that you have to put in the information that is in the informational leaflet. But our job is to see that the ad does not exceed the claims in this product information brochure. And also that it refers to internal medicine or the allied medical specialties. We don't take anything that does not relate to our specialty.

Senator NELSON. Thank you.

Dr. POLLARD. In a recently released report by the Government Task Force on Prescription Drugs it was pointed out that physicians rely to a considerable extent upon advertising by the pharmaceutical manufacturers for their knowledge of drugs. The advertising carried in the Annals of Internal Medicine compliments the other educational activities of the college. Attached hereto is a copy of the December 1968 issue of the Annals of Internal Medicine, to be made a part of this report, as exhibit A.¹

I think you have a copy there before you.

Mr. GORDON. May I ask you a question at this point?

Dr. POLLARD. Yes.

Mr. GORDON. Do you have any idea how many ads you rejected in the last couple of years?

Dr. ROSENOW. I could get accurate information as to that. I would say many less than we did 4 or 5 years ago before the new regulations came along, because at the present time the ads are a little bit more stereotyped. But I know now that we have turned down at least several. One that I can remember is one of the penicillin agents in which the statement was made that this should be the doctor's first thought in infection. Our committee felt that it should be about the second thought in an infection. The first thought should be to prove the infection was due to an organism that would be susceptible to this agent, and we wanted them to put it this way. And at that time they decided that they would not do it. So we did not run the ad for a couple of years. As a matter of fact, this company canceled all of its penicillin advertising in the annals for several weeks. And I think they felt that this would make us feel pretty bad. And it did

¹ Exhibit A has been retained in committee files.

not. And I notice that just recently they have submitted copy which includes our recommendations. This is one that I can remember.

Senator NELSON. What company was that?

Dr. ROSENOW. I would have to rely on my memory for this, but I can furnish this for you. I really would prefer to go and look it up and submit it to you.

Senator NELSON. Would you submit it for the record?

Dr. ROSENOW. Yes. And I would be glad, if you would like, to give you information about any other ads that we have refused.¹

Senator NELSON. Thank you.

Dr. POLLARD. There are other activities of the college worthy of note, all intended to make physicians better able to administer to the health requirements of the public. Teaching and research scholarships are granted for a period of 3 years. The 1969 budget contains \$116,500 for this purpose. A residency loan fund of over \$200,000 is used to assist young physicians to pursue graduate training in accredited institutions. Annual appropriations are made to the Joint Commission on Accreditation of Hospitals, by the American College of Physicians in cooperation with other national medical associations, to underwrite the administrative costs of this organization which seeks to assure the general public of receiving highest quality medical care when hospital confinement is necessary. The appropriation for 1969 is \$43,253.

An innovation in medical education was started by the college 2 years ago. The medical knowledge self-assessment program is a very comprehensive examination of approximately 700 questions covering the entire field of internal medicine. The physician, on a purely voluntary basis, answers the questions, then takes the correct answers out of a sealed envelope and marks his own answers. The confidential nature of the assessment encouraged 11,000 physicians, both members and nonmembers, to participate.

Senator NELSON. May I ask a question there?

Dr. POLLARD. Yes.

Senator NELSON. How many members did you say are affiliated with the American college?

Dr. ROSENOW. Just under 15,000.

Senator NELSON. And how many of your own members took the self-assessment examination?

Dr. ROSENOW. 6,375.

Senator, I might qualify this a little bit by stating this, that we have about 4,000 of our members who are in allied medical specialties who might not take this examination. For example, dermatologists, neurologists, psychiatrists, radiologists, and pathologists belong to our college and are a part of the total number, so they would not be expected to. I think the 6,375 realistically represents a little more than 60 percent of the ones who would benefit by taking this one.

Senator NELSON. I notice that a couple of clinics with which I am familiar require their physicians to take the self-assessment exam. Is this a widespread practice?

Dr. POLLARD. I will answer that. I think that it will be increasingly widespread. As I go on in this description here you will find that it is being adopted not only in this country but in areas overseas. So I

¹ See information beginning at p. 4734, *infra*.

am sure that it will be utilized. It is utilized in many ways in this country by the young individuals preparing for examinations, and by older individuals who want to reassess their own knowledge. And I would not be at all surprised but what on an individual basis clinics may well require it.

Senator NELSON. Thank you.

Dr. POLLARD. This idea has since been adopted by several other national medical organizations and the American College of Physicians' medical knowledge self-assessment program is now being translated into the German language for the use of the German medical community. We were recently informed that the program is being used in South Africa, in their education program.

Dr. ROSENOW. May I interrupt here, please. On this test translated into German—and this is very appropriate to the hearing that you are having. As you know, many foreign countries depend even more for their educational efforts in medicine on pharmaceutical companies. I am not absolutely sure that we are going to go through with this, because I have not yet gotten from the German colleagues that want to do this conformance to what our agreement with them was. One of the agreements that we made was that they would have to distribute this exactly as we printed it originally. And what they want to do with it is send it out in serial form, cooperating with a drug company that wants to put some ads in it. And we have refused to do this. So we may not do it, because we do not want to get mixed up in a kind of gimmick for selling drugs.

Senator NELSON. Thank you.

Dr. POLLARD. There are other programs that the college uses to fulfill its purpose. Unlike many educational organizations, it makes no public appeal for gifts, neither does it receive support from the Government. The principal sources of funds are dues, subscriptions and advertising from the Journal, exhibits at the annual scientific session and income from investments.

Senator NELSON. May I interrupt? Doesn't the breakdown, I think it is your exhibit B, show the specific sources, that is, how much of the income is from journals, exhibits, investments? Do you have that figure?

Dr. ROSENOW. Yes, Senator, I can give it to you in more detail later if you like. At the present time—let us take 1968. When you first told us what you wanted, you wanted the breakdown between advertising revenue. And we have given you this. But in addition to the breakdown in the other total revenue, other than the Journal, the largest amount is \$370,438 in dues, \$33,000 in initiation fees. We have a total of about \$160,000 of income from our endowment investment. And we have \$187,000 of income from postgraduate tuition fees. This is almost—they go right out on the other end as expenses, so we do not really make anything on this. The medical knowledge self-assessment program, when we originally handled it we estimated a deficit of \$90,000 and now we—I hate to use the word profit—but an excess over expenses of about \$50,000.

Exhibit income is \$121,000. Guest fees are \$22,000.

This, however, I must also tell you, is not an even balance, but on our annual session we go in the hole about \$48,000 over this income.

Senator NELSON. The income from what kind of exhibits?

Dr. ROSENOW. This is for what we call our technical exhibits, which is the place where the pharmaceutical companies, the instrument people like electrocardiogram machinemakers, and other diagnostic things that are used in our profession, and book publishers.

Dr. POLLARD. Textbooks.

Dr. ROSENOW. There are about 200 exhibits at our annual session.

Senator NELSON. And these are the only exhibits? Do you have regional sessions?

Dr. ROSENOW. We have regional meetings but not regional exhibits.

Senator NELSON. And what amount of the exhibits is income from pharmaceutical manufacturers exhibits?

Dr. ROSENOW. Versus the others?

Senator NELSON. You gave a total on the exhibits. What amount was pharmaceutical?

Dr. ROSENOW. I would have to go back and actually count that up. But I would imagine it is about two-thirds.

Senator NELSON. Would you submit that for the record, also?

Dr. ROSENOW. Yes, sir.

Senator NELSON. And on the income from advertising, as I understand the testimony of Dr. Pollard, it is advertising from—

Dr. ROSENOW. Internal medicine advertising.

Senator NELSON. From pharmaceuticals, books, scientific instruments. What amount of the subscription revenue is pharmaceutical advertising?

Dr. ROSENOW. I would have to look this up. I can submit this to you.¹ I would suppose it is about the same.

Senator NELSON. Two-thirds?

Dr. ROSENOW. I would think so.

Senator NELSON. You used the figure subscription revenue on exhibit B, subscription revenue net of commission. What do you mean by that?

Dr. ROSENOW. Excuse me, I did not get it.

Senator NELSON. In exhibit B you used the figures subscription revenue net of commission, and then you have advertising revenue.

Dr. ROSENOW. Right. I would suppose that more than half of our subscriptions for the Journal which come from nonmembers comes through an agency that takes up subscriptions. This is quite common in medical publications, that a man puts all of his medical journal subscriptions through one agency. And I believe the discount there is 15 percent.

In the advertising revenue the same thing. Very few of the pharmaceutical companies, for examples, put their ads in with us direct, but go through an agency. And this is what that is called. And the discount is 2 or 3 percent if they pay by the end of a certain period of time.

Senator NELSON. So what you are referring to, then, is the advertising revenue received by the publication after payment of the fee, 15 percent of whatever it may be to the advertising agency that places the ad?

Dr. ROSENOW. That is right. It is money that we can use.

Senator NELSON. I have one more question. What kind of investment? Do you have any pharmaceutical investments?

¹ See p. 4734, *infra*.

Dr. ROSENOW. We do not restrict—we do not ordinarily take pharmaceutical ads, investments, but we do not say that we cannot. I would say at the moment that we do not have any, but I am not absolutely sure. We had Smith Kline & French a few years ago, but we do not have that any more. We do not have a policy against it. This is run by an investment company we work with, Drexel, Harriman & Ripley Investment Counselors. We are a little bit touchy about tobacco investments; we do not take those. But we have no firm rule against it. So that essentially I would say that we would have to be a little extra persuaded that a pharmaceutical company was a good investment for our college.

Senator NELSON. If you have an investment in pharmaceuticals now, would you notify the committee as to what they are?

Dr. ROSENOW. Yes.

Dr. POLLARD. I believe it is true that there are none in pharmaceutical houses at the present time.

Senator NELSON. Thank you.

Dr. ROSENOW. You asked the total amount of our investment account.

Senator NELSON. Yes.

Dr. ROSENOW. I would also have to furnish this. But I think at its mark value it is somewhere around \$3 or \$3½ million.

Senator NELSON. Please go ahead.

Dr. POLLARD. Because of increased activities, additional office space is required. We are in the planning stages of plant expansion which could cost up to \$1 million. The funds to pay for this addition must come from the sources mentioned above.

A committee on diagnostic and therapeutic agents has been appointed recently under the chairmanship of Dr. Carter Smith, of Atlanta, Ga. They plan a continuing study of all aspects of these agents. Although no specific policy statements have been developed on some of the matters of concern to your committee, such policy statements will be forthcoming from time to time. However, the following general comments I believe fairly represent what would reflect the attitudes of a majority of our members:

COMPENDIUM

Physicians must have accurate, up-to-date information about drugs. A number of methods are helpful in this regard. Physicians' Desk Reference is a convenient source of information about the drugs included, but is incomplete. The objection raised that there is no editorial review of what goes into PDR has been corrected by requiring that the FDA-approved package insert information be included.

Senator NELSON. The FDA doesn't require the PDR to print the whole package insert. I think it requires that it conform to it, however.

Dr. ROSENOW. That is right. But PDR has adopted, I believe, that they put in the product insert as their writeup.

Senator NELSON. In toto?

Dr. ROSENOW. I believe so.

Senator NELSON. I did not realize that.

Dr. POLLARD. That is essentially what the PDR is.

Senator NELSON. From some that I have looked at in the past, it was

my impression that they were condensations of the package insert or that the requirement was that they conform and not conflict.

Dr. ROSENOW. I am not absolutely sure of that, either. I have been told that the PDR editors themselves are requiring this.

Senator NELSON. The committee counsel reminds me that there have been recent corrective "Dear Doctor" letters based on the advertising in the PDR which did not conform to FDA regulations in the last 2 years.

Dr. ROSENOW. I believe that is correct. I think my information on this is that it is only very recently that they are doing this.

Dr. POLLARD. I have the impression it was in the last 2 years.

Senator NELSON. We will check it. Please go ahead.

Dr. POLLARD. The AMA's Council on Drugs has announced a new publication, "AMA Drug Evaluation." When available, this should be a very useful reference book. We are impressed by the preliminary chapters which have been circulated.

Probably the most useful source of information is the advice and counsel of a physician's colleagues. Very few physicians prescribe a new drug for the first time without discussion with colleagues or having read about it in a first-class journal article, or having heard about it at a medical meeting.

Direct-mail advertising, journal advertising, exhibits at medical meetings, and the work of detail men are all important sources of information. It must be recognized, however, that the latter, though giving the doctor accurate information, are primarily directed to selling products. We believe our physicians accept advertising for what it is in our free enterprise system and judge it accordingly.

We would have no objection to a compendium, and certainly would approve the inclusion of generic and trade names. Probably the inclusion of the chemical name should also be included. We are not convinced that inclusion of prices would necessarily reduce the cost of drugs to the consumer.

Senator NELSON. Why do you think that?

Dr. POLLARD. I think largely because the actual pricing is out of the hands of these people—because the actual pricing is out of the hands of anything that is listed in the book.

Senator NELSON. I do not follow that.

Dr. POLLARD. It is not the responsibility of the book to dictate the final selling price.

Senator NELSON. But might it not make a difference if the price were stated, in other words, if the doctor had a choice between several companies, and the drug of one of them was a fraction of the price of the other, might that not affect the price to the consumer?

Dr. POLLARD. I can see where that should influence it, or it could influence it.

GENERAL PRESCRIBING

In general, our view would be that each physician should use his own judgment about how he prescribes a drug. It has never been shown that generic prescribing necessarily insures comparable quality or a lower price. The experience with chloramphenicol and Chloromycetin is an example much cited. A study in Chicago by the AMA indicated no relationship existed between prices of drugs ordered generically even in the same drugstore chain.

Senator NELSON. May I interrupt a moment, Doctor? If the brand name is the only drug that the drugstore has stocked, because that is the name the doctor is prescribing most frequently, then when the pharmacist receives a prescription using the generic name, he can substitute any brand name he wishes. Therefore, in the AMA study, the patients probably got the same drugs, whether they were prescribed by the brand or generic name. And many drugs that are cheaper may not be stocked at all simply because the doctor is prescribing them by brand name, and under the law in some 40-odd States a pharmacist cannot substitute another brand or another generic name. So the test that was used by the AMA in my judgment was not a fair test of the issue. The fact that the drug was ordered by generic name didn't mean that it was supplied on that basis.

Dr. POLLARD. I have not any great comment on that.

Senator NELSON. I might add that a year ago the Peoples Drug Stores and the Gray's Drug Chain, one out in Ohio and the other here, announced that they were going to stock a line of generic drugs manufactured by Strong, Cobb & Arner, and that in their public statements the price of the generic would average one-half of the brand name, which I think is a pretty convincing case to demonstrate that you could get a lower price from the generic. And Strong, Cobb & Arner, of course, is a very distinguished generic manufacturer.

Dr. POLLARD. Well, I am impressed with that statement.

Senator NELSON. Please continue.

Dr. POLLARD. We are told by pharmacologists that equivalency is sometimes variable merely by the physical methods of drug preparations. In some hospitals, where it is possible to have a committee of physicians review all drugs, purchasing drugs by generic titles can save considerable sums of money. Physicians sometimes prefer to order certain drugs by trade name merely because they can identify the various pills they have prescribed for a patient who might call by telephone to ask question about his medication. Most physicians really believe they can be more confident their patients will get reliable, consistently potent drugs if they prescribe products made by firms in which they have confidence.

Senator NELSON. Why do doctors believe that?

Dr. POLLARD. I think in most instances they believe it because of past experience.

Senator NELSON. What experience could they have had that would indicate otherwise? Most of them prescribe brand names anyway. How would they get the experience? Wouldn't the experience be testimonial?

Dr. POLLARD. Sometimes when a drug house comes out with a drug product in the beginning they look upon that as being a dependable drug, as with any new product that comes on the market. And I am afraid that they then get into the habit of prescribing that drug because they have learned how to use it and depend upon it.

Senator NELSON. But your statement is that physicians believe that they can be more confident that their patients will get reliable, consistently potent drugs if they prescribe products made by firms in which they have confidence. I do not quarrel with your statement. I think that is probably what they do believe. But my question is, What scientific foundation is that belief based on?

Dr. POLLARD. It is just based on their past experience.

Senator NELSON. The one large test that we have had that I am aware of in the last 2 years was the FDA report on 4,600 drugs released October 15, 1966, from 250 manufacturers in which 2,600 were generic drugs that they had tested and 2,000 were brand names. And the generics had a better potency, consistently met the standard for potency better than the brand names. In fact 7.8 percent of the generic products were not of acceptable potency, they varied from the USP standard, the established standard, 7.8 percent of the time. But with the brand names, 8.8 percent varied from the potency standard. I just raise this question because I think the fact is—it is my judgment from looking at this over a period of 2 years of hearings—that what has happened is that the brand name companies have convinced the physicians of this, but there is no scientific basis for that.

Dr. ROSENOW. Senator, this statement in itself is true.

Senator NELSON. I do not doubt it. I said I did not quarrel with that.

Dr. ROSENOW. When we wrote this up we recognized that it is probably possible and susceptible of proof that they should not believe this way. But I think it is a fact that they do believe this way. And it is a little bit like everything that you buy in this country, some people have confidence in one kind of product because it is made by a certain company. Even though your experience might be different from this, you may have a lot of different things that you do this way.

I would also say that part of it is—I think what you do is sort of—let me take the drug digitalis, for example. I am a physician who likes to use the whole leaf digitalis. I always used the Davis Rose digitalis, not because I really thought it was a lot better, but because as far as my treatment of this patient was concerned I could do it better by knowing that I always prescribed this same kind of pill. For one thing, it was easily identified, because it was a kind of a round pill instead of an oblong one, and when they called up and wanted to know whether they should take one less pill or one more—digitalis is a pretty toxic drug—I felt more confident if I knew they had this. I recognize that there are many good products of digitalis, including generic ones, that I could have used. We are just trying to make a point that this is one of the reasons why doctors are opposed to not being permitted to prescribe by brand names.

Senator NELSON. I could not in any way differ with you in your statement. I think it is absolutely correct. A substantial percentage, maybe a large percentage, of the medical profession are more confident of the consistency and potency of the brand name drug than the generic even though the tests do not come out that way, and perhaps the generics are better. The reason I raised the question is that it does involve the issue we have been raising over the past few years, that is, the very powerful influence of the propaganda of the manufacturers upon the medical profession. And consistently that statement is made before this committee—the same statement that Dr. Pollard says they believe in, which I think is an accurate statement. Many of those who testified and commented on it simply asserted flatly that it is a fact. And this committee has been raising the issue of the effectiveness of the promotion by the companies of their products under their brand names versus generic names, and so forth. And that is why I raise the issue here, that so far as testimony before this committee, we have

not been able to find any evidence that demonstrates that the generic or the brand, either one, was any better than the other, consistently or otherwise.

Thank you.

Dr. POLLARD (reading).

DETAIL MEN

Many detail men offer the physician useful information about a product he is selling. Many times he renders a real service in getting a supply of a medicine his company makes in small amounts for rare diseases. If he is the kind of man who is poorly trained or a pressure type of salesman, his chances of getting to see the doctor again are pretty slim. In other words, there are detail men both good and bad and most physicians have no difficulty telling the difference.

TESTING DRUGS

Drugs should be treated by someone who knows about testing drugs. Many of our members are superb clinical investigators and do in fact carry on a lot of the clinical testing of drugs. With the kind of regulations being required by FDA, it would seem logical that the experts in a pharmaceutical company should continue to test drugs. Any good company would be as interested as anyone else in the quality uniformity and effectiveness of its products.

RELATION OF DRUG INDUSTRY TO THE MEDICAL PROFESSION

It would seem obvious that such a relationship would be a close one, because the therapeutic agents developed by the pharmaceutical companies can only be used for patient care upon order of a licensed physician. Probably the physicians exert more control over the industry than vice versa. In any case, we will attempt to delineate what relationship exists between the American College of Physicians and the pharmaceutical industry.

As we have already stated, the college's only function is to provide its members and other physicians with adequate educational opportunities in our specialty. One part of this educational activity relates to educating the physician about drugs and other therapeutic agents. Although the college's educational program is much broader than offering only information about drugs, we will outline at this time the ways in which we help educate physicians about drugs.

The college publishes the *Annals of Internal Medicine* which is the leading journal in our specialty. Its circulation is 47,000, of which approximately 15,000 are members of the American College of Physicians.

In this journal, as you can see, we display advertisements for a variety of products, including drugs, instruments, books, and educational opportunities. The policy of the college is that advertising pages will occupy no more than 40 percent of the total. Usually the percentage is less than this. Each advertisement is subject to review by a committee of four physicians. The work of this committee has been considerably lessened since the FDA rules on advertising copy have been adopted. However, the committee does look carefully at

the copy and determines whether claims or emphasis are in keeping not only with the FDA required information but in addition conform to good medical practice. If one member of the committee votes against an ad, it is reconsidered by the committee and the ad agency is notified and requested to make changes. Usually the required changes are made and the ad is approved. If changes are not made, the ad is declined. And we will supply you with the number that we have declined in the past 2 years.

The decisions are based upon adherence to the code which is furnished to all advertisers—copies are herewith included.¹

The college has resisted all efforts by the advertisers to incorporate ads within the editorial pages of the journal. As a matter of fact, we separate the editorial pages from the ads even more by having the executive director be in charge of the advertising and publishing of the journal and by restricting the two physician editors' responsibilities to the editorial pages.

The income we derive from journal advertising is considerable and one of the principal sources of income. However, it can in no way be considered of such importance that the college would change any of its policies in order to maintain this income. Furthermore, the percentage of advertising income related to total journal income (subscriptions plus advertising) is probable smaller than comparable figures from newspapers, nonmedical magazines, and medical journals published by commercial publishers. The controlled circulation journals such as *Modern Medicine*, *MD* and *Medical Economics* depend entirely on journal advertising revenue.

Our percentage of advertising income related to the total income of the college for the past 5 years is attached, labeled exhibit B.¹

Inasmuch as this income is used completely in the total continuing education program for physicians, we feel it offers a way in which physicians may participate in our programs at a lower cost. If the physician has to assume the entire cost of his educational activities, the costs would be passed on to the public in higher fees. In any case, the public benefits by this arrangement through the education of physicians.

The college sponsors an exhibit at its annual session. The same rules apply to screening the exhibits to be sure they are of high quality and have relevance to our specialty. Last fall, we surveyed physician attitude about our annual session. Of interest to you should be the fact that 86.4 percent of the respondents voluntarily visited the exhibits regularly and 86.7 percent of these found them to be informative and useful. The total physician registration at the Boston annual session was 5,232. The net income incidentally from this activity falls far short of paying the entire cost of the annual session.

We do have a few other activities sponsored jointly with drug companies. You should be interested in the general policy of our college regarding good will support of an activity by a drug company. It is as follows:

The college does not solicit drug companies for financial support of any of its activities but will consider accepting any grants offered on an individual basis.

¹ See pp. 4730-4733.

The following are important activities supported in part by pharmaceutical companies:

1. Smith Kline & French has for 20 years operated sophisticated color television equipment in order that we can conduct hospital clinics at the time of our annual session and bring these conveniently to the doctors at the site of the session. All parts of the program are planned by the American College of Physicians. Smith Kline & French is repaid solely by acknowledgement in the program that the technical production of the TV program is sponsored by them.

2. Mead Johnson & Co. furnishes the college with 14 fellowships which the college grants to young men during their training. Incidentally, prior to 1962, this company furnished \$3,500 for entertainment at our annual banquet. In 1962, we declined further support of this activity and suggested increasing the number of fellowships accordingly. Thus, \$4,000 more was granted for this purpose by Mead Johnson.

3. The Wyeth Foundation for Postgraduate Medical Education has over the years helped finance new parts of our annual session programs. A new section devoted to basic science lectures was given financial support. Recently a part of our program called "Meet the Professor" was given support.

4. Merck Sharp & Dohme recently offered to support several of our postgraduate courses in South America. Several years ago, they financed a film which one of our committees planned. The title of this is "Portrait of an Internist." It is an excellent educational film which depicts for the public what a specialist in internal medicine really does. It has had widespread appeal and we are told it has been shown to approximately 10 million people over public television and at public meetings. No products are mentioned and only a line of credit is given to the company.

5. The Eli Lilly Co. has offered some support to our postgraduate courses in South America. Parke, Davis & Co. and the Kellogg Foundation have also helped us start these important programs. The Kellogg Foundation incidentally has also provided financial support to a Latin American fellowship activity which our college supervises. In this program, young medical school teachers from South America are brought to this country for a period of training after which they return to their own countries. Of interest also is the fact that all of these 200 teachers have remained in their own countries.

Each year the college awards two honorary fellowships. These are made to distinguished medical scientists from other countries. They are brought to our annual session where they give lectures and receive their honorary fellowship. Eli Lilly supports the cost involved in bringing one of these and the college finances the other. Both are selected independently by the Committee on Awards of the College of Physicians.

We think all of these activities are manifestly in the public interest and indicate a wholesome and worthwhile relationship between our college and the drug industry. We remind you again, however, that what we have just described is only one small part of our entire educational program.

Senator NELSON. Thank you very much, Doctor.

Do you recall an article or a study that was made by Upjohn last fall? Sometime in November of 1968 Upjohn released a study they had

made on tolbutamide. They are the only manufacturers, and they took the standards of USP which were, in fact, the standards of the company, because it was the only product in the market. And they set up a comparison making some variances in the production of the drug product, yet staying within the USP standards which, as I say, were the standards of the company, and those were the only standards there were. They came out with a result which showed that the two drug products were not equivalent. And the Journal of the American Medical Association on November 18, 1968, ran an article entitled "The Generic Inequivalence of Drugs."

Did your publication treat with that at that time?

Dr. ROSENOW. I don't know without looking. You mean on this same subject?

Senator NELSON. In other words, did your journal report this finding which was reported in the American Medical Association?

Dr. ROSENOW. It would be unlikely, Senator. If the article was published in another journal, they would not submit it to us as well. It is seldom that an original article is submitted—it may be submitted to several journals, but the editors do not particularly like to publish it. They have a little pride of ownership, as they call it. So I do not think there would be any likelihood that it would be published in two places. The one thing that might happen in our journal is—and I do not know whether it did in this instance—is that someone else might refer to this article in, say, Clinical Notes, or something like that. But it would not be an original article.

Senator NELSON. And you do not know whether your publication commented on that editorially or otherwise?

Dr. ROSENOW. No; I do not.

Dr. POLLARD. I am not familiar with it if they did.

Senator NELSON. That occurred November 18 in JAMA. Would you mind just checking since November to see what coverage your publication gave to it, if any?

Dr. ROSENOW. Yes; I would be glad to.¹

Senator NELSON. I want to thank you very much for your testimony. I just make this point. You have been raising the point here, and others who testified have expressed the view that the relationship between the pharmaceutical manufacturers and the medical profession is not an unhealthy one. I think there is some question to be raised about that. But we notice in the testimony we have had that you have pharmaceutical manufacturers starting out at the medical school level and supplying various things to the students, stethoscopes, medical bags, research grants, and so forth; most of the journals receive substantial support in advertising from the pharmaceutical manufacturers; they provide income from exhibits at conventions; that they, in fact, in some instances—in one instance that we know of, paid part of the cost across the board in sponsoring of conferences, the medical conference itself, that there are free samples directly to doctors; that detail men see the physicians regularly, and \$4,000 to \$5,000 per year is spent in advertising per physician in the country; that the medical press, as contrasted with the journals, many of them are 100 percent supported by advertising by the pharmaceutical manufacturers; that you almost never see a critical editorial of the pharmaceutical manufacturers themselves.

¹ See p. 4734, *infra*.

I have never seen one. I do not say there have never been any, I have never seen one; news stories about the industry, especially when there have been conspiracies as to prices, seem to have played them down in the medical press if covered at all; that the AMA itself gave wide prominence to tolbutamide USP which Dr. Miller of the USP, destroyed by his analysis of it; that the task force report of the FDA found a significant difference in generic and brand names does not seem to be covered in the medical press very prominently at all; that the 4,600 drug tests do not seem to be publicized widely if at all; and that the testimony before this committee—I am not referring specifically to anything in particular to any of yours, I am just referring generally—by representatives of medical groups and by individual doctors recites consistently exactly the same arguments that the pharmaceutical manufacturers made; that you cannot trust the generics, that they are not equivalent, that brand-name companies do research, and therefore they are entitled to our support, that in general, as I said, the one group of people who are qualified in the profession to make criticisms of practices in the profession—practices by the manufacturers—is, I think, effectively silenced by the close information check.

Now, there have been very distinguished individual physicians, pharmacologists, clinicians, and experts of various kinds who have made some very strong criticisms of the practices of the pharmaceutical manufacturers in relationship to the subject, but we did not find that, at least I did not, in the journals I look through or in the medical press. So does it not really raise the question that there is a very close relationship here, just in the nature of it, and everybody is so friendly that everybody ends up by not criticizing anybody else; is not that the kind of thing we get?

Dr. POLLARD. Well, Senator, if I may express my own reaction to your comments, my information and my knowledge about this problem is really not in keeping with your comments.

Senator NELSON. Pardon?

Dr. POLLARD. I said my reaction and my knowledge is not in keeping with the comments which you have just made.

And let me tell you why I say that. Your one comment was that there were very few if any critical comments about drugs or pharmaceutical products appearing in medical journals. Is that—that has not been my experience. In medical journals—and I brought with me a group of programs of regional meetings throughout the United States just the past 12 months, and I ticked off in here the papers that were presented in all of these relative to drug intolerance, drug sensitivity, damage to the liver, damage to the stomach—

Senator NELSON. Were these papers delivered at medical conferences?

Dr. POLLARD. Oh, yes. These are regional meetings of the American College of Physicians—and by region I mean usually a State or, in some instances, two or three States together. Now, these are just our ways and means of educating our physicians. And all I am doing is pointing out that I think we attempt to keep the doctor educated by meetings. By publications, by articles in the annals, and by our annual scientific sessions, plus our postgraduate courses on all of the complications that go along with it. And then for that reason, while we must

maintain close cooperation with the drug companies—I would not deny that 1 single minute, because we are dependent upon drug companies in a great way for the development of new products and for the refinement of products—yet we are totally independent in our opinion and decision as to how effective those products are.

Senator NELSON. I wasn't suggesting that at medical conferences the profession did not call upon its most distinguished members to present the best possible papers on all aspects of medicine. I don't suppose you could find experts who would be willing to say anything other than what they believed in at these conferences, and I could not expect that anyone in the profession would think that any other presentation ought to be made in medical conferences. I was raising the question as to what the publications themselves really say about practices in the industry. For example, what kind of prominence did your publication give to the FDA findings on 4,600 drugs in which the generic came out better in terms of potency than brand names?

Dr. ROSENOW. May I try to clarify a little bit how this operates. If a physician or a clinical investigator interested in that report would send to our journal an article that he wanted to put in here about that, then our editors would do this.

Now, sometimes our editors look for these things themselves, and would write an editorial about this. I am quite sure that in this particular instance this was not done. And we do not have a mechanism where we screen every single release that comes out from the Food and Drug or from any of these other agencies. But our editors would not hesitate to put this in if they felt and their editorial staff felt that this was important information for our members to get.

Senator NELSON. The point I am making is that the argument—that you must rely upon brand names, that you cannot trust generics, that generics are not as good as brand names—that that argument is widely spread to all the medical journals in this country, it is advertised and widely spread to physicians in promotion. And here comes a study that is a significant one, it is a very significant study by the FDA of great importance to the medical profession. My point is—I have not looked at your journal, you may have run something, I am not addressing myself specially to your journal on this question—but this finding was rather massively ignored so far as I was able to determine. And all I am saying is that if you have this kind of relationship, don't you end up, because of the closeness of such a relationship, as a matter of human nature, muting the criticism of the independent industry whose relationship is so close? It seems to me that through years and years and an expenditure of millions of dollars, that doctors have been convinced, as Dr. Pollard said in the beginning of his statement, that they can rely upon the consistency and the potency of the brand name more than the generic, that all the journals ought to have a positive moral responsibility to run big editorials saying, it has been found that the claim made by the brand name people does not stand up.

Now, if it were a separate, completely separate situation—for example, when we introduced the legislation involving tire safety, a number of journals hit the issue real hard with editorials, big stories about the tires being put out by the automobile manufacturers. It is a shocking story, they ran it big, but they are not relying upon their support from the independent industry. But here is a case where

there is faith by the profession, as stated by Dr. Pollard, that the consistency and the potency of the brand named drug is better, and suddenly a finding by a massive study is made, and most all the journals who have ads are silent, or play it down. This is the question I am raising.

Dr. ROSENOW. May I make one other comment about the Food and Drug Administration, and what we try to do. This was over 4 or 5 years ago. And we have repeated it over, that any time the Food and Drug would like to reach the members of the American College of Physicians—I have made this as a personal offer, and also as a letter from our colleagues—if they will send us information that they want published to go to our doctors, we will publish it. The first time I made this offer it was very quickly that I got on apparently nine different mailing lists. And I got piles of material, and, I did not really personally have the time to go through every one of these things to find out what I wanted. And I had made the offer that I did not have time if they did not have time to state exactly what they wanted in, not just give me—everything came with no selection whatever, volumes this big [gesturing]. And you probably have some problem getting through the mail, too. I finally wrote them, I said, I would really like to get just one copy of everything.

The girl said I would have to tell her which mailing list I was on. And of course I did not know.

We have made this offer many times, and we will still make it, that if FDA wanted to make an announcement they could reach our 15,000 members within the next publication date.

One other time, I might add—you will recall the thalidomide episode several years ago. The first notice to the professional public was made at our annual session, it was at one of the meetings—I am not quite sure whether it was—where we rearrange the program to have announcement made at our meeting about this.

Dr. POLLARD. It was in San Francisco.

Dr. ROSENOW. This was the first notice to this company. So I am not quite sure—the thing that I would like to assure you of, I really do not think it is always kind of a conspiracy of silence so much as it is poor communications as to how we get this information from that report you have, how it gets to our editors.

Senator NELSON. I would assume that every medical journal in this country has somebody who is responsible for keeping track of the major pronouncements by the FDA. We do not quarrel with that.

Dr. ROSENOW. I was trying to explain how we keep track of it. We do not have enough people on our staff so that we can read all the material they send us.

Senator NELSON. There was a major drug report by the National Academy of Sciences.

Dr. ROSENOW. This was done by the Committee on Drug Efficacy.

Senator NELSON. This was done by the FDA itself, and the Committee on Drug Efficacy of the National Academy of Sciences/National Research Council, made another report in which they observed, paraphrased, that there did not seem to be any significant difference between the generic drugs and the brand name drugs. But I am simply raising the questions that these are major issues—this was a task force report—these are major issues that directly affect the drug

industry and the medical profession. And I just wonder how vigorous anybody can be in raising this kind of an issue when the relationship is so close. I do not know of any circumstance in human relations where the relationship is close financially and socially or otherwise in which the parties are inclined to be as vigorous in their criticism of each other as they are if there is no relationship. It is just in the nature of the human animal. And I think it will always be so. This is one of the questions we are raising. When the drug industry makes such a major point of this lack of equivalency between generic and brand names, they have been able apparently for one reason or another—the reason I think is that the relationship is too close—for one reason or another they get by without having the major authoritative inspective body in this country, the American physicians, and their journals and their spokesman, rising up and saying, they have been pushing this phony propaganda for 20 years. And now we find a study which shows that they have been fibbing to us. I would think that this would be a major, important point right off the bat. The whole profession ought to be told that they have been living by a propaganda pitch which the drug industry has promoted for years, and here is an answer to it. Why not?

Now, I say that the inclination is to draw the conclusion that the relationship is so close that criticism by the profession of the industry has not occurred in the past and will not occur in the future. Individuals, yes, we have had them before the committee. But that is the problem that this relationship raises, I think.

Dr. POLLARD. Senator, if I interpret your point, it is whether or not generic versus trade names is the answer to the whole drug problem. And I am not sure that even you believe that.

Senator NELSON. I am not saying that is the answer to the whole drug problem, I am just saying that the assertion has been made for years by the drug manufacturers—and now here is a scientific report of major consequence which refutes the claims that have been made for years by the brand-name companies. And the general profession is quite silent about the matter.

Dr. POLLARD. Let us interpret that with a little bit of caution. Because this comment that the profession has said nothing about it, I will still go back to the point that I made, that where we spend our time in the medical profession is evaluating drugs and reporting upon their complications in our scientific meetings. Now, perhaps we have not touched on generic versus trade name as the key to the whole drug problem. And I still think what we have attempted to do is to keep the doctor educated about his drugs, what they are, and what their applications are in a very fair and open way. And that is where we have been beating our drums, as it were. And maybe we have not made a great issue about the brand name versus the trade name. Frankly, I do not think we have any strong feelings about it one way or the other. There probably are other studies that would take generic named drugs, make studies of them and find disturbances there. Just because one chooses one or the other I do not think necessarily will resolve the whole drug problem. It may help it, but I do not think it will resolve it. And I think what the medical profession is after, what we in the college of physicians prefer, is that the physician be left to make his own choice.

Senator NELSON. In the 2 years that we have had the hearings, we have announced publicly on several occasions that we will hear all viewpoints and that anybody who manufactures drugs is entitled to first preference to appear before this committee. In that period of time we have not had any scientific testimony that proves the claim that the industry consistently makes, that the brand name is better than the generic name. The assertion by the USP and the National Formulary and the distinguished pharmacologists before the committee is that if two drugs meet the official compendium standards they are equivalent. And there are rare exceptions, which do not even count up to one, and they are not even certain of that. But the profession becomes convinced that that is not the case. My point is that the profession believes what you stated in your opening remarks, I agree—I think that is exactly what they believe. But what responsibility do the journals and the medical press have for pointing out that the claim that is being made consistently to the profession is not true, it has not been true? That is my point.

Dr. POLLARD. Senator, may I just comment on this recent publication of the AMA drug evaluations. This, I believe, is their first chapter on this, published May 20, 1968. As you go through the listing of all of the drugs they are listed by generic name in bold type, and in very small parenthesis is the trade name. I think that is a little along the line that you are talking about.

Senator NELSON. Yes.

Dr. ROSENOW. Senator, may I ask a question?

If your feeling is that doctors should prescribe by generic name, would you have objection to them including also the brand name or the manufacturer?

Senator NELSON. First let me say, doctor, that I would not make any independent judgment of my own about what a physician ought to do. I have not decided what some of the authorities would do because I do not have any independent expertise of my own. The testimony of experts before the committee consistently has been that doctors ought to prescribe by generic name, but the doctor would have complete freedom to designate the brand that he wants. No one has testified before this committee that the doctor must prescribe by generic name and not indicate the manufacturer or brand. All of our testimony has been that he should be able to select the company if he desires to do so. So we have introduced legislation based upon the testimony of a number of highly regarded pharmacologists and physicians that the label should contain the generic name, and if desired by the physician, the brand name or the manufacturer himself. What is your view of that?

Dr. ROSENOW. I personally would have no objection—in fact, I would say over 30 years my attitude is changed about how much you should let the patient know anyhow. I think they ought to know as much as they can. That is as I get older. It is harder and harder to find out how to take care of people anyway. But I think with the American public traveling as much as they do and moving from place to place it is really a good idea to have on the label what the drug is, what drug he is taking, and what the dosage is. And preferably, I think I would like to know not only the generic name of that drug

but I would like to know which company makes it to see whether it is the one I am used to or not. I would have no objection to this.

Dr. POLLARD. Senator, in our own institution, the University Hospital in Ann Arbor, we have required our pharmacy there that fills the prescriptions for any patient that we write prescriptions for to put on the label specifically what the product is and what the dosage is, and how many grains or milligrams, and what each tablet contains. So that is required, unless one ticks off a little area and indicates that this is not to be noted. Otherwise every prescription going out of there for at least, I think, the past 7 years has had written on the prescription exactly what it is.

Senator NELSON. By official name or generic?

Dr. POLLARD. I would have to check that to be sure. I think they write it merely the way the doctor has written it. And I say, in keeping with your comments, that the Chairman of our Department of Internal Medicine encourages openly and constantly when the residents write their prescriptions, when they are ordering drugs, that they use the generic term. He prefers that.

Senator NELSON. Thank you very much. We appreciate your taking the time to come here and present your very valuable testimony.

Dr. POLLARD. Thank you very much, Senator, for this privilege.

Dr. ROSENOW. Thank you very much.

Senator NELSON. We are pleased to have you.

Dr. ROSENOW. And I will send the information that you have requested.

(The supplemental information submitted by Dr. Pollard follows:)

THE AMERICAN COLLEGE OF PHYSICIANS

ADVERTISING IN THE ANNALS OF INTERNAL MEDICINE—EXHIBITING AT THE ANNUAL SESSIONS

The following criteria will be used in screening product advertising to be carried in the Annals of Internal Medicine publication and for exhibition of the Annual Sessions of the American College of Physicians. The Committee on Advertising makes the final decision regarding the acceptability of all products and services to be advertised and exhibited and gives final approval of the advertisement or exhibit. The Committee reserves the right to change these standards in the light of developments in medicine or in industry.

A. Eligibility for advertising and exhibiting

1. *Products or services.*—Only those products or services relevant to the practice of internal medicine or in allied specialties shall be eligible for advertising and exhibiting.

2. *New drug applications.*—No pharmaceutical products will be eligible for advertising or exhibiting until a New Drug Application from the Food and Drug Administration has become effective.

3. *Institutional-type advertising.*—Only that copy which is relevant to the practice of internal medicine and "public service" messages of interest to our physicians will be considered eligible for appearance in the ANNALS OF INTERNAL MEDICINE.

4. *Special-purpose foods.*—Foods which are used by certain specific segments of the population who have specific diseases or conditions requiring foods with certain properties, are permitted.

B. Products not acceptable for advertising and exhibiting

1. *General purpose foods.*—Foods promoted for use by the population in general; Examples—Fruits, meats, eggs, bread, processed fruits and vegetables.
2. *Beverages.*—Alcoholic Beverages.
3. *Miscellaneous products.*—Tobaccos, cosmetics, patent drugs, automobiles, etc.

C. Detailed information required on modified old and new products

1. *New drugs.*—A new drug is defined as follows: As a single active ingredient (e.g. reserpine, deserpidine), or an extract from a single source (e.g. alseroxylon, rauwolfia).

2. *Modification on drugs of approved products.*—A drug previously approved must be re-submitted for review if a modification of the drug has been made subsequently, for example such as a new salt or ester.

3. *Combination of one or more drugs.*—Combination of one or more drugs already considered acceptable-clearance will depend on rational grounds for justifying such a new combination.

4. *Additional brand of product.*—An additional brand of a product already considered acceptable (copy of proposed advertisement only need be submitted).

In order for a pharmaceutical manufacturer to become eligible to advertise the products in the ANNALS OF INTERNAL MEDICINE, or to exhibit them at the annual meetings, the following data concerning a product must be submitted to the Committee for review before acceptance. This ruling applies to new products and on established drugs or equipment which have been modified.

(1) Five copies of the currently approved package insert be forwarded to the American College of Physicians and addressed to the attention of the Advertising Manager.

(2) Indicate whether approved by FDA.

(b) Indicate whether approved by AMA or other publications.

The Advertising Committee frequently seeks the opinions of consultants in determining the eligibility of products and suitability of claims. The Advertising Committee expects that the medical department of the pharmaceutical company has approved not only the product but the advertising copy before its submission. Drugs introduced before 1961 should include if available the package insert and other data supporting the efficacy, instructions of uses and relative safety of the product. Evidence of such medical department approval must be furnished on request.

D. Advertisements for specific types and classes of products and services

1. *Apparatus, instruments and devices.*—The eligibility of medical equipment intended for preventive diagnostic or therapeutic purposes is determined by the Advertising Committee. Advertisement for new products and new claims should be accompanied by FIVE COPIES of information, presenting full and adequate scientific and technical data concerning the products' safety, operation and usefulness, including the results of laboratory and clinical examination. These data may be either published or unpublished. Samples of apparatus, devices, equipment or instruments should not be submitted unless requested by the Committee.

2. *Books.*—A book may be requested for review so that its eligibility for advertising may be determined.

(3) Miscellaneous products and services.—Products or services not in the above classifications may be eligible for advertising provided they are closely related to the practice of internal medicine and can meet all requirements.

E. Advertising or exhibit copy

After a product or service has been submitted for advertising in the ANNALS OF INTERNAL MEDICINE, the Advertising Committee makes the final decisions regarding the acceptability of new copy. The Committee's decision in this regard will be guided by the following principles:

(1) Advertisements should not be deceptive or misleading. The layout, art work and format of the advertisement should be such as to avoid confusion with the editorial content of the publication and be in good taste. The Committee reserves the right to reject the format of the advertisement as it would appear in the ANNALS. It is understood this would be at a stage beyond the approval of ordinary advertising copy.

(2) The Committee reserves the right to reject the format of any exhibit.

(3) Advertisements should clearly identify the advertiser and the product being serviced or offered.

(4) Unfair comparisons or offensively forward and unwarranted depreciation of a competitor's products or services will not be permitted.

(5) Advertisements will not be accepted if they appear to conflict with the principles of medical ethics.

(6) Exaggerated or extravagantly worded copy will not be allowed. Any claims for superiority must be supported by evidence acceptable to the Committee.

(7) Excerpts or quotations from published papers are acceptable providing they do not distort the meaning intended by the author. Claims made within quotations must conform to the standards as unquoted claims.

All exhibitors are prohibited from using any of the following tactics for promoting their products at our meetings:

(1) Exhibitors shall not use any gimmicks, door prizes, lucky number drawings, etc.

(2) There shall be no button-holing doctors in the aisles.

(3) High pressure "pitch" of any kind will not be permitted.

(4) All exhibitors must conduct their exhibits, at all times, in a clean and dignified manner and at no time display a side-show atmosphere.

Those exhibitors not abiding by the above regulations while attending the meeting will be immediately expelled.

DEADLINE DATES

Receipt of material for committee review

Proposed advertising copy on pharmaceuticals or biologicals not previously advertised in the ANNALS, and NEW advertising copy only, on products already approved for advertising or exhibiting, must be submitted for Committee review at least two weeks before the Closing Date for advertising in the scheduled issue. It is imperative that FIVE COPIES each of currently approved package inserts and proposed advertising be submitted. Indicate whether approved by FDA, AMA, or other publications.

Closing date

The Closing Date for insertion orders is the 20th of the second month preceding publication.

EXHIBIT B
ANNALS OF INTERNAL MEDICINE

	1964		1965		1966		1967		1968	
	Amount	Percent	Amount	Percent	Amount	Percent	Amount	Percent	Amount	Percent
Subscription revenue net of Commission.....	\$221,688	16.4	\$244,511	17.3	\$272,056	16.5	\$291,078	15.6	\$343,278	15.7
Advertising revenue net of Commission and discount.....	374,060	27.6	432,597	30.7	602,802	36.3	719,747	38.4	796,947	36.5
Total revenue from annals.....	595,748	44.0	677,108	48.0	874,858	53.0	1,010,825	54.0	1,140,225	52.2
Total revenue including annals.....	1,353,489	100.0	1,409,301	100.0	1,649,617	100.0	1,872,435	100.0	2,184,286	100.0

(The subsequent supplemental information submitted by Dr. Rose now follows:)

THE AMERICAN COLLEGE OF PHYSICIANS,
Philadelphia, Pa., April 7, 1969.

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

(Attention of Mr. Gordon):

This letter is to give you additional information in response to Senator Nelson's questions asked of Dr. Pollard and me recently.

First of all the following is a breakdown of Exhibit B of our report to show what percentage of Advertising Revenue was represented by pharmaceutical advertising in the annals.

	1967		1968	
	Amount	Percent	Amount	Percent
Pharmaceutical.....	\$823,738	95.5	\$898,019	94.41
Instruments.....	21,296	2.5	34,470	3.62
Books.....	13,250	1.5	13,020	1.37
Other (miscellaneous).....	4,160	.5	5,670	.6
Breakdown for exhibit revenue:				
Pharmaceutical.....	58,011	60.0	65,350	53
Instruments.....	15,795	16.0	27,950	23
Books.....	11,391	13.0	11,325	10
Other.....	11,091	11.0	19,100	14

A second question concerned our endowment fund and whether we had any stock in a pharmaceutical company. At the present time our total portfolio in invested capital is as follows:

	Cost	Market, as of Feb. 28, 1969
Operating fund.....	\$307,912	\$426,416
Endowment.....	3,524,830	3,945,303
Building fund.....	889,835	1,051,064
Total.....	4,722,577	5,422,783
Holdings in pharmaceutical stock:		
Baxter Laboratories convertible 4 percent, Mar. 1, 1987.....	49,688	56,400
Rorer-Amchem.....	60,788	54,000
Total.....	110,476	110,400
Percent.....	2.3	2.0

It can be seen that 2% of the total invested capital is in pharmaceutical companies. I remind you that we invest our funds upon advice of Drexel, Harriman and Ripley.

I have checked with our Editors and we have not commented on the AMA journal article November 18, 1968 on Generic Inequivalence of Drugs by Alan B. Varley, M.D.

During the past couple of years we have rejected a number of ads which were so totally unsuited to a journal devoted to Internal Medicine that we did not circulate to the committee. The following represent those we would have rejected if the agency did not comply with our request to make certain changes.

1. Stuart Company—Ad submitted by Sudler & Hennessey Company for Mylicon (brand of simethicone). We asked that the statement "This liberating action of Mylicon is unlikely to mask organic disease—And side effects and seldom reported—even during prolonged use." They dropped this and the ad appeared in the August, 1967 issue of *Annals of Internal Medicine*.

2. Rowell Laboratories—Agency Barickman & Shelders Advertising, Inc. Product—Cortenema! Attached is copy of our letter dated October 4, 1967. The company did not submit further ads for this product.

3. A. H. Robins Company—Agency Martin & Woltz, Inc. Product—Robitussin DM, Entozyme, and Exna—attached is copy of our letter of December 28, 1966. None of these have run as ads in our journal.

4. Pharmacia Laboratories Inc.—Agency Paul Klemtner & Company—Product Azulfadine. Attached is copy of our letters of December 14, 1966 and December 20, 1966 indicating their willingness to comply.

5. Organon, Inc.—Agency Erwin Wasey, Inc.—Product Accellerase. Attached note dated December 15, 1966—Did not comply with suggestion so agency cancelled contract.

6. Massengill Laboratories—Agency Ramsdell Buckley & Company—Product Obedrin LA. Attached is letter of November 23, 1966 speaks for itself.

7. Lederle Laboratories—Product Levoprome submitted for exhibit. Rejected by committee because no reprints were submitted to substantiate claims made.

8. Key Pharmaceuticals—Product Nitroglyn. See attached letters dated January 13, 1967, to the company and letter of January 24, 1966 making changes requested.

9. Bristol Laboratories—Product Prostaphlin—Agency Sudler & Hennessey. This is the one I mentioned at the hearing. I was in error at the time this occurred and also that they cancelled all ads with us. They only cancelled the ads for Prostaphlin but continued advertising other products namely, Kantrex—January to June, 1967 and April to November, 1968—Polycillin—all of 1967 and January, 1968; May & October to December, 1968. Attached letters explain our impasse over Prostaphlin.

Memo to me October 18, 1963

Letter to Mr. Phillips, A.C.P. Advertising Manager from Mr. Wilkins.

Letter, October 28, 1963 to Mr. Wilkins from Mr. Phillips.

Intermittently we had inquiries about again considering a Prostaphlin ad—My letter of March 18, 1963 is self explanatory.

Finally my letter of March 19, 1969 resolves the problem because the company has submitted copy satisfactory to the committee.

If there are other questions we can answer please write me.

Sincerely,

EDWARD C. ROSENOW, Jr., M.D.,
Executive Director.

Memo to: E. C. Rosenow, Jr., M.D.

From: Andrew P. Phillips.

Date: October 18, 1963.

Re Bristol Laboratories, Prostaphlin advertisement scheduled for the November issue.

In reviewing the November proofs sent from Lancaster Press I noted that the changes which the committee requested has not been made. The changes are as follows:

The heading of the advertisement reads "Whenever You Suspect Staff", the committee suggested that this copy be changed to read "In Staff Infections." Also the word "suspected" appearing on the first line in the first paragraph would be changed to the word "present" and that the asterisk appearing in the close of the first sentence and foot note at the bottom of the page be deleted.

I immediately called the agency regarding these changes. After a lengthy conversation, the agency called Bristol Laboratories and they had informed us that no change would be made in the copy as it is a repeat of the October advertisement. Their interpretation of our letter was that they felt this being a repeat would not require a change. However, they are aware that all future advertisements must be approved by the committee before they procede in preparing plates.

The complete issue is at Lancaster Press and locked-up to run. If we cancelled this spread it would have meant using College ads, which unfortunately we cannot supply. Therefore, I informed the agency and client that we would run this advertisement for this issue.

I realized our instructions could be interpreted as future copy as opposed to *New Copy*, to future advertisement which could be repeats of previous insertions.

SUDLER & HENNESSEY, INC.,
New York, October 21, 1963.

Mr. ANDREW P. PHILLIPS
Advertising Manager,
The American College of Physicians, Philadelphia, Pa.

DEAR Mr. PHILLIPS. Regarding your letter to Mr. Rich of October 18th, we intend to rerun the present Prostaphlin ad "Whenever you suspect staph" in the December issue of the *Annals of Internal Medicine*. We do not intend to change this ad at this time or in the foreseeable future.

As I believe I mentioned to you before, the decision to accept or reject the ad is yours. Bristol supports this position.

Sincerely,

WALTER K. WILKINS.

OCTOBER 28, 1963.

Mr. WALTER K. WILKINS,
Sudler & Hennessey, Inc.
New York, N.Y.

DEAR Mr. WILKINS. Thank you for the reply to my letter regarding the copy revisions for your client's Prostaphlin advertisement, scheduled to run in the December, 1963 issue of the *Annals of Internal Medicine*.

Unfortunately, there seems to have been a misunderstanding on the acceptance of our request for copy changes. We understood from Dr. Kitto's conversation with our Executive Director, Dr. Rosenow, that your client knew the October and November advertisements were accepted on the premise that the revisions would be made in all forthcoming advertisements on this product. The copy changes though slight were important, e.g. quoting one of the Committee members, "I do not like the statement, 'whenever you suspect staph—start with Prostaphlin'. One should never start treating staph just on suspicion and an A-1 physician would consider the best drug. In other words this advertisement constitutes poor teaching".

The word "suspect" in the caption of the advertisement was to be deleted and "suspected" in the body of type to be changed to "present". The caption would read "In staph Infections". Also, the asterisk at the end of the first sentence and the footnote to be deleted.

I have referred your letter to Dr. Rosenow and he feels inasmuch as the ruling for copy changes requested by authorized members of our Committee, applies to all of our advertisers, the Prostaphlin advertisement could not run in our journal without being revised.

Sincerely,

ANDREW P. PHILLIPS,
Advertising Manager.

JANUARY 13, 1966.

Mr. BERNARD FRIEDLAND,
Assistant Medical Director,
Key Pharmaceuticals, Inc., Miami, Fla.

DEAR Mr. FRIEDLAND: While "Nitroglyn" may be a fine product the Committee on Advertising feels the copy is ambiguous and misleading when you state "Gives 24-hour protection against attacks and possible myocardial damage". This claim is not substantiated in the material forwarded to us, if it was please indicate where or submit additional information which will prove this statement.

It will, therefore, be necessary for you to substantiate this claim or revise your ad copy before this ad can appear in the *Annals of Internal Medicine*.

Sincerely yours,

EDWARD C. ROSENOW, JR., M.D.
Executive Director.

KEY PHARMACEUTICALS, INC.,
Miami, Fla., January 24, 1966.

ANNALS OF INTERNAL MEDICINE,
The American College of Physicians,
Philadelphia, Pa.

(Attention of Edward C. Rosenow, Jr., M.D.).

GENTLEMAN: In reply to your letter of 13 January concerning the advertising copy for our product Nitroglyn®, we have studied your comments, and wish to

submit the following change in the copy which you brought to our attention. Item 1. has been amended to read "Give 24-hour protection against attacks, taken twice or three times a day;"

We trust that this change now meets with the approval of the Committee on Advertising, and will be satisfactory for the desired insertions.

Sincerely yours,

BERNARD FRIEDLAND,
Assistant Medical Director.

NOVEMBER 23, 1966.

Mr. FRANK HENSCHER,
*Ramsdell, Buckley & Co., Inc.,
Philadelphia, Pa.*

DEAR MR. HENSCHER: This is to confirm our telephone conversation of yesterday regarding the advertisement your client wishes to run in the January, 1967 issue of the *Annals of Internal Medicine*.

As I mentioned the members of our committee feel "Holy flabbergast—it's Fatman," does not lend itself to our journal.

At the present time I understand you will repeat the "Jim Nathans sat here" advertisement which ran in the December issue. I would like to mention, however, several members of the committee have told me they feel the "Jim Nathans" ad is more in keeping with our journal and an eye-catcher.

I will assume that a revised insertion order will follow shortly.

Sincerely yours,

ANDREW P. PHILLIPS,
Advertising Manager.

DECEMBER 14, 1966.

Mrs. LORRAINE MOORE,
*Space Buyer, Paul Klemtner & Co., Inc.,
New York, N.Y.*

DEAR MRS. MOORE: I have submitted the "Azulfidine" advertisement #4706 one drug has distinguished itself by having a place in the treatment of almost any patient with ulcerative colitis—Azulfidine, the mainstay of therapy for colitis. The following, therefore, is an excessive claim.

"But, to achieve the ultimate aim of restoring normal intestinal function, one drug has distinguished itself by having a place in the treatment of almost any patient with ulcerative colitis—Azulfidine, the mainstay of therapy for ulcerative colitis."

Unless this is revised we will not be able to run this advertisement in our journal.

Sincerely yours,

(Miss) BARBARA RAUSCH,
Secretary to Mr. Phillips, Advertising Manager.

DECEMBER 15, 1966.

Dr. ROSENOW: Organon, 'Accelerace' #4706 Rev. has been submitted to appear in the February, 1967 Issue. The following comments were made regarding this product:

Dr. Rosenow.—"We have no objection to Accelerase but do object to combining with P-B. Therefore, they should remove that from ad."

Dr. Frost.—"This product is no different from numerous others in our advertising. If we are not going to accept this product then I think we should review our position entirely and eliminate all products that are not scientifically proven to be effective. Believe Committee should establish a few guidelines and principles that are consistent rather than saying as was the old procedure of "it isn't valuable but won't do harm."

Dr. Rouse.—"No clinical material included. It appears to me to be 'shot gun' therapy."

Dr. Wise.—"See letter from Dr. Franz Goldstein."

Please advise.

DECEMBER 20, 1966.

Mrs. LORRAINE MOORE,
Space Buyer, Paul Klemtner & Co., Inc.,
New York, N.Y.

DEAR MRS. MOORE: This is to confirm our telephone conversation of today regarding the "Azulfidine" advertisement #4706 which has been revised to read:

"Many patients—many measures—from the use of simple antispasmodics to intensive psychotherapy. But one drug has consistently proven its value in the treatment of each and every stage of ulcerative colitis—Azulfidine (salicylasulfapyridine) the mainstay of therapy of ulcerative colitis."

The Committee has approved the above for insertion in the *Annals of Internal Medicine*. Your insertion order was received in this office yesterday.

Sincerely yours,

(Miss) BARBARA RAUSCH,
Secretary to Mr. Phillips, Advertising Manager.

REVISED COPY FOR PHARMACIA LABORATORIES "AZULFIDINE"

Many patients—many measures—from the use of simple antispasmodics to intensive psychotherapy. But one drug has consistently proven its value in the treatment of each and every stage of ulcerative colitis—Azulfidine (salicylasulfapyridine) the mainstay of therapy of ulcerative colitis.

DECEMBER 28, 1966.

Miss HELEN R. LLOYD,
Martin & Woltz, Inc.,
Richmond, Va.

DEAR MISS LLOYD: Earlier this month you sent material to us for Committee review on "Robitussin-DM," "Entozyme" and "EXNA" for your client, A. H. Robins Company. These products have been submitted to our Committee, however, they feel that no evidence has been given to show that adding DM to Robitussin does anything more than Robitussin alone.

"EXNA" has been approved but ad copy was not submitted and must be in the future before it appears in the *Annals*, as I am sure you are aware.

Regarding "Entozyme", although there is no advertising copy presented this product is acceptable as a pancreatic substitution therapy but is unrelated to the relief of functional gastrointestinal disorders and any copy should not include such an inference.

I would appreciate it if you could send additional information on the Robitussin DM product and ad copy on all of these ads for further consideration by our Committee.

I will be looking forward to hearing from you in the near future.

Sincerely yours,

ANDREW P. PHILLIPS,
Advertising Manager.

OCTOBER 4, 1967.

Miss ELAINE SKJELSTAD,
Barickman & Shelders Advertising, Inc.,
Minneapolis, Minn.

DEAR MISS SKJELSTAD: This is to inform you that the "Cortenema" advertisement for your client, *Rowell Laboratories, Inc.*, has been approved by our College Committee and was scheduled to appear in the October and November, 1967 issues of the *Annals of Internal Medicine* as per your instructions received in this office.

Our Committee feels, however, that the advertisement should state that significant absorption occurs. They also feel it is an exaggeration to say "an absorbable steroid is safe and should be used in most cases of chronic ulcerative colitis". They feel it would be better to say "in cases of chronic ulcerative colitis in which steroids would be indicated".

We would appreciate your revising this advertisement before it reappears in the *Annals*. Thank you so much for your cooperation in this matter. If you should have any questions regarding this revision please feel free to contact me.

Sincerely yours,

ANDREW P. PHILLIPS,
Advertising Manager.

MARCH 18, 1968.

Mr. WILLIAM W. GORDON,
Product Advertising Manager,
Bristol Laboratories, Syracuse, N.Y.

DEAR MR. GORDON: Referring to your letter to Mr. Phillips, you do not interpret his letter of March 8th correctly. I can understand why you interpreted it as you do, however, the long standing objection goes back to 1963 and the objection we have is to the statement which you have put in the middle of the second page in bold print which states "Start therapy immediately with Prostaphlin".

The members of the Committee feel that this is generally bad advise and is not acceptable unless it is agreed by a clear statement that a staphylococcus or other suitable infection has been diagnosed.

Until you are willing to change this statement the Committee will not accept the ad as proposed.

In January of 1967 Dr. Robert Wise wrote a long letter to your President, Mr. J. D. McNitt, explaining in detail our feeling about this type of advertising statement. I would be happy to discuss this further with your medical department.

Sincerely,

EDWARD C. ROSENOW, Jr., M.D.
Executive Director.

MARCH 14, 1969.

Mr. JOHN L. ROBINSON,
Director of Promotion,
Bristol Laboratories, Syracuse, N.Y.

DEAR MR. ROBINSON: I am pleased to inform you that the College Committee on Advertising has approved ad #8433 for your product Prostaphlin. Also approved is "Kantrek" advertisement #8345.

These ads will be scheduled to appear in the May, 1969 issue of the Annals of Internal Medicine upon receipt of your further instructions.

Sincerely,

(Miss) BARBARA RAUSCH,
Secretary to Mr. Phillips, Advertising Manager.

Senator NELSON. Senator Hruska of Nebraska is here, I believe, to introduce our next witness. We are very pleased to have the distinguished senior Senator from Nebraska appear here this morning.

STATEMENT OF HON. ROMAN L. HRUSKA, A U.S. SENATOR FROM THE STATE OF NEBRASKA

Senator HRUSKA. Thank you, very much.

It is my happy privilege today to introduce your next witness, a constituent and good friend of mine, and a long-time practitioner in the city of Omaha. He is Dr. Robert S. Long.

He got his doctor of medicine degree in the University of Nebraska.

He served as intern and resident of the Harvard Medical Service City Hospital, and was a fellow in internal medicine at the Lehigh Clinic in Boston.

He served as a major in the Medical Corps of the U.S. Army, and has engaged in the practice of internal medicine in Omaha since 1947.

He is a fellow of the American College of Physicians, and currently president of the American Society of Internal Medicine.

I would ask unanimous consent, Mr. Chairman, that a biographical sketch a little more detailed in character be inserted in toto in the record.

Senator NELSON. Senator, Dr. Long has submitted a biographical sketch. And it will be printed in the record immediately prior to Dr. Long's statement.

Senator HRUSKA. And now, Dr. Long, I turn you over to this very generous and distinguished chairman of this subcommittee.

Dr. LONG. Thank you very much, Senator.

Senator HRUSKA. And with your permission I will go back to the Appropriations Committee where I have a hearing.

Senator NELSON. On the way out you may get into some argument about the use of that word "generous".

Thank you, Senator.

We will place Dr. Long's biographical statement in the record at this point.

(The biographical sketch follows:)

BIOGRAPHICAL SKETCH OF ROBERT S. LONG, M.D., OMAHA, NEBR.

1. President, American Society of Internal Medicine.
2. Diplomate, American Board of Internal Medicine.
3. Fellow, American College of Physicians.
4. Associate Professor Internal Medicine (Volunteer Faculty), University of Nebraska College of Medicine.
5. Associate Medical Director and Consultant on Medicare for Mutual of Omaha.
6. Member, Medical Relations Committee Health Insurance Council of America.
7. Member, Public Relations Committee Medical Section American Life Convention.
8. Chairman, Insurance Committee Omaha Douglas County Medical Society.
9. Member, Coding and Relative Values Committee, Nebraska State Medical Association.
10. Member, American Therapeutic Society, American Rheumatism Association, American Heart Association, American Medical Association, and other medical scientific societies.
11. Clinical Investigation of New Drugs prior to release Cortisone, ACTH, Diuril, Orinase, Tapazole, Decadron, Prostaphlin, Valium, and others.
12. Past-President Medical Staff Nebraska Methodist Hospital.
13. Private practice of Internal Medicine in Omaha, Nebraska since 1947.
14. Major, Medical Corps, AUS, World War II with overseas service as Assistant Chief of Medical Service, 98th General Hospital.
15. Born Cowles, Nebraska, February 25, 1916. B.Sc. and M.D. University of Nebraska, Intern and Resident Harvard Medical Service City Hospital, Fellow in Internal Medicine The Lahey Clinic, Boston, Massachusetts, Married, 2 children.

STATEMENT OF DR. ROBERT S. LONG, PRESIDENT OF THE
 AMERICAN SOCIETY OF INTERNAL MEDICINE

Dr. LONG. Senator, I brought with me some items which I would like for you to see. And I brought some extra copies of the memorandum which will illustrate my statement.

One of my organizations I represent here today does in general deal with internal medicine. And I have here some specific data that you requested in your letter that I did not have available before.

Senator NELSON. Thank you very much, Doctor.

Do you have an extra set of these memorandums?

Dr. LONG. Yes, I have it here.

Senator NELSON. May I ask at the beginning, does this memorandum that you submit have a breakdown of the advertising by source, that is, drug manufacturers and other sources?

Dr. LONG. The advertising in the Internist, of which you have a copy in that little bundle right in front of you, is almost entirely drugs.

Occasionally I have an advertisement for an instrument. But I have no breakdown, sir.

Senator NELSON. It is almost entirely pharmaceutical.

Dr. LONG. Pharmaceutical products, yes.

Senator NELSON. This memorandum will be printed in the record at this point.

(The document referred to follows:)

MEMORANDUM

AMERICAN SOCIETY OF INTERNAL MEDICINE,
San Francisco, Calif., March 11, 1969.

To: Robert S. Long, M.D.

From: W. R. Ramsey.

Subject: ASIM finances—5 year period.

The following figures are provided in accordance with your request:

Period	Dues income	Advertising income	Donations	
			Cash	Services ¹
1968-69.....	² \$401,046.50	\$4,275.83	-----	-----
1967-68.....	³ 363,200.00	10,113.84	\$5,000.00	\$476.09
1966-67.....	⁵ 261,505.00	8,558.90	500.00	619.54
1965-66.....	233,790.00	5,830.80	⁴ 5,711.15	338.10
1964-65.....	225,600.00	3,941.76	⁶ 3,216.20	497.54
			⁷ 200.00	-----
1963-64.....	152,105.00	1,606.45	⁶ 4,300.00	-----
			⁷ 700.00	-----

¹ Binders for house of delegates meeting and plastic briefcases for delegates.

² Dues increased to \$50 per year.

³ Dues increased to \$40 per year.

⁴ Exhibits: Our records indicate exhibits were discontinued after the 1966 annual session.

⁵ Dues increased to \$30 per year.

⁶ Exhibits.

⁷ Grants.

Senator NELSON. Dr. Long, we are very pleased to have you take the time to come here today to present your testimony. You may present it in whatever fashion you desire. If you wish to depart from it and elaborate on any aspect of it, feel free to do so.

Dr. LONG. Thank you, Senator Nelson.

I think my statement is relatively short and it will take me only a few minutes to read it for the record. I think our best interest would be served timewise and otherwise if I might read this first. This will then perhaps give you a clue as to any questions you might wish to ask subsequently.

Senator Nelson and members of the committee, I am grateful for this opportunity to appear before your committee to present my views regarding some of the matters you have under consideration, particularly the responsibilities of practicing physicians in the prescribing and administration of drugs, biologicals, and chemical agents in the treatment of patients, and the relationships between physicians and organizations of physicians and the drug industry.

I am the president of the American Society of Internal Medicine, an organization of approximately 10,500 specialists in the field of internal medicine.

Senator NELSON. What is the total number of internists in the country?

Dr. LONG. This would be a little hard to judge. There are some 40,000 physicians who are self-designated internists in the AMA Directory

of some 300,000 physicians. A sizable percentage of those are not men whom those of us who took the additional training would categorize entirely as specialists in internal medicine. By that designation I think they mean to indicate that they restrict their practice to the field, in other words, they do not do surgery, let us say, or deliver babies, and so forth, whereas in our organization, as I will indicate in a moment, our 10,500 specialists who must meet certain requirements of training in order to belong.

I think a realistic figure, in answer to your question, as close as he could get it, would be somewhere in the neighborhood of 25,000, perhaps, 20,000 to 25,000.

Senator NELSON. Who are internists?

Dr. LONG. Who are qualified specialists in the field; yes.

On February 4, 1969 I mailed to you a copy of the bylaws of our organization, several copies of our monthly Newsletter, a pamphlet entitled "Aims and Purposes of ASIM", and a brief biographical sketch of myself, I have brought with me today a few of the pamphlets and other publications of our society as well as a roster of our membership and a list of our committees and councils.¹

All our active members are doctors of medicine who have completed an internship, three years of special training in internal medicine and 2 years of practice in the specialty. Our basic goal is to assure that high quality medical care is rendered to all. We are especially concerned with the working domain of medical practice, and with the professional, socioeconomic and political conditions under which such practice is carried out, whether in the hospital, the physician's office, the patient's home or elsewhere. Our efforts have to do primarily with the practical aspects of how to translate medical science and knowledge into the day-to-day care of sick patients in the most efficient, effective, and economical way possible without sacrificing any of the quality of such care.

Inasmuch as the specialty of internal medicine has to do with the diagnosis and treatment of diseases and disorders by nonsurgical means, you would know that my training, experience, and interest have been in the use of drugs and related materials in the practice of medicine. While I have had some experience in the clinical investigation of drugs both in my private practice and in connection with my teaching of students at the University of Nebraska College of Medicine, my principal knowledge and experience have been gained in the study and use of drugs and related materials in the day-to-day practice of medicine with private patients.

I served for many years on the pharmacy committee of the Nebraska Methodist Hospital in Omaha, Nebr. on the executive committee for 10 years, and was chief of staff for 2 years. In these positions I gained some knowledge as to the practical problems involved in operating a pharmacy in a large, private, general, metropolitan hospital.

My father was a pharmacist, so I know something, too, of the private druggist's problems from his side of the counter.

I have been active in several organized medical societies for many years, including the American Therapeutic Society, an organization which has to do with the scientific study and practical application of

¹ Material retained in committee files.

the use of drugs in clinical medicine, the American Diabetes Association, the American Rheumatism Association, the American Heart Association and others. These activities have naturally brought me in contact with many pharmaceutical companies and their representatives in scientific matters as well as in business matters having to do with arrangements for meetings, contributions for clinical research and similar joint projects.

With respect to the internal organization and operation of medical societies themselves, I have had experience as an officer in many of them at the State and local level. For the past 6 years I have been a member of the board of trustees of the American Society of Internal Medicine and president this past year.

In this position I have necessarily become familiar with the financial as well as all other aspects of the operation of these organizations. As the principal liaison officer. I have spent a great deal of time with the officers of other professional organizations in the health care field as well as with governmental agencies having to do with health care matters both at the national and State level.

I have been interested and active in the health insurance field for many years. This, of course, involves the insurance considerations related to the use of drugs as well as other matters pertaining to health care insurance. I am associate medical director of Mutual of Omaha and their consultant on medicare. Mutual is one of the fiscal intermediaries for the Department of HEW in this program as well as for the Department of Defense in the CHAMPUS program, formerly known as military medicare. I will be in Baltimore at SSA headquarters the next 2 days for a regional meeting of medical directors and consultants of the fiscal intermediaries for the medicare program. One of the important subjects we will discuss is the use of drugs and related materials in the program.

I have read many of the press releases and some of the official testimony given to this committee. If I can make any contribution which might be of help to you I believe it would be in the area of the relationships between the drug industry and organized medical societies and in the areas involved in the practical translation of medical scientific knowledge to the care of patients. I will be glad to answer any questions that I can.

PHYSICIAN RESPONSIBILITY

With respect to the prescribing drugs, I believe it is the physician's responsibility to be fully informed about any of the drugs he prescribes—the dose, the expected pharmacologic effects, side effects, toxicity and all similar matters. It is equally important for him to know his patient because the identical drug may produce an entirely different pharmacologic effect in one person than another. Dosage requirements and tolerances may vary widely in different patients and even in the same patient at different times. Treatment with drugs, as with all other modalities, should be highly individualized.

Physicians have an economic responsibility to their patients too, and some consideration should be given to the cost of drugs prescribed so long as cost is not the sole determining factor. If a cheaper drug will not accomplish the desired result, then obviously it is not cheaper

at all but really more expensive and the delay in obtaining the desired result might be harmful to the patient. Naturally, no prescribing physician should have any secondary financial gain in prescribing one drug or one brand as compared with another. He should always be guided by what he believes to be best for his patient.

Senator NELSON. In what way does the sole practitioner decide to prescribe one drug at a certain price and not another which may be equivalent?

Dr. LONG. In the final analysis, Senator, it is not the advertising or the claims of the pharmaceutical houses that determine what we prescribe. Myself and all the physicians whom I know, and have known over the years, decide what kind of a drug to prescribe and which drug, based upon our examining our patient, and talking with our patient, and prescribing for the patient, and then reexamining, reevaluating, and assessing the results obtained.

When we start out initially to prescribe a new drug for the very first time, this, of course, happens. Then we depend upon information we have obtained about this drug from reading in the scientific medical literature, from hearing about it at medical meetings as previously described this morning by Dr. Pollard, or by talking with our colleagues formally and informally as we meet together.

Senator NELSON. What I was getting at, if you have a cheaper drug which would not accomplish the desired result, then obviously it is not cheaper at all?

Dr. LONG. Yes.

Senator NELSON. To use the example I have used here before because it is based on the medical letter on prednisone, the price to pharmacies is \$17.90 for Meticorten and \$17.80 for Paracort. It drops down to \$2.45 for Merck, and then to \$1.80 and 50 cents for Wolins. And then the Letter said that the laboratory testing was done for them and all met USP standards, and that in their consulting with clinicians they found they were equivalent. On what ground would the doctor, the sole practicing physician, decide that, say, Meticorten, at \$17.90 to the pharmacist, was better than Merck's Deltasone at \$2.20? How does a physician practicing on his own make that decision?

Dr. LONG. A practitioner practicing alone makes a decision based on his results and his experience with the drug. And if he prescribes a certain drug, and in his hands it works well, and in his hands he can predict with reasonable accuracy how his patients will respond to it to given dosage levels, and can predict with reasonable accuracy, when, at what levels, and what periods of time he may be in trouble with side effects or complications or unwanted effects from the drugs, if he becomes, then, thoroughly familiar, I think it is understandable that he might be hesitant to change on the basis of price alone, unless and until the time comes that someone—and this does come to all of us in some instances—and I think prednisone is a good example—unless and until it can be shown and demonstrated to him on the basis of the experience of people in whom he has confidence, on the basis of reports in medical journals in which he has confidence, if then it can be demonstrated that an equivalent product at a lower price is in fact therapeutically equivalent, not just USP, which does not really mean much.

Senator NELSON. Pardon?

Dr. LONG. I think therapeutic equivalency is an entirely different matter than chemical equivalency.

Senator NELSON. Do I understand you to say that the USP standard did not mean very much?

Dr. LONG. It does not mean very much with respect to therapeutic results. Let us take the old common aspirin, for example, aspirin grains five, USP. You can find on the market lots of different kinds of aspirin, some at 9 cents a hundred, if you will, and some at 49 cents a hundred. And in some instances there is no difference, perhaps, between the 9 cents and 49 cents. But in other instances there is. Because there is a difference in the way the tablet is compounded, the disintegration rate, the permissible—even under USP standards the permissible variations in quantities of something other than pure acetylsalicylic acid may be permitted up to certain tolerances of purity. So that, therapeutically, equivalency is a good deal more important to the physician than the term USP alone. So I think perhaps I should change my statement to say that USP does not mean anything. It means a good deal, of course, because it does tell you about the chemical quantities that are in there, and the tolerance limits that are permitted for impurities, if you will, within a given product. USP does provide for that. But in addition to that, one needs to know something about biologic or therapeutic equivalency, which may be affected by many many things, as you know.

Senator NELSON. It is the position of the USP as well as many others, including Dr. Modell who testified here, that if a drug meets USP standards it is therapeutically equivalent until they find some evidence to the contrary. In other words, the best knowledge that the profession has, physicians as well as pharmacologists, is put into the USP standards, they may not have all the knowledge, but when something new is discovered they put it into the standard. So their position is that if it meets the standard it is therapeutically equivalent according to the best available expertise.

I notice you are shaking your head.

Dr. LONG. I do not agree, Senator.

Senator NELSON. Do you have a specific example of a case where two drugs meet the USP standards and were proven not to be therapeutically equivalent?

Dr. LONG. Oh, yes. FDA has that, for example, in chloramphenicol.

Senator NELSON. As an example, the FDA does not say they were not therapeutically equivalent. They just did not reach the same blood level. Dr. Ley will tell you that they did not have any test to find Chloromycetin vis-a-vis the two that did not meet the Chloromycetin level. There is no test to say that they are not therapeutically equivalent. So apart from that, FDA simply says there is no proof on therapeutically equivalency. Do you have another example?

Dr. LONG. I think there are many examples. I did not research this subject because I did not come prepared to testify on that particular line of testimony, Senator. But I can tell you, on the basis of my own experience, and on the basis of experience of many of my colleagues with whom I visited, that there are situations in which there is not therapeutical equivalency.

Senator NELSON. You say in your own experience. Do you have a case in which you had the drugs assayed, two drugs, and they both met USP standards, and they were not equivalent?

Dr. LONG. That is correct.

Senator NELSON. Testimonial proof or clinical proof?

Dr. LONG. This is clinical proof. In the final analysis, Senator—and this is really the only point I want to make—in the final analysis it is not what it says in the drug manufacturers' advertising. It is what does the patient tell you about how he feels after he has taken this drug or that. And it is the clinical examination of the patient by physical means, physical examination, and examination of the patient by laboratory means, if you will, in addition, the total evaluation of the patient. This to me is the therapeutic result. This is what happens to the guy who is sick.

Senator NELSON. Do I understand you to be saying that if you prescribed a particular drug—

Dr. LONG. Let us take a common one like aspirin. I treat a lot of people with arthritis. And I have over the years had many patients who on a given kind of aspirin—I cannot even tell you the name of it—let us say a cheap aspirin, if you will, or let us say a low-cost aspirin, if you will—and these patients with rheumatoid arthritis, for example, will take a dozen tablets a day, and do badly, they are just not comfortable, their joints are still stiff and painful and swollen, and then they will change to a different brand of aspirin—both of them plainly labeled USP—and they will immediately get relief from their symptoms on the same dose.

Senator NELSON. Did they meet USP standards, is the question. You recognize—

Dr. LONG. Let us say they are plainly labeled USP in both instances.

Senator NELSON. That is not the question, because we know that brand names and generic name drugs go into the marketplace lacking adequate quality control and supervision and they cannot meet USP standards. The testimony before the committee by USP and other distinguished pharmacologists is that if they meet USP standards they are therapeutically equivalent. I am asking did they, in fact, meet USP standards?

Dr. LONG. I have to assume so, if the manufacturer is following the labeling law. I have the impression that he is violating the law if he labels it USP and it is not USP.

Senator NELSON. Correct, and that is what is happening in both brand and generic names. And many of them are pulled off the market every year. But the real question we are getting at is—do you have a case? We have been seeking one. The reason I raise this, Doctor, is that we have been seeking one publicly in this forum for 2 years, and I would think that the manufacturers themselves would come up with an example. But they do not. And all I am saying is, do you have an example of two drugs meeting USP standards and not being therapeutically equivalent? I do not mean testimonials, because I do not think that means much. Do you have a case in which you have done double blind testing with an adequate sample and proved that the 20 drugs that were assayed to meet USP standards are not therapeutically equivalent? That is the case that we have not been able to get.

Dr. LONG. Well, as I say, I did not research this scientifically or in the medical literature. I am persuaded on the basis of my nearly 30 years of experience as a practicing physician, and my contacts with

hundreds and thousands of physicians, I am persuaded that there is something else besides chemical equivalency that has to do with therapeutic results in the treatment of patients.

Senator NELSON. I think the USP will say that. Of course chemical equivalency—that includes coating and tablet pressing and all that?

Dr. LONG. That is what I mean.

Senator NELSON. But USP insists, they take all the best available knowledge, based upon all of their consultants, and put into the standard, the best knowledge that is known today. They will concede that some better knowledge may come later, and then they will put it into the standard. But as to the standard today, until additional evidence is produced they say that if drugs meet USP standards they are therapeutically equivalent. And only in the rarest of circumstances has this not been true.

Dr. LONG. I wonder why the statement is always put that way? Why would you not say that they are not therapeutically equivalent until it is proven that they are?

Senator NELSON. The experience of the consultants and clinicians, pharmacologists, and authorities when they establish the standard is that if they meet the standard, they are equivalent.

Dr. LONG. I think this is not the consensus of the opinion in my experience, or in my contacts with practicing physicians who have been taking care of sick people day after day and week after week and month after month. That consensus of experience is that therapeutic equivalence and chemical equivalence are not always identical, that with the same dose of a given drug in the same patient for the same disease, that brand X, let us say, the therapeutic results are not the same as with brand Y, if you will. Now, this may be true in many instances, that X and Y will result in the same. But I think there are many other instances in which this is not true.

Senator NELSON. You see, the drug companies will argue, well, the coating will make a difference, the excipient will make a difference, the size of the granule will make a difference, how hard the tablet is pressed will make a difference. Everybody knows that.

Dr. LONG. Yes.

Senator NELSON. Including the USP. So they set a standard for dissolution, and the excipient, and so forth. And the amount of the active ingredient can only vary, depending upon again the consultation with the experts, it has to have X percentage of the active ingredient, and in aspirin it is 95 to 105 percent pure aspirin. And their consultants advise that if you get within that tolerance you get the same result. All I am saying is, we have been asking for proof of instances where they meet the standard and were not equivalent, and we have received testimonials, but we have received nothing scientific from the drug industry or from any clinician or anybody else, except what they state what their personal experience has been. Well, in that kind of case it might be very well true that maybe they did not meet USP standard. None of the testimonials we have had, in the case where the drug was assayed to see whether it met USP standards first—that is our problem, trying to get that kind of a case.

Dr. LONG. I think maybe if I read a little further I may answer your question in part, and then perhaps we will come back to it if you wish.

RELATIONSHIP OF PROFESSIONAL MEDICAL ORGANIZATIONS
TO THE PHARMACEUTICAL INDUSTRY

It is not only natural and inevitable but highly desirable that there be a close relationship between the pharmaceutical industry and the medical profession. This is essential in the public interest and necessary in order for us to provide the best care and treatment that we can for our patients. That is what we all want in the final analysis with the best care and treatment that we can get for our patients. We are providing professional services for our patients in the course of which we use drugs, biologicals, instruments, and supplies of various kinds. We need to know something about the companies that provide these materials.

At the same time, the drug, instrument, appliance, and other producers of materials used in health care need to know a good deal about the problems we practicing physicians have in using these materials in the care of patients. They need to know how and when and under what circumstances we use their products, and what the results are—both good and bad.

There is no way for us to find out what we need to know from each other without a continuing dialogue and exchange of information between us, in person as well as in writing. This necessarily takes place at an individual level, such as between the individual physician and the individual manufacturer's personal representative, and at an organizational level. The latter is particularly important because of the complex matter of logistics. There are more than 300,000 physicians and several hundred manufacturers. To provide the necessary exchange of information on an individual basis obviously would be impossible. To try to do it on the basis of a single publication or even a few would be as impractical as to try to do it on the basis of a single meeting. Each of us has to get our message to the other in many different ways.

The science of medicine, particularly as related to drugs and instrumentation as well as techniques, has advanced so far and so rapidly in the past 20 years that no one method of disseminating information, acquiring information, or translating it to the care of sick patients can suffice. It has become necessary for many different techniques and many different organizations to be developed to do the job.

Just as we are all dependent on each other in the philosophic and scientific sense in the pursuit of our common goal, it necessarily follows that there is a certain amount of financial interdependence too. It costs money to do research, to produce a drug or an instrument, to publish literature, and to have a meeting. It seems natural and logical that a manufacturer of drugs would provide information about his products in a magazine or journal published and read by physicians. In the same journal, of course, medical scientific information is transmitted from one physician to others. So long as the advertising and the medical scientific information in the articles written by the physician-authors is ethical, accurate, and honest then the best interests of the public are being served.

It is not the advertising campaign of the drug manufacturers, nor their contributions to medical organizations for scientific or social affairs that convinces the practitioner of the virtues or safety of a new or old drug, but only his own personal experience gained from listen-

ing to and examining his patients and his knowledge of the experience of his colleagues.

I hope that this very sincere and dedicated committee will not be diverted in its efforts to help identify and solve some of the troublesome socioeconomic problems related to the health care field by those few persons who presume to see some sort of collusion between the drug industry and practicing physicians which they believe exists to take unfair advantage of the public. Believe me, gentlemen, there is no exchange of material goods or services or money that I know of which is contrary to moral or statutory law or ethics.

NATIONAL DRUG COMPENDIUM

The matter of publication of a national drug compendium has been discussed at length and in detail by medical, governmental, and other organizations for several years. The consensus of opinion of practicing physicians generally is, I believe, that such an effort would not be desirable, practical, useful, or in the public interest. If such a book were to be all-inclusive, several volumes more than 3 inches thick would be required. It would have to be loose leaf and updated regularly and frequently. It would have to be compartmentalized for the best use of the different medical specialties, yet there is sufficient overlap in all that there would have to be some duplication of entire. It would, indeed, be difficult to find any agency or group of physicians, however knowledgeable, who could put such a mass of information together in readily usable form.

By the time it was published and distributed, much of the information would be outdated. The editors would not dare put in anything too new, yet much of the new is very good and useful as time and experience later prove. It would be difficult to leave out some of the old, yet much of it is outdated or so very well known generally that it would be in the way.

However much disclaimed, if published by or with the approval of the Government, the material contained in it would be interpreted as having legal Federal sanction. Then if a drug were used in the treatment of a condition not listed in "the book," or in a different dosage range, the physician might be presumed guilty of malpractice.

Conversely, if a drug were listed as useful for a certain condition and the attending physician did not use it even for very good and acceptable reasons, then he might also be presumed guilty.

A further disadvantage would be its use as a lever to impose compulsory prescribing by generic name. This simply cannot be, in my opinion, handled by the majority of practicing physicians. All of us prescribe some drugs by generic name, but we cannot possibly remember all of the generic terms for all the drugs we are accustomed to prescribing. To be required to look them up in "the book" would use up too much valuable time and would further aggravate our existing health-manpower shortage.

Further, and more importantly, a compendium would further confuse the question of generic equivalence. We have already found out, as has the FDA, that drugs identified as being the same generically are not always the same clinically.

Senator NELSON. I am not familiar with what the FDA found on that point.

Dr. LONG. I do not have the citation with me. All I can tell you is that I have read this. And as I say, I did not come prepared to discuss that in detail. But I have read this in what I consider to be a reliable and authoritative publication.

Gentlemen, the last book on therapy has not yet been written. What person, or committee, or agency is to say with finality that this or that vitamin is better than another, that this or that antibiotic should or should not be used, that the dosage range of this or that drug is from here to there but no less and no more, that this or that drug is very good for this condition but must never be used for that? I can think of nothing worse for the health and care of the American people than for individual physicians to be compelled, directly or by implication, to treat their patients according to a majority vote of a committee of other physicians or scientists, however honest, capable, and sincere the members of that committee might be.

Treatment must be individualized and scientific areas where preciseness of measurement is almost nonexistent should not be highly regulated. Pharmacology, toxicology, absorption factors, excretion factors, blood levels, bacterial sensitivity studies in the test tube and the like fail to inform us really of what drugs do at the cellular level. Until we have better methods for making such determinations, these studies, while necessary and important, are only gross guides for drug therapy. There are no "standardized" patients and I do not believe there can be any "standardized" drugs to meet their needs.

Previous testimony before this committee indicates that more than 90 percent of prescriptions filled called for a product by brand name or the product of a particular manufacturer in whom the physician had placed his confidence. It also has been stated here that 86 percent of the dollars spent by the Federal Government went for the purchase of products of brand name manufacturers when all the testing and elaborate screening procedures were completed.

Physicians, depending on manufacturer integrity to secure the highest quality medicines for their patients—and Government, refusing to accept anything except scientific proof of quality—both arrived at the same drug counters to secure healing agents for those for whom they were responsible.

DRUG LABELING FOR PATIENT

The matter of labeling prescription drugs dispensed to a patient is a highly individual matter and often involves medical judgment which only the attending physician who knows his patient should exercise. I hold no brief for the physician who labels a bottle of medicine "take as directed," unless those directions are given in writing to the patient by the physician. This is necessary in certain situations. It is my own practice to identify the name of the drug, the dosage schedule, and the purpose for which it is prescribed in most instances. Even here, there are exceptions. For example, there are certain patients who develop so much anxiety from seeing the name of a drug on the bottle when the possible harmful side effects of that drug have been discussed in recent newspaper and magazine articles, that it is better for them just not to know the name of it.

Again, the doctor has to know his patient and act accordingly. A patient should almost never be given the usual "package insert" to read. They already have enough anxiety about their condition without be-

ing frightened by reading information which they cannot possibly interpret properly without a medical background.

One other item that I do not have in this written statement. Sometimes when medicines are labeled to exactly what they are, it is quite surprising sometimes how often patients prescribe for other patients, or they exchange medicine, when the name of it is on the bottle. And there has been an article by one of the columnists in the newspaper telling how, for example, some friends, neighbors, grandma, a relative, or someone else, say, you have got some of that so-and-so medicine, I should take some, and how in that respect sometimes people take drugs that they should not be taking because their friend has it and they saw the name of it and recognized it from some article in the lay press.

So that is one disadvantage. I think there are many advantages, but there is occasional disadvantages that I have run into.

From the testimony given here previously as I have read it, I believe most witnesses and also this committee recognize the advantages and disadvantages of generic prescribing and everyone is generally agreed that the attending physician has the privilege and the duty to prescribe what he believes to be best for the particular patient in the particular circumstances which exist at the time the decision must be made and that dispensing pharmacists should never make substitutions for the specific preparation prescribed.

I will be glad to answer any questions I can. Thank you for your kind attention.

Senator NELSON. Just so that it will be clear, I think, no witness that has testified here has suggested that the physician should not be able to designate the manufacturer or the brand.

Dr. LONG. Yes, I read your statement in the testimony to that effect.

Senator NELSON. Thank you very much, Doctor, for taking time from your busy schedule to come here and testify. It has been very helpful to the committee. Thank you.

Dr. LONG. Thank you, sir.

Senator Nelson. The committee will meet at 10 o'clock tomorrow morning in room 4221, the Foreign Relations Committee room.

(Whereupon, at 12:10 p.m., the subcommittee was recessed, to reconvene at 10 a.m., Wednesday, March 26, 1969.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

WEDNESDAY, MARCH 26, 1969

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

The subcommittee met, pursuant to recess, at 10:10 a.m., in room 4221, New Senate Office Building, Senator Gaylord Nelson (chairman of the subcommittee) presiding.

Present: Senators Nelson and Dole.

Also present: Chester H. Smith, staff director and general counsel; Benjamin Gordon, staff economist; and Elaine C. Dye, clerical assistant.

Senator NELSON. Our witness this morning is Dr. Maynard I. Shapiro, president of the American Academy of General Practice.

Dr. Shapiro, the committee is very pleased to have you take time from your busy schedule today and appear before the committee.

STATEMENT OF PETER CHUMBRIS, CHIEF MINORITY COUNSEL OF THE ANTITRUST AND MONOPOLY SUBCOMMITTEE, COMMITTEE ON THE JUDICIARY, U. S. SENATE

Mr. CHUMBRIS. Good morning.

My name is Peter Chumbris, I am chief minority counsel of the Antitrust and Monopoly Subcommittee of the Senate Judiciary Committee, and I am appearing here this morning on behalf of Senator Dirksen and Congressman Annunzio to introduce to you the witness, who is from the State of Illinois, Dr. Maynard Shapiro, president of the Academy of General Practice.

Dr. Shapiro is a very highly professional gentleman and highly respected gentleman in his community. And it gives me great pleasure to introduce him to you this morning.

Senator NELSON. Thank you very much. He comes here with very distinguished credentials and we are pleased to have you, Doctor, why don't you introduce your associates for the purposes of the record, and then if either of them wishes to comment, see that they identify themselves so that the record will be straight.

STATEMENT OF DR. MAYNARD I. SHAPIRO, PRESIDENT OF THE AMERICAN ACADEMY OF GENERAL PRACTICE; ACCOMPANIED BY MAC F. CAHAL, EXECUTIVE DIRECTOR AND GENERAL COUNSEL; AND WALTER KEMP, SECRETARY, COMMISSION ON PUBLIC POLICY

Dr. SHAPIRO. With me today on my right is Mr. Mac F. Cahal, executive director and general counsel of the academy. And on my left, Mr. Walter Kemp, secretary of its Commission on Public Policy.

Senator NELSON. Your statement will be printed in full in the record.

Did you submit a separate statement of biographical data, or did you wish to present anything in that regard?

Dr. SHAPIRO. That can be submitted, Mr. Chairman.¹

Senator NELSON. If you wish, we would be pleased to print it in the record preceding your statement.

Dr. SHAPIRO. Thank you.

Senator NELSON. You may proceed to present your statement in any way you desire. If you wish to depart at any time to elaborate on anything you have said, feel free to do so. I assume you have no objection if we interrupt occasionally with questions, and if your associates wish to comment at any time, they are free to do so.

Dr. SHAPIRO. We have abbreviated this statement to the maximum extent, Mr. Chairman, and possibly the flow of our prepared testimony would be best uninterrupted. However, I have no objection if it is necessary for clarity to stop at any time.

Senator NELSON. Very well.

Dr. SHAPIRO. Mr. Chairman, I am Dr. Maynard I. Shapiro, a family physician with offices at 7531 Stony Island Avenue in Chicago. I am also clinical associate professor of medicine at Chicago Medical School and director of medical education at Jackson Park Hospital. I am a member of the Medical Assistance Advisory Council of the Department of Health, Education, and Welfare. I am here today as president of the American Academy of General Practice. The academy is the Nation's second largest medical association and presently has more than 31,000 members.

I have not read all or even most of the testimony presented since your committee hearings started almost 2 years ago. I will not pose as an expert on all health care matters but I can and do speak as a practicing family physician who is primarily concerned with people—be they healthy, ill, injured or infirm.

Your letter asked for information about the academy, its membership, its admission requirements, its publications, its advertising acceptance criteria, its advertising revenues and its other financial relationships with the drug industry. The letter closed with a suggestion that I comment on drug compendium proposals. I will attempt to give you the information you have requested and then add a few comments—in my official capacity as president of the academy.

To become an active member of the academy, a physician must be engaged in the general practice of medicine, be a graduate of an approved medical school, be duly licensed to practice medicine and be a member of his State medical society. But, to remain a member, he must complete 150 hours of academy-approved postgraduate study every 3 years. The academy is the only national medical association which requires continuing postgraduate study.

This should adequately illustrate the academy's continuing determination to maintain high health care standards. As another example, most recently, the academy, in conjunction with the section on general practice of the American Medical Association, has been successful in its determined efforts to establish an examining board for family practice. This board will certify to the competence of family physi-

¹ See pp. 4786-4788, *infra*.

cians who render the major portion of medical services delivered in this country today. We believe this latest development will swell the ranks of family physicians, an increase which is sorely needed in order to assure the availability of continuing comprehensive health care for the people of America.

The academy publishes two journals, both primarily scientific.

Senator NELSON. Would you name the two, Doctor?

Dr. SHAPIRO. GP and the American Family Physician.

Senator NELSON. I do not recall that you recite any place in your statement the circulation of each—or do you?

Dr. SHAPIRO. GP is circulated to members on a subscription basis. The American Family Physician is circulated to all nonmember general practitioners in the country.

Senator NELSON. Is that by subscription?

Dr. SHAPIRO. No, sir.

Senator NELSON. Is the GP by subscription?

Dr. SHAPIRO. Yes, sir.

Senator NELSON. And the one that is circulated to all family physicians is the American Family Physician?

Dr. SHAPIRO. Yes, sir.

Senator NELSON. And that is in the form of a newspaper?

Dr. SHAPIRO. No, sir; it is a journal.

Senator NELSON. The circulation is a total of how much, just in round figures?

Mr. CAHAL. It is about 40,000. And GP is about 32,000.

Senator NELSON. Thank you.

Dr. SHAPIRO. Mr. Chairman, the American Family Physician contains the leading scientific articles from GP. But the difference in the two magazines is that GP contains much Academy information.

Senator NELSON. Much Academy information?

Dr. SHAPIRO. Yes, sir.

Senator NELSON. What do you mean by that?

Dr. SHAPIRO. Reports from chapters, reports on postgraduate courses for Academy members, things of that type.

Senator NELSON. Are they separately edited and printed?

Mr. CAHAL. Mr. Chairman, GP is the official journal of the American Academy of General Practice, and as Dr. Shapiro stated, it goes on a subscription basis to all Academy members 31,000 and about 1,500 nonmember subscribers, including libraries, et cetera.

American Family Physicians is actually a reprint of the leading scientific articles which have appeared in GP magazine. American Family Physician goes to all general practitioners in the United States under age 65 who are not members of the Academy, who have not maintained the 150-hour postgraduate training requirements. The combined circulation, therefore, is around 70,000.

GP contains internal business matters pertaining to the organization. American Family Physician does not.

Senator NELSON. On that point, the GP is supported by subscriptions. Is the American Family Physician supported by advertising?

Mr. CAHAL. It is not self-sustaining. It takes advertising, but it is not fully supported by that revenue. The Academy subsidizes it from its general revenues.

Senator NELSON. What percent is the subsidy?

Mr. CAHAL. Well, we have lost about \$100,000 a year on it in recent years.

Senator NELSON. That is what percent of the total cost of getting it out?

Mr. CAHAL. I am afraid, Senator, I would only hazard a guess, but I would be glad to look that up and communicate with the committee secretary if you wish. I would say roughly its total revenues are probably \$300,000, and it costs approximately \$400,000 to publish. But this is a hazardous guess on my part.

Senator NELSON. Could you submit that for the record?

Mr. CAHAL. I shall be glad to, sir.¹

Senator NELSON. Thank you. You may continue, Dr. Shapiro.

Dr. SHAPIRO. One magazine goes to American Academy of General Practice members, the other goes to nonmember family physicians. Advertising is screened by a group of physicians, all of whom we considered qualified to perform their task. We do not list the names of these physicians in our magazines because we believe they prefer a degree of anonymity. All are medical school faculty members and all, in our opinion, are well qualified to screen pharmaceutical advertising.

In your letter, you asked about Academy income from pharmaceutical advertising. Exact figures would take substantial digging because our advertisers include equipment companies, book publishers, and so forth. However, it would not be far off to say that our drug industry advertising income has run between \$1 million and \$1.5 million a year since 1962.

Our total advertising revenues—from both publications and including nondrug advertising—are as follows:

1962, \$1,155,000; 1963, \$1,236,000; 1964, \$1,493,000; 1965, \$1,587,000; 1966, \$1,725,000; 1967, \$1,538,000; for 11 months, because the fiscal year ended on November 30, 1968.

Senator NELSON. But your books do not show a breakdown by source?

Mr. CAHAL. Yes, Mr. Chairman, our annual financial statements show the revenues from subscription versus advertising. This is only advertising revenue, though, that Dr. Shapiro has given.

Senator NELSON. That is what I was inquiring about. What amount is pharmaceutical industry, what amount is books, and what amount is surgical instruments, and so forth?

Mr. CAHAL. As a matter of fact, our financial records do not segregate those classifications.

Senator NELSON. We have a breakdown done by the Library of Congress, but it is only for the American Family Physician. I will submit it for the record. We did not get it from them on the GP. This one shows that in terms of space, we do not know what the dollars are, but in terms of space—drug advertising—as a percent of all advertising in 1967, was 91.5 percent.²

Mr. CAHAL. That would be my guess also.

Senator NELSON. Do you have a figure on what percent of total income all advertising is, percent of total income for the Academy?

Dr. SHAPIRO. Approximately 50 percent.

¹ See pp. 4781–4786, *infra*.

² See app. XIII, "A Study of Pharmaceutical Advertising in Selected Medical Journals," pp. 4863–4998, *infra*.

Senator NELSON. Fifty percent of the total income of the Academy is advertising?

Dr. SHAPIRO. Yes, sir.

Senator NELSON. And the rest is——

Dr. SHAPIRO. Dues.

Senator NELSON. Do you have, as a number of the other organizations, have, revenue from displays at conventions, for example, by the drug industry?

Dr. SHAPIRO. We do have, but our conventions are always a loss.

Senator NELSON. But you do have have an income from that source from the pharmaceutical industry?

Dr. SHAPIRO. There is an income for exhibit space which only partly displaces the cost of our meeting.

Senator NELSON. Do you have a figure on the amount of that income?

Mr. CAHAL. It approximates in recent years \$108,000, the gross revenue from the sale of exhibit space at our annual convention. As Dr. Shapiro has pointed out, this is about half of the annual convention.

Senator NELSON. And what percentage of that \$108,000 would be pharmaceutical advertising?

Mr. CAHAL. I would guess, Mr. Chairman, that ratio would be lower than the one for advertising in the journals. And I would estimate that the revenues for exhibit space for drugs is 70 percent at the annual convention, the balance being other classifications.

Senator NELSON. The figure we discussed a moment ago from the Library of Congress, 91.5 percent for advertising in the American Family Physician, is that roughly an equivalent percentage of the advertising in the GP.

Mr. CAHAL. I would imagine, sir.

Senator NELSON. Apart from advertising and exhibits, are there any other funds from the drug industry?

Mr. CAHAL. No, sir; there are no other revenues from any source except the sale of supplies to members.

Senator NELSON. Any other from the drug industry of any kind?

Mr. CAHAL. No other sales to the drug industry.

Senator NELSON. Or any other grants or scholarships or research, and that sort of thing from the drug industry?

Mr. CAHAL. Occasionally, Mr. Chairman, there are grants from pharmaceutical companies to endow a speaker at a meeting. Or, for instance, Mead Johnson & Co. makes a grant to the Academy which is used to subsidize preceptorships, medical students who go out and spend a portion of their time with practicing family physicians. This is a grant from Mead Johnson & Co., a pharmaceutical company. We have had occasionally grants of that nature.

Senator NELSON. Thank you.

Go ahead, Dr. Shapiro.

Dr. SHAPIRO. Mr. Chairman, in this next paragraph we have some changes in the arithmetic which are substantial. This was our error in calculating. I will read them correctly.

If our drug advertising income averaged out at \$1¼ million per year, it is then reasonable to state that the pharmaceutical industry supports our publishing efforts to the extent of approximately \$18 per family doctor per year.

Senator NELSON. This is in place of the figure \$41?

Dr. SHAPIRO. Yes, sir.

Senator NELSON. And when you say family doctor, are you talking about all family doctors in the country?

Dr. SHAPIRO. Yes, sir.

Senator NELSON. What is the total of the family doctors by that mathematics?

Dr. SHAPIRO. 68,000.

Senator NELSON. And your publications go to about 40,000 of those?

Dr. SHAPIRO. No, sir. We cover them all. GP goes to 32,000 and the American Family Physician goes to the remainder.

Senator NELSON. There is no duplication?

Dr. SHAPIRO. No, sir.

With this \$18, what can we do for the individual doctor? We can deliver, to the door of his office or his home, about 84 original scientific articles and 240 well-edited abstracts. We can also tell him about the government medical programs and about hundreds of postgraduate study programs. In short, we can provide him with more useful information than we could if we sent him a first-class letter every day. We think it is \$18 well spent—by both the Academy and the pharmaceutical industry.

Allow me to touch on another point which involves liaison between the Academy and the pharmaceutical industry. In January, we started publishing a six-installment course on the "Diagnosis of Diabetes." The course was programmed to our specifications by a firm in New York City. However, it was made possible by a no-strings grant from the Upjohn Co.

What does Upjohn get for its money? A small credit line, a letter of appreciation, hopefully some satisfaction—and that is about all. Please note that the course is concerned only with the diagnosis of diabetes—not the treatment of diabetes.

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

Dr. SHAPIRO. Yes.

Senator NELSON. What would your view be of the reason for Upjohn sponsoring such a program if there is not any credit in doing that?

Dr. SHAPIRO. As an important cog in the health team, the pharmaceutical industry feels that this is necessary. They are totally involved in continuing education.

Senator NELSON. The only question I would raise—and I do not say that there are no public spirited people in all industries, I am sure there are—but tolbutamide is Orinase, is it not?

Dr. SHAPIRO. Yes, sir.

Senator NELSON. And that is the only drug of its kind in the marketplace, is it not? There is no other tolbutamide but Orinase?

Dr. SHAPIRO. Not to my mind.

Senator NELSON. So would it be fair to say that there is a benefit in the promotion of their drug Orinase?

Dr. SHAPIRO. There would be an indirect long-range benefit to them as well as to all other manufacturers of oral antidiabetic drugs, or insulin. Basically we are hopefully uncovering unfound diabetics who must be treated, not necessarily by Upjohn's product.

Senator NELSON. I know. But Orinase is the only tolbutamide in the market, and it is under patent, and it is only made by Upjohn.

And is it not correct that if they can establish the name Orinase widely in the mind of the physician in the 17-year period of the patent protection then there is an expectation on their part that when the patent runs out the doctor will continue to prescribe under the brand name of Orinase.

Dr. SHAPIRO. But Orinase is only one of the antidiabetic agents.

Senator NELSON. But it is the only tolbutamide?

Dr. SHAPIRO. Yes, sir.

Senator NELSON. So if the doctor wants to use tolbutamide and the company has established it under its brand name Orinase, and the doctors have been writing Orinase for 17 years, and the patent runs out, isn't it the hope of the company and the expectations based on experience that the physician will continue to write Orinase even after the patent has run out? That is my point.

Dr. SHAPIRO. Possibly, yes. But my point, then, is that this will not alter the percentage of the number of diabetics that are being treated by their medication. There is also Diabinese, or DBI, and other agents available to us.

Senator NELSON. I realize that. But isn't there expectation—that is part of the advertising program—that when any doctor desires to use tolbutamide, after 17 years of advertising and prescribing by the name Orinase rather than by the name tolbutamide, that when the patent runs out and competition comes into the marketplace they could maintain a better position than they otherwise could, because the doctor will continue to write the name Orinase, or at least a good percentage would; isn't that the expectation?

Dr. SHAPIRO. I believe so, yes.

Senator NELSON. I just wanted to point that out, that there certainly are additional reasons other than the desire to promote continuing education. There is a very good, sound selfish reason for this kind of program.

Dr. SHAPIRO. However, Mr. Chairman, this sales pitch for their product will not be included in this series.

Senator NELSON. Upjohn is identified with the product, and everybody there will know it is Orinase, won't they?

Dr. SHAPIRO. There is no product. This is on the diagnoses of diabetes.

Senator NELSON. But it is Upjohn that sponsors it?

Dr. SHAPIRO. Yes, sir.

Senator NELSON. All right.

Mr. CAHAL. Mr. Chairman, it is not Upjohn that sponsors it. The articles are prepared by the medical editorial staff of GP magazine. A company is employed in New York to structure this in programmed learning. This is an innovation in medical teaching of the American Academy of General Practice. The series is not sponsored by Upjohn.

Senator NELSON. I meant paid for, rather.

Mr. CAHAL. A small portion of the total cost is paid for with the grant, no strings grant from Upjohn. There is no reference to it in the article.

Senator NELSON. How much is the grant?

Mr. CAHAL. Mr. Kemp?

Mr. KEMP. \$36,000.

Senator NELSON. Did you say this is a four-part program?

Dr. SHAPIRO. Six installments.

Senator NELSON. Over a period of how many months?

Dr. SHAPIRO. Six months.

Senator NELSON. Please go ahead.

Dr. SHAPIRO. There will be no "plugs" for Upjohn products, no waving of banners, no coupons, no sales pitch, nothing commercial at all. Is the cost of this program part of the \$3,000 per doctor that the pharmaceutical industry is supposed to spend each year? I do not know. Also, I do not know if it is always possible to draw a line between (a) the educational and (b) the advertising efforts of the pharmaceutical industry.

To my personal knowledge, there is no other industry that spends a larger share of its dollars not only on research but on professional education.

Senator NELSON. How much do they spend on research?

Mr. CAHAL. Are you referring to the industry?

Senator NELSON. Yes.

Mr. CAHAL. This figure has been produced in testimony before this committee, I believe, but I do not have it at my fingertips.

Dr. SHAPIRO. Not on research alone.

Senator NELSON. We have never been able to get from the companies a real breakdown on research. We do not know whether they consider detail men part of the research and promotion and advertising. We really have not been able to get that. And the assertion is made continually by the industry that they spent more on research than anybody else. And then we have distinguished people like you appearing and saying they spend more on research than everybody else, but we cannot get anybody to tell us exactly what it is and what kind of research. That is our problem. I wonder where you got the information that they spend more on research than anybody else?

Dr. SHAPIRO. I do not have any figures on this, Mr. Chairman. But having visited many varied industries, including the pharmaceutical industry, I am very much impressed myself on the amount of their plant that is earmarked for research.

Senator NELSON. The only witness we have had who would have reason to have knowledge was Mr. George Squibb, who said it was about 6 percent. And that is not a tremendous percentage.

Dr. SHAPIRO. You raised the point yourself, Mr. Chairman. If we were to follow their annual financial reports, they show the portion of their income that is earmarked for research. But as you mentioned, we do not know where they draw the line, where research ends.

Senator NELSON. That is right. We have had other independent industries claim they are doing great things in research, but when you go to breaking it down we found out that it really does not qualify as research. I would be very pleased to have the industry—I guess we will have to ask them again—come in and just say, here are the dollars, and here is the breakdown, and here is the kind of research, and here is how much we spent. But as many hearings as we have had I do not think either the late distinguished Senator Kefauver or anybody else ever got from the industry anything other than this assertion.

I notice that the very authoritative and distinguished Task Force on Prescription Drugs Final Report states on page 8:

Since important new chemical entities represent only a fraction—perhaps 10 to 20 per cent—of all new products introduced each year, and the remainder

consists merely of minor modifications or combination products, then the Task Force finds that much of the drug industry's research and development activities would appear to provide only minor contributions to medical progress. We likewise find that to the extent the industry directs a share of its research program to duplicative, noncontributory products, there is a waste of skilled research manpower and research facilities, a waste of clinical facilities needed to test the products, a further confusing proliferation of drug products which are promoted to physicians, and a further burden on the patient or taxpayer who, in the long run, must pay the costs.

Doesn't that strike you as a rather powerful indictment of the claim for the research by the independent industry?

Dr. SHAPIRO. It sounds very condemning.

Senator NELSON. That is the Task Force on Prescription Drugs composed of some very distinguished people. And this was issued on March 16, 1969.

Dr. SHAPIRO. I have no knowledge of this report, Mr. Chairman. It comes to my mind that possibly something that you read is a little out of context, and could be qualified. I do not know the report, I am very sorry.

Senator NELSON. This is the summary. And we would be entitled to go back, of course, and check the basis of their finding. But this is the finding that they made.

The thing that is disturbing to me, just as an observer, is how often it is asserted by representatives of the medical profession that no other industry in the United States invests more in research than the drug industry, which is the drug industry line, yet no one from the medical profession can ever explain how they came to that conclusion except that they are repeating what the pharmaceutical manufacturers said. Doesn't that bother you a little bit?

Dr. SHAPIRO. In that context, yes, Mr. Chairman. But having been out of school now for a little over 30 years, and watching the great innovations and the changed health care so completely, this came from some place.

Senator NELSON. The statement came from the pharmaceutical manufacturers.

Dr. SHAPIRO. I mean the progress that we have enjoyed. It did not just grow like Topsy, someone had to do it. We know it has been done.

Senator NELSON. No witness before the committee of which we have had a large number, has ever said that the industry has not made a valuable contribution in terms of research, and neither has any member of this committee said that. The committee is concerned about overdrawn claims. And when we have tried to chase this one down we never can get the answer. But the task force, which is a very distinguished group, makes a rather telling indictment of some of the kind of research and dissipation of money and presumed valuable research that the industry makes. That is my point.

Dr. SHAPIRO. We have no further information. As a matter of fact, you have more information than we have.

Mr. GORDON. Mr. Chairman, may I interrupt for a moment?

Dr. Goddard on April 6, 1966 at Boca Raton, Fla., at the annual meeting of the Pharmaceutical Manufacturers' Association said this:

Let me begin with investigational new drugs. I can say that I have been shocked at the quality of many submissions to our IND staff. The hand of the amateur is evident too often for my comfort. So-called research and so-called studies are

submitted by the cartonful, and our medical officers are supposed to take this all very seriously.

This confirms what the task force says about the quality of research.

Dr. SHAPIRO. That is, I believe, why we have regulations to control the releases. And they are good.

Senator NELSON. Please continue.

Dr. SHAPIRO. Allow me to comment on drug compendium proposals and make a point that perhaps has been overlooked in previous pro and con discussions. Think for a moment, please, about the use to which physicians put drug compendia. The drug compendium is not a catalog and thus does not serve the purpose that a catalog serves.

When you and I consult a catalog, mail order or otherwise, we expect to find that each item comes in a variety of shapes, sizes and colors—and we choose the one we want. On the other hand, a doctor does not normally use a drug compendium to help choose between products A, B, C and D. Instead, he uses it to check out a drug he already expects to prescribe; to review, if necessary, the contraindications, et cetera. This does not mean that he never changes his mind after consulting a compendium but this happens only occasionally.

In short, the compendium is a reference book—not a catalog. In this connection, let me make one more point quite clear: If a physician knows nothing about a drug, he is most certainly not going to prescribe it simply on the basis of compendium listing—no matter how many compendia are available or who published them. As an aside, I hope that my own health and well-being are never entrusted to a physician who feels he must consult a drug compendium every time he writes a prescription. So a compendium is a reference volume—nothing more.

How, then, do we learn about drug products? We read, listen, observe—and discuss. I read many scientific articles—not all of them but as many as possible of the ones that I consider of value to a physician in active family practice. I attend medical symposia and other meetings and I talk to my colleagues and detail men—about whom I will comment in a moment.

In other words, gentlemen, drug compendia are not an integral part of my drug therapy education. The scientist has his book of mathematical functions, the physician has his compendium. Both are useful, both are valuable—but neither is a substitute for knowledge.

I hope I have made this point clear because perhaps you will then understand why I see no urgent need for still another compendium.

Senator NELSON. Do we have an authoritative, objective compendium available now?

Dr. SHAPIRO. I believe I touch on this further on in the testimony, Mr. Chairman, I make reference to the AMA. May I continue?

Senator NELSON. Yes, sir.

Dr. SHAPIRO. In the months that have passed since the compendium proposal was first mentioned, I have not had a single colleague tell me that he thinks we need another compendium. So if there is no demand, isn't it then a bit unfair to suggest that the drug industry spend \$6 million for an item that physicians do not seem to really want or need?

Senator NELSON. I might say on that, Doctor, that the proposal that Dr. Goddard made was that the \$6 million that was spent on the package insert be used for the compendium, and that the package

insert not be required, since the physician does not see the package insert very often; it goes to the pharmacist.

Dr. SHAPIRO. The package insert has not done a great deal for me, Mr. Chairman. I can read everything I want to except the package insert, and that is why I got these glasses. The printing is so fine and everything is so piled on a thin piece of onionskin that it is difficult to handle.

If the Government does decide to publish its own compendium, I am afraid that the printed product will not be of substantial value or use to the practicing physician. It will be little more than a collection of package inserts, neatly bound together but almost unreadable. When you start listing every adverse reaction to every listed drug—such as one minor skin lesion in 10,000 patients—you cannot emerge with anything but a tome.

Senator NELSON. Doesn't the doctor when he checks on the drug want to know all adverse reactions? If the doctor is going to prescribe a drug, doesn't he want to know all indications and all adverse reactions?

Dr. SHAPIRO. Yes, sir.

Senator NELSON. Then what is his objection to having it in the compendium?

Dr. SHAPIRO. You are assuming that a doctor will prescribe a drug from a compendium. And my assumption is that he will not, he will have the information that he needs before he will consider using a drug.

Senator NELSON. Where does he get the information on all the drugs that he might need?

Dr. SHAPIRO. He does not use all the drugs.

Senator NELSON. Where does he get the information on all of those that he does need?

Dr. SHAPIRO. As I have covered already in this testimony by reading proper scientific articles, attending meetings, symposiums, discussions with colleagues, hospital staff meetings.

Senator NELSON. You have been told by a number of physicians that a lot of them rely on PDR, for example?

Dr. SHAPIRO. To that extent, I question very much. I use PDR for one specific function. In being cost conscious for my patients, I usually check PDR to see what the trade size package is, and I usually prescribe that amount. This enables the pharmacist to merely add a label to the trade size package, and not use another bottle. I have found that if a liquid item is supplied in, say, 60 cc. form, and I write for 40 cc., the patient will be charged with the full 60 cc., and I am cost conscious for all my patients. This is the major use that I put to the PDR.

Senator NELSON. I do not know what the compendium would answer, I am not an expert in that, of course, or anything in this field. But I quote from the final report of the Department of Health, Education, and Welfare's Task Force:

We find that few practicing physicians seem inclined to voice any question of their competency in this field of therapeutics. We also find, however, that the ability of an individual physician to make sound judgments under quite confusing conditions is now a matter of serious concern to leading clinicians, scientists and medical educators. A distinguished pharmacologist, for example, has stated that lack of sophistication in proper use of drugs is perhaps the greatest deficiency of the average physician today.

Do you have any comment on that? In other words, they are saying that there is something wrong here.

Dr. SHAPIRO. There is a need, Mr. Chairman, for continuing education in therapeutics and drug use. We in the Academy are attempting to do this through a section in our journal called Practical Therapeutics. The results that appear in print are not always complimentary to the drug or the pharmaceutical house. We attempt to give the doctor basic information that he can use. We have run editorials on drugs—the thing that sticks in my mind right now is that we had run advertising for Merrell and MER-29, and of course when this thing blew up and it was known in the market, we were one of the first journals to run a full editorial on this and bring all the information to the physician, those who had not possibly read the letter that was mailed out. The need for continuing education is great here, this I will not question at all.

You are aware that the American Medical Association is publishing a compendium for physicians. I do not know when copies will be available but I would want to examine it in detail before planning still another compendium.

Senator NELSON. But there is not now a general compendium.

Dr. SHAPIRO. I believe some portion of this has already been published, I have not seen it.

Senator NELSON. You mean a total compendium?

Dr. SHAPIRO. Not yet.

Perhaps prices should be included, but this is not necessary, because when the doctor needs price information, he can obtain this information from a pharmacist. To satisfy this need and obtain information on actual costs, I keep a copy of the pharmacists' Red Book in my office. In short, there seems to be no real need or demand for another compendium of the kind that has been proposed.

Please also remember that most physicians do not prescribe on a strict cost basis—for the same reason you do not shop around for a bargain-basement doctor. It is not my intention to become involved in the generic-equivalency debate because I am not a pharmacologist, but as a practicing family physician I am certainly quality-conscious.

Allow me to give you an example. A doctor knows that product X is manufactured by the ABC company, a first-line pharmaceutical firm that each year spends millions of dollars on research. He has read two or three articles by eminent physicians who have used product X and found that it is effective. He has also talked to colleagues who have prescribed product X for patients with similar conditions.

On the basis of the results they have obtained, which correlate with his findings, he determines the best product to prescribe. Would you then expect him to prescribe product X—or a so-called generic equivalent that is supposed to be "just as good" or "almost as good"?

If the patient happened to be your wife—or one of your children—would you want your doctor to prescribe a product in which he has less than complete confidence? Medicine does not lend itself to either production lines or bargain-basement economics and I would certainly not want anyone to tell me when to prescribe, how to prescribe, or what to prescribe. I would call your attention to the words of John Ruskin who wisely pointed out that "there is hardly anything in the

world that some man cannot make a little worse and sell a little cheaper, and the people who consider price only are this man's lawful prey."

A moment ago I mentioned detail men and I would now like to add a comment or two. Detail men are often referred to as salesmen and in a sense, they are. But I must again urge you to think of the detail man's function and his relationship with the individual physician.

He—the detail man—is a source of information. I said earlier that I would not prescribe a drug just because it is listed in a compendium and by the same token, I would also not prescribe a drug just because a detail man has listed its indications, contraindications, et cetera.

I have read some of the newspaper stories generated by these hearings and it seems to me that one important point has been almost entirely neglected. Medicine, and thank God this is true, is practiced by physicians—not by detail men, not by advertising agency copywriters, not by the Food and Drug Administration and not, with all due respect, by the Congress of the United States. To get an M.D. degree, you need 4 years of pre-med, 4 years of medical school and at the very least, a 1-year internship. You do not have to be a mental giant to be a doctor but most of us are not witness ninnies ready to be gulled by a sharp-tongued detail man or a clever copywriter. So instead of pointing one finger at the detail man, another at the copywriter and a third at the fellow who mans an exhibit, take a look at the composite and remember that most physicians are involved in a series of 1 to 1 relationships with people—people who are sick, ill, injured, or infirm. When I see a sick child or a pregnant woman or an elderly diabetic, I am Dr. Maynard Shapiro and that person is my patient and I am his doctor. Whatever you do, please do not destroy or impinge upon that relationship.

Health legislation, or related legislation, has enjoyed fantastic popularity in recent years. Such legislation has a certain emotional and political appeal and I would be the last to claim that the Nation's health care structure is perfect. But as it is not all good, it is not all bad—and I would urge you not to destroy the good while seeking to improve the bad.

Senator NELSON. May I ask a question here?

Dr. SHAPIRO. Surely.

Senator NELSON. I do not understand these general statements, "Whatever you do please do not destroy or impinge upon that relationship," and the sentence, "I would urge," meaning the committee—"not to destroy the good while seeking to improve the bad."

What is the basis of those statements, something the committee has done?

Dr. SHAPIRO. No, sir. This is referring more to a tendency, not the committee specifically. If you will notice in what I have presented just now, I did not refer to a health care system, I referred to a health care structure. It is my contention that we do not have a system in this country for the delivery of health care.

Senator NELSON. So you were not referring to issues raised before this committee?

Dr. SHAPIRO. No, sir.

Senator NELSON. Please go on.

Dr. SHAPIRO. I think we could all agree that the pharmaceutical industry has been raked over some pretty warm coals in recent years and let me again emphasize that I am in no way wedded to the industry. However, I have many patients—perhaps literally hundreds of patients—who are alive today because pharmaceutical industry research came up with the drug they needed. And where is most of this research being done? Right here in America. The Russian pharmaceutical industry, for example, cannot hold a candle to the American industry.

This is why I shudder when someone suggests that we impose rigid controls on drug industry prices or profits.

Senator NELSON. May I ask a question?

Dr. SHAPIRO. Yes, sir.

Senator NELSON. What do you refer to there? Nobody before this committee has suggested that.

Dr. SHAPIRO. The excess profits that have been discussed so widely in the newspapers, supposedly from this committee hearing.

Senator NELSON. But nobody, if I recall, has suggested imposing rigid proposals on the drug industry prices or profits, have they? They have been criticized for the profits and for the pricing structure, and I have criticized them myself.

Dr. SHAPIRO. The unions have suggested this in some of their releases to the press. I am not referring to the committee or testimony. We are here trying to give you our ideas—

Senator NELSON. I just thought that you might be referring to some comments that have been made by the committee suggesting rigid controls.

Dr. SHAPIRO. I do not believe that anyone will deny that lower profits will mean less research and although drug industry profits are certainly substantial, I know of no industry more committed to research. Drug industry research will not put men on the moon or speed up an SST but it will save a great many young and not-so-young lives. I firmly believe that the relationship which now exists between the individual physician and the drug industry is essentially healthy and I hope it will not be stifled.

Thank you.

Senator NELSON. Thank you very much, Doctor.

Your last statement raises a question that has been discussed before the committee, as you well know, by a number of witnesses, including representatives of some of the other distinguished medical organizations before this committee, AMA and the American College of Surgeons in the past week. So I will just raise with you some of the same questions that I raised with them. This involves the relationship between the drug industry and the medical profession, which, as I say, we have raised with every representative of medical organizations appearing before the committee as well as with the drug industry itself, so that we can explore it and see what the relationship is and see whether or not it is a relationship that is not healthy for either the profession or the country as a whole. And pursuant to that line of questions, I would like to ask some of the same ones that I have asked of other organizations.

In 1967 you published a brochure called "News and Views of Interest to the Pharmaceutical Industry." As you know, this brochure is made

up of editorial comments that occurred in the GP, or American Family Physician. I am puzzled by the purpose of it. It says, "News and Views of Interest to the Pharmaceutical Industry."

Why would you be interested in publishing a brochure that recites a group of editorials, all of which, as I read them one way or another, defend the pharmaceutical industry position? What is the purpose of the brochure?

Mr. CAHAL. Dr. Shapiro has asked that I comment on that, Mr. Chairman.

This brochure was published for the very reason you stated, sir, that we thought it would be of interest to the pharmaceutical industry, the things we had to say about this matter. By the same token, the pharmaceutical industry sends to our office many of its publications. The pharmaceutical companies regularly send us their annual reports, because the pharmaceutical industry and the medical profession and the nursing profession and the hospital profession are all engaged on the same team, and I think have a natural and healthy interest in each other.

Senator NELSON. Did the PMA distribute this?

Mr. CAHAL. No, they did not distribute the original.

Senator NELSON. Did they reprint it and distribute it?

Mr. CAHAL. I would not know. I doubt it without our permission.

Senator NELSON. What was the circulation of it? It is printed, and it is the views of the pharmaceutical industry—how many did you print?

Mr. CAHAL. I cannot answer that at this moment, Mr. Chairman. A few hundred, I presume.

Senator NELSON. And it was sent to the pharmaceutical manufacturers?

Mr. CAHAL. Yes, sir.

Senator NELSON. You don't know whether the PMA circulated it themselves or reprinted it and circulated it?

Mr. CAHAL. Of my own knowledge I do not, sir.

Senator NELSON. Does anybody?

Mr. KEMP. I do not believe that they did, sir, I do not know that they did.

Senator NELSON. I am still puzzled by the purpose. The editorials appeared in GP and the American Family Physician. They all defend, directly and frankly, right down the line, the manufacturer's position on every issue that is discussed. And looking at it as an outsider, if I were in business, I would say that it is a direct and blatant appeal to the industry for more advertising. What other purpose does it have?

Mr. CAHAL. Mr. Chairman, it has been some time since this was published, and I do not remember all the editorials that were in it. I would like to repeat what Dr. Shapiro said in his direct testimony, that our journals, GP and American Family Physician, have from time to time published articles and editorials quite critical of the industry and of individuals in the industry. And I would like to report to you, sir, and for the record, that some of these editorials have resulted in a cancellation of heavy advertising schedules.

Senator NELSON. Who has canceled because of some editorials?

Mr. CAHAL. One that I specifically recall is Wallace Laboratories. Another, I think, was Pfizer—for editorial comments we made, as a

result of the editorial comments we made critical of them or the industry, they have canceled out.

Senator NELSON. When was this?

Mr. CAHAL. Well, they were at different times, different occasions.

Senator NELSON. For how long did they cancel them?

Mr. CAHAL. I think Wallace is still canceled.

Senator NELSON. When did they cancel?

Mr. CAHAL. I think about 2 years ago.

Senator NELSON. Do you have file copies of the editorial comments that caused them to cancel?

Mr. CAHAL. I shall be glad to send them to you, sir.¹

I remember one editorial of ours which offended some of our friends in the industry. It was one in which we stated that we were suspect of any pharmaceutical company which manifested an interest in a scientific article we were preparing to publish in our journal, that we were sacrosanct in our scientific and editorial material and we did not want any pharmaceutical company to have any interest in it, and if they manifested one, it would put us on guard that they had an interest.

Senator NELSON. Did some company cancel based on that, do you know?

Mr. CAHAL. I suspect they did. I do not know that they told us, frankly, that they were canceling because of that editorial attitude of ours, but I know that it resulted in critical and complaining comment in the industry.

Senator NELSON. How many times has any drug industry, any manufacturer canceled, based upon critical material in the publication?

Mr. CAHAL. Well, Mr. Chairman, we were not always certain of the reason for the cancellation of advertising, or a failure to buy advertising. But from our intimacy in the field we have reason to believe that sometimes our editorial posture has resulted in a loss of advertising sales in our journals.

Senator NELSON. But do you have any specific case that you know of where the industry did cancel because of a specific adverse editorial comment in either of your publications?

Mr. CAHAL. Yes, sir. I refer to Wallace Laboratories, which advised us that they were canceling because of an editorial.

Senator NELSON. Pfizer and Wallace?

Mr. CAHAL. Yes, sir.

Senator NELSON. Are those the only two specific cases?

Mr. CAHAL. That I can recall at this moment, sir.

Senator NELSON. And they were how recent?

Mr. CAHAL. Wallace was 2 years ago, at least 2, maybe 3.

Mr. KEMP. Closer to 3, I think, on Wallace. I do not remember when Pfizer did.

Mr. CAHAL. The two had no relation to each other, they were two different episodes.

Senator NELSON. The point that this whole issue continues to raise, it seems to me, and I am saying this not just as to your publications, but with regard to all journals and all medical news publications, some of which are 100 percent supported by advertising from phar-

¹ See pp. 4779-4781, *infra*.

maceuticals, and some of which are substantially supported, such as yourself and other distinguished medical associations—the point it continues to raise is that, since there is a heavy dependence on advertising, do the respective journals of the respective professional medical organizations pursue as vigorously a policy of criticism when it is appropriate as they would if there was no dependence on advertising? It seems to me that that is the issue that is continually raised here. And in looking at a large number of the publications I rarely find anything critical of the industry itself, even though there are critically important issues that are raised. For example—maybe you can tell me about your publication, I do not know about this—but I cannot find any publication that ran big strong stories pointing out the misuse of chloramphenicol. Did your publication?

MR. CAHAL. Mr. Chairman, I cannot speak for all publications, but I have just tried to make it clear to you, sir, that the journals of the American Academy of General Practice are independent editorial spokesmen, and are not the slave of their advertisers any more than the Washington Post is the slave of its advertisers. I shall be glad to furnish for your committee, Mr. Chairman, copies of editorials which have appeared in GP magazine critical of individuals and of the industry. As for the misuse of chloramphenicol, we have from time to time had articles in GP written by distinguished authorities about the dangers of abuse in antibiotic therapy, and I do know that we reported fully the antitrust action.

DR. SHAPIRO. Some of the members of the industry—

Senator NELSON. The problem, it seems to me, of the medical publications is that as contrasted with a large daily newspaper, their dependence is on two things: One, the dependence of the journal upon a single industry source, that is, pharmaceuticals, is very high. In the case of American Family Physician, 91½ percent of the advertising is pharmaceuticals. A publication that accepts advertising from a single source is quite a different case from one that accepts advertising from many sources.

Secondly, it seems to me that there is a very special relationship and responsibility toward the public on the part of the medical profession as the custodians of the public health, so to speak, a very special ethical responsibility that I think is unique. That is why I think this poses a serious question. In reading through this brochure "News and Views of Interest to the Pharmaceutical Industry," and I read it through twice last night and once this morning, it seems to me it raises some very serious questions. I made some notations on it as I went through.

For example, on the next-to-the-last page of the brochure, "News and Views," it says:

From time to time and with increasing frequency we get weary of listening to all the flack which relates, however remotely, to pharmaceutical prices. We hear that company A sells a particular tablet for 8 cents apiece, but company B charges only 3 cents for its version of the same product. In the first place, let there be no mistake about this, most of the people who make noises about "generic equivalents" do not know an aspirin tablet from a jelly bean. They will shout that frozen tutti-frutti pies "are not as good as mother used to make" and then turn right around and claim that generic and trade name products are like two peas in a pod. You can buy a cow for \$25—or \$250. A local jeweler tells us that we can buy a one carat diamond for \$300 or \$2300. In other words, we are always required to make decisions based on the quality of the merchandise and this axiom applies to anyone who wants to buy anything.

We are a bit amused by acquaintances who will go out of their way to consult a high-priced specialist—and then complain when he gives them a prescription which costs \$3.50. The average retail prescription charge is \$3.48—on which the manufacturer nets 18 cents. We have made these same statements, perhaps more diplomatically, in earlier "Publishers' Memos." We may be compelled to repeat them again—perhaps even less diplomatically. Our parting plea is this: When you run across what seems to be an outrageous fact concerning prescription drug prices, consider the source, consider that the statement may have been made with ulterior motives—and remember that a bargain basement price almost always bespeaks bargain basement quality.

Now, this is a strong direct plea, really, for the brand-named drugs. But let me recite a case which we have used a number of times before and will continue to use. We could give you a dozen, but this one is based upon the conclusion of the Medical Letter, and it would not be subject to the same kind of attack that another example might be.

But referring to the prices now, a cow for \$25 or \$250, the Medical Letter of June 1967 published an analysis on prednisone tablets. And referring to the paragraph in here which says:

Our parting plea is this: When you run across what seems to be an outrageous fact concerning prescription drug prices, consider the source, consider that the statement may have been made with ulterior motives—and remember that a bargain-basement price almost always bespeaks bargain-basement quality.

The Medical Letter concluded from testing done by an independent lab and in consultation with clinicians around the country that all these drugs, all 22 prednisones by 22 different companies were therapeutically equivalent. The prices have changed since our hearings on this, but Meticorten, which was the original and most widely prescribed, was \$17.90 a hundred to the druggist, and Paracort, \$17.88. And it got down to Merck at \$2.20, and McKesson at \$2.25, down to Upjohn \$2.25, and finally to Wolins at 59 cents a hundred. Now, here they are, with a price differential of 30 times. What is your conclusion about that?

Dr. SHAPIRO. Mr. Chairman, I think this committee has won its badge on this particular instance. You were successful in having the prices brought within a range of reality. And I would say nothing to support this 30-times price differential.

Senator NELSON. But the problem that your editorial, which went to about 60,000 physicians, raises is that it tells them the pharmaceutical manufacturers' line. And this is a national refutation of it. This is just one of many examples. I use the Medical Letter repeatedly, since I do not find anybody in the medical profession or pharmacy or pharmacology who does not highly regard the integrity and the quality of the letter. If I used another example they would say "Yes," but Wolins' is no good, or McKesson's product is no good, or they aren't as good as Meticorten. Schering claimed before us, that they respected the Medical Letter, but some were not as good—

Dr. SHAPIRO. In this particular instance I believe that the therapeutic equivalence was proven, not the generic equivalency, of the cheaper products. And I believe that across the country every doctor who has read anything at all in the journals regarding the corticosteroids is aware of this.

Senator NELSON. But the same thing on prices goes across the board. We have lots of examples. When the editorial takes the position that when you run across what seems to be an outrageous fact concerning

a lower price, consider the source. Well, what I do not understand is then why—for, example, you take Serpasil, reserpine. Ciba sells this to the pharmacies for \$39.50 a thousand. Now, American Pharmaceutical sells it to New York City for 72 cents a thousand. Now, there is the low price, 72 cents. Thirty-nine dollars is 50 times as high. How does that fit in with the statement here that the price is low, consider the source? You just have dozens of examples which absolutely refute the editorial claim made in your magazine.

Dr. SHAPIRO. As a practicing physician and not as a pharmacologist, I would not like to use this particular example of an extract of rauwolfia Serpentina, because each company has purified a different fraction of the alkaloid. And in my practice I have found that a trade name made by Lilly, Sandril, gives me better results than generic rauwolfia.

Senator NELSON. As you know, New York City, the Defense Supply and the Veterans' Administration use their own independent testing to see that the drug meets the appropriate NF or USP standards. Well, then let me ask you this one on prices, again referring back to this paragraph. How would you explain why Ciba's Serpasil is sold to the pharmacist at \$39.50, but when they wanted to sell to New York City in competitive bidding they bid a \$1.10 a thousand?

Dr. SHAPIRO. I cannot defend it.

Senator NELSON. As I understand this editorial, it is an across-the-board defense of the prices.

Dr. SHAPIRO. I believe the words are "usually," or "most of the time," toward the end.

Senator NELSON. It says:

Our parting plea is this: When you run across what seems to be an outrageous fact concerning prescription drug prices, consider the source, consider that the statement may have been made with ulterior motives—and remember that a bargain-basement price almost always bespeaks bargain-basement quality.

Dr. SHAPIRO. The sense of it seems to be—there was something before that, I believe. I may be mistaken.

Senator NELSON. The article starts out "Attacking generic equivalence," and ends with this conclusion. All I am saying is, you can take their own products, you can take Ciba Serpasil, and they are charging this outrageously high price, and then when they bid in New York City in competition, they bid \$1.10. Well, that is one-thirtieth as much. Now, that is outrageously low compared with what they are charging the pharmacist.

All I am saying is this editorial is really a defense of the drug industry, they are saying you pay for what you get when you see the big price differential, and what they are really trying to say is that generics are not as good. They start out with that. If it is not a brand name, then you had better watch out, you are getting what you pay for, whether it is cows or diamonds. All I am saying is that that same company will come in with \$1.10 when they have to bid honestly in competition, but \$39.50 when they are running on their brand name to the pharmacist. Now, you say you cannot explain that. I simply say your editorial defends the pricing structure. If it defends the pricing structure right across the board as it does here, what is your comment about this aspect of the pricing structure?

Senator DOLE. He does not write the editorial.

Dr. SHAPIRO. No, this editorial was written by the staff, I had nothing to do with it.

Senator NELSON. Dr. Shapiro is the president of the organization.

But we are on the whole question here of the close relationship of the drug industry. I give you a dramatic example of an all-out defense of the pricing structure and the attack on generic drugs, and a caution to watch out:

When you run across what seems to be an outrageous fact concerning prescription drug prices, consider the source, consider that the statement may have been made with ulterior motives—and remember that bargain-basement price almost always bespeaks bargain-basement quality.

Well, I can give you dextroamphetamine, I can give Thorazine and Compazine, all the same pattern here. And all I am saying is that it seems to me that each one of the representatives of the medical profession who appear here and defend the pricing structure and the cost of drugs ought to be prepared, then, to discuss the pricing structure, you must be prepared to defend it. If you cannot defend the pricing structure, then it seems to me that it is hardly justifiable to run an editorial like that and then claim that you are not influenced by the drug industry.

This is the whole problem.

Mr. CAHAL. Mr. Chairman, I think the thrust of that editorial, if I understood it correctly, is directed toward another situation. During the past couple of years, I think doubtlessly as a result of the hearings conducted by your distinguished committee, there has been a rash of articles appearing in lay magazines and newspapers which tended to frighten the consumers of medical care, or to convey the idea that they are being gouged by their pharmacists or drug manufacturers. And I think the thrust of that editorial is directed toward this. I am sure you have seen such square headlines and articles in lesser consumer magazines, "Are you paying too much for drugs?" "Are you being gouged by your druggist?" "Can you afford for your parents to be sick?"—I recall such editorials. And I think that was the thrust of that point.

Senator Nelson. You are correct that articles have appeared saying in one way or another that the public is being gouged. I have said that the pricing structure is inexplicable by any rational competitive standard in a free enterprise system.

You talk about being gouged. I think there is a reason for it. Let me point something out which I do not think the medical profession as a general rule is familiar with. For example, if you are going to use the word "gouging," let us take a look. Ciba sells reserpine, its brand name is Serpasil, a thousand 25-milligram tablets for \$39.50 to the pharmacist. They bid \$1.10 to New York City the same day, across the State in city hall, they bid \$1.10 to New York City, and they lost it to American Pharmaceutical for 72 cents. But now they package it overseas and they sell it, not for \$39.50, but in Bonn, Germany, for \$10.53 a thousand versus \$39.50 here; in Berne, Switzerland, \$11.09, and in London, \$11.20—in every case less than a third of the price they are charging the American pharmacist. Take prednisone. Schering ships it overseas. They sell it for \$170 a thousand for 5-milligram tablets to the pharmacists in this country. They offered to sell to New York City at \$12. They sell to the pharmacist at \$170, but in competi-

tive bidding they dropped to \$12, which is \$1.20 a hundred, and they lost it to Lannett, which bid not \$170 but \$4.58 a thousand. That is 45 cents a hundred. On prednisone they go overseas, and they charge not \$170, as they charge the American pharmacist, but \$43.70 a thousand in Berne, \$53 in Rio, and \$70 in Australia. One of them is one-fourth the price, and one of them is less than a third the price, and one of them is less than half the price.

Then another distinguished company, Smith Kline & French—for Thorazine they charge the American pharmacist \$6.06. This drug is sold in Paris for \$1.18; in London for \$1.08; and in Bonn for \$2.40. This is why the stories appeared in the paper saying that the public is getting gouged. There has been no explanation from the industry as to why they will charge a third and a fourth as much to a foreign pharmacist after shipping it overseas as they charge the American public. If that is not gouging I cannot think of a better word for it.

But the medical profession is appearing here with considerable regularity defending the pricing structure of the industry. The industry is the heaviest support of all the professional organizations. The professional organizations defend the structure and claim that they are not influenced by the industry.

I think that is a fair question to raise. I raised it with everybody else. What is the answer?

Dr. SHAPIRO. To what?

Senator NELSON. What is the answer to the proposition that you are influenced by the industry because you accept and use their line of propaganda while at the same time we can give you examples of all these discrepancies in the pricing structure.

Mr. CAHAL. Mr. Chairman, if I may, I have pointed out that our publication is not a captive of the industry, and we are prepared to submit evidence to your committee to prove that.

I have also stated that it seems to me understandable and reasonable that those two members of the health team would be close together, have mutual understanding. They are engaged in the same business, the same as the lumber industry and the nail industry.

Senator NELSON. I would be attacked all over this country in all the medical journals if I compared the medical profession and the drug industry with the lumber and nail industry, but it is your comparison. I would have thought that the—

Mr. CAHAL. I did not say which was the nail.

Senator NELSON. Or who was getting nailed. As I said to the AMA, I have raised as tough a question as I can think of, and you are entitled to answer as extensively as you please. But I think, if I sat on a jury, the physical facts would lead me to believe as a juror that the tie between the industry and the profession is close, and very close, too close, and that the profession is too dependent upon the money from the industry, that the industry is too influential with the profession, and that the profession defaults substantially in its responsibility to put the industry under the kind of critical view that the public is entitled to have them do in terms of industry practices in the promotion of the drugs and in prices they charge. If you look through the record, I would think it would be an embarrassment. But it is true that doctors who have appeared here and the representative of every organization that has appeared has in one way or another

given every single argument that the industry itself gives in behalf of its research and in behalf of its prices, and in behalf of the generic brand name argument. You could not tell the presentation of the medical profession in terms of content from that of the pharmaceutical manufacturers. I would think that that would give one pause—unless you are prepared to say that the industry is right on every single claim they make.

Now, let me turn to something else. I will read something here. This is from an article by Morton Mintz. Mr. Mintz is probably the most distinguished writer in this field in the lay press. In his article "Medical Press Shifts News for Physicians," let me read something:

Another case in point is the handling of an October 13 hearing by the general practitioners, GP, the witness was Richard M. Furlaud, President of E. R. Squibb & Sons. He came before Nelson's subcommittee with a lengthy prepared statement defending the system of dual prices under which a medicine prescribed by brand name can be very expensive, but prescribed under its generic or chemical name can be quite inexpensive. An editorial in the New York Times found Furlaud's case unpersuasive. But GP was so impressed that it turned over four and one-half glossy pages in its February 1968 issue to excerpts from Furlaud's text. GP did not, however, tell its 30,000 doctor readers of a development at the hearing that was not in Squibb's script. This was the subcommittee's introduction of documents which the FDA had prepared in recommending criminal prosecution of Squibb. They recited a long history of "mix-ups, recalls and warnings," that indicated in the agency's view that the firm had "failed to understand its responsibilities as a drug manufacturer." In March 1967 Squibb pleaded no contest to the charges in that case, although it has sweepingly rejected the FDA allegations at the hearing.

How do you account for the fact that you select four and a half pages to write a praiseworthy defense of Squibb, but neglect informing your readers about the long history of mixups, recalls and warnings? This is a pattern of—I want to emphasize, I am not trying to select your publication, but this is a pattern that runs all through the medical press, the criticism that ought to come, comes but rarely.

Dr. SHAPIRO. Mr. Chairman, it is not our duty or thought to defend an industry and say that everything they do is perfect. On the question of influence, I believe there is a reciprocal influence. We would be less than honest not to admit that ads have some impact, and we are carrying ads in our journal. At the same time, the industry generally, and specifically certain companies that I could not possibly mention without research, are influenced in what they are doing by our needs, by our stated needs. As far as the major question that you are posing, I have no expertise in this purely business matter, and I watch what the committee accomplishes with great interest. I have no defense for these things, nor am I trying to present a defense for the industry. As for prednisone, I believe every doctor to my knowledge is ordering it without even a manufacturer's name after it. And this is all due to the good efforts of this committee.

Senator NELSON. The questions I have been raising, though, with the distinguished spokesman of the various professional medical organizations is this very question, that there is heavy reliance upon advertising. And it does not seem to me there is almost total absence of the kind of critical analysis and comment about industry practices that would be made by purely independent journals. And the pattern runs so clearly, the continuous praise and promotion of the industry. Then when a dramatic case occurs, the medical journals, medical press in general, ignore it. That is what disturbs me.

Dr. SHAPIRO. No, sir; we do not ignore it. I mentioned earlier our section on practical therapeutics which is serving for drug therapy education to our readers, and which is written by medical faculty members. And they may be laudatory or they may be critical. And we do not have editorial privilege on these, we print them. And we have many critical practical therapeutics articles.

Second, the advertising we are carrying is not only the business aspect of what a corporation is selling, but it is a service to our members to bring them more detailed information than they may have on a visit from a detail man, if you will, or present some use of a drug in an article where the actual total insert is not printed. So we are using this as a service to our members.

Senator NELSON. But the point raised in this one, Doctor. President Richard Furlaud of Squibb made a presentation to the committee in defense of the system of dual prices under which a medicine prescribed by brand name can be very expensive, but prescribed under its generic or chemical name can be quite inexpensive. On this economic issue—which is critically important, the point is critically important to the manufacturers—your publication gives them four and one-half glossy pages. Have you ever run four and a half glossy pages on what they charge overseas and what they do at the Defense Supply Agency, and how they offered to sell at one-tenth, one-twentieth the price to Defense Supply in competitive bidding versus what they are charging the pharmacies where the doctor's patient goes? If you can run Furlaud's stuff, why not the other?

Dr. SHAPIRO. I have asked Mr. Kemp—it seems to me that we did run something on Defense Supply prices, but I cannot be certain. Editorially I would state that our editorial staff could easily work up such a presentation. And I would be most happy to bring this up before the board of directors and see if we will direct them to do so.

Senator NELSON. I think that would be laudable. But the point I am making is that this pattern of treatment of the drug industry is the same throughout, roughly the same throughout all the publications, the medical journals, and the medical press. And that is a historical fact right up to this day. That certainly leaves unresolved the question of the effect of the close relationship. I do not think anybody has suggested that they are directing, or dictating. It is just the question of—if I have just like you—a good personal friend, and he has some faults, they "ain't" half as bad as the same faults in someone I don't like. And if I am economically dependent upon somebody—that is human nature—I am not as critical of the person I am economically dependent upon as I am of one I am not dependent upon. I think that that is recognized universally among human beings, and that is why you have independent audits in Government and in industry, the board of directors is not permitted by the stockholders to audit their own books, because they are pretty friendly to each other, and the errors and mistakes would not be exposed. And in exposing what is wrong in Government, if you left it up to the Congress or the Legislature to tell the country what is wrong with what they are doing, you would never hear about it. Because there is a special interest in not exposing what is wrong. It strikes me that this is the kind of case this presents. When you look at what happens editorially and in the news within the journals themselves, that kind of picture shows up, does it not?

Dr. SHAPIRO. Yes, sir. We are dealing with the third largest industry in our country. I think the Secretary of HEW says 50 billion, and growing at the rate of 5 billion per year. It is peculiar and different from any other industry that we can consider, in that the frontline men like myself are involved with life and health and the well-being of the people. I am sure that the pharmaceutical industry at the other end feels some of the pressures that must pass over to them because they are the suppliers to us. And I hate to say "lumber and nails," because in a great way they are involved with the health and well-being of the people.

Senator NELSON. Let me cite another one here along the same line. I do not know whether you commented off the cuff on that or not. But on page 3 here in your brochure—do you have this there?

Dr. SHAPIRO. No, sir.

Senator NELSON. This is a question again involving the dispute over generics and brand names, and referring back to the fact that your editorials have taken the side, I think, quite clearly, of the brand name companies on this argument. In June of 1967—first, the FDA did a study of 4,600 drugs that were in a miscellaneous way collected from 245 manufacturers. And 2,000 of these were generic and 2,000 were brand names. That study by FDA was solely for potency—did the drug meet the USP-NF standards of potency. The variance outside the range established by the official compendium was that 7.7 percent of the generics did not meet the standard for potency, and 8.8 percent of the brand names did not meet it. So here is a case of a substantial size study—which did not claim to be a scientific selection—it was just a selection from 245 companies, I believe, but the generic came out better in that test than the brand name.

Now, it says in this June 1967 editorial:

Four days prior to the date set for the opening of the Nelson subcommittee hearings, the Pharmaceutical Manufacturers Association issued a stinging and factual rebuttal of an earlier FDA study on the potency of prescription drug products. Mr. C. Joseph Stetler, PMA president, said that the FDA study contained "gross inaccuracies" and demanded that the FDA "repudiate the survey outright." Stetler said that four PMA member firms have already received letters from the FDA, admitting that the FDA erred when it claimed that their products were below acceptable potency limits. Said Stetler: "Isn't it fair to require that an agency which demands the truth delivers the truth?" The FDA claimed that 7.6 percent of the products studied "deviated to a material extent from the declared potency," but followup studies, done by the firms and often reconfirmed by independent laboratories, showed that only 1 percent were out of line with acceptable potency limits. Furthermore, of the 42 firms which reputedly sold subpotency products, only six were so advised by the FDA during the seven months after the survey was completed. The other 36 were not told of the source of the samples checked or given a reasonable opportunity to check on alleged potency violations.

Well, this is a pretty strong rejection of the FDA report. I do not have everything that you have written on it, but I raise this question. Did you publish the answer made by Dr. Goddard to Mr. Stetler's charge? Dr. Goddard said:

There were 245 manufacturers represented in these 4,575 samples examined.

And then he goes on to say:

In six samples involving five firms, six samples out of 4,573 involving five firms after the review of the original data, we did concede that we had made an error. Now in three of these six samples involving two firms the NDA potency limits were incorrectly tabulated. In the other three samples the examining laboratory

had not followed the prescribed methodology, and the letter acknowledging the error was sent to five firms.

Now, the other original findings I still say are correct. We stand behind them.

Did you run this answer in as prominent a way as you ran Mr. Stetler's attack on the FDA study? I would think that six samples out of some 4,600 on the tabulation error is a very small computation error on the part of the FDA.

Mr. CAHAL. Mr. Chairman, subject to correction, to the best of my recollection we did make mention of Dr. Goddard's refutation of that statement. I think it can be found.

Senator NELSON. Then why would it not be in this publication?

Mr. CAHAL. It probably was after that was published.

Senator NELSON. Would you—so that the whole record would be clear then—would you send for the record what you published and on what date, and we will print it in the record at this point?

Mr. CAHAL. To whom do we direct those, to Mr. Gordon?

Senator NELSON. Yes.

(Material not received.)

Senator NELSON. If there is anything you would like to respond to in what I have raised or said, we would be happy to hear you.

Just one more point to make. There is an editorial in September 1967 on prescription policies, and it recites an AMA study which was not scientific, to say the least, the AMA study of price of generics versus brand names in the drug industry. And I will not get into an elaboration on that, except to say that, of course, if you go to the drugstore and you have a generic-name prescription, and the drugstore only is carrying one brand name, you are going to pay the same price, because you can substitute as you would for the brand name. But it states here: "The AMA study showed that generic-name prescriptions are filled with brand name 63 percent of the time," that obviously would be because that is what is stocked and that is what is prescribed.

But I would just like to make one point for the record here, and that is on the question of whether, contrary to the conclusion of AMA on the price of generic versus brand names, Gray's drug chain and Peoples announced a year ago that they would put in stock a line of generic drugs made by Strong, Cobb & Arner, which I guess everybody recognizes as a distinguished manufacturer of generics, and that the average prescription price would be one-half the average brand-name price. But again here in the editorial is support of the brand-name companies. If there is anything you would like to add to the question I raised, I want to be fair and be glad to have you answer it. But it disturbs me to see how consistently the professional groups support the industry and how rarely they put them under tough criticism.

Is there anything you want to add, Doctor?

Mr. KEMP. I would only say this, Mr. Chairman, not in a full defense of what you are saying, but I do think that sometimes our liaison or our communications with, for example, the Food and Drug Administration, is not what it might be. I believe you were reading a few moments ago from some remarks made by Dr. Goddard after the earlier study or after the comment by the PMA. I do not know. I have no reason to know or have no way of knowing at the moment whether we received these. I would call your attention, sir, to the fact that the "Dear Doctor" letters, if you will, which are being mailed periodically to members of the medical profession—we do not receive them.

Senator NELSON. You do not receive copies of the "Dear Doctor" letters?

Mr. KEMP. No, sir. I have often thought this would be a good idea.

Senator NELSON. I agree with you, you ought to receive them, and I think it would be a good idea to print them.

Mr. KEMP. That is my thought, too, sir.

Senator NELSON. Well, thank you very much. I appreciate your taking the time from your busy schedule to come here and testify today.

Thank you.

(Subsequent information follows:)

AMERICAN ACADEMY OF GENERAL PRACTICE,
Kansas City, Mo., April 9, 1969.

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

Dear Mr. GORDON: In obedience to the request made by Senator Nelson at the time Dr. Maynard Shapiro testified on March 26 before Senator Nelson's committee, I am sending by parcel post today the following:

(1) A biographical sketch of Dr. Maynard Shapiro, myself and Mr. Walter Kemp, who accompanied us.

(2) Annual financial statements of *American Family Physician* showing the losses incurred on that publication.

(3) Copies of representative editorials appearing in GP and AFP.

(4) Copies of "Practical Therapeutics" series which have appeared in GP magazine.¹

It was a pleasure to make your acquaintance.

Sincerely,

MAC F. CAHAL.

U.S. SENATE,
SELECT COMMITTEE ON SMALL BUSINESS,
Washington, D.C., April 22, 1969.

MAC F. CAHAL, J.D.,
Executive Director and General Counsel, American Academy of General Practice,
Kansas City, Mo.

Dear Mr. CAHAL: During your appearance before our Monopoly Subcommittee on March 26, you stated: "... that our journals, GP and AMERICAN FAMILY PHYSICIAN, have from time to time published articles and editorials quite critical of the industry and of individuals in the industry." You also stated that you would supply us with copies of these editorials and articles.

Since the editorials and articles you have sent us are not responsive to the Chairman's request, we would appreciate your sending us the relevant material as soon as possible.

Sincerely,

BENJAMIN GORDON, Staff Economist.

AMERICAN ACADEMY OF GENERAL PRACTICE,
Kansas City, Mo., April 25, 1969.

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

DEAR Mr. GORDON: The material we sent you may not, by your standards, be considered critical of the pharmaceutical industry but you may rest assured that this view was not fully shared by the industry.

May I respectfully point out that we do not normally index material by the degree to which it is favorable or unfavorable to the drug industry and we

¹ "Practical Therapeutics" series has been retained in committee files.

have thus not perused every page of every issue. (GP was first published in April, 1950.) However, if members of my staff turn up additional material, I will see that copies are sent to Senator Nelson.

Sincerely,

MAC F. CAHAL.

[From American Academy of General Practice, January 1965]

VIVE LA DIFFERENCE

Another instance has recently come to our attention in which members of the "weaker sex" have demonstrated a superiority over their masculine counterparts. Experimental work both in dogs and in rabbits has indicated that the female of the species is more resistant to digitalis cardiotoxicity than the male. This extra tolerance seems to be due to estrogen and related steroid compounds.

A survey of hospitalized patients under age 40 with rheumatic heart disease indicated that approximately 20 percent of the male patients receiving digitalis develop signs of digitalis intoxication at some time during hospitalization. In the group of females, only 10 percent of those receiving digitalis develop digitalis-induced arrhythmias (*American Heart Journal*, September 1964).

Because of the limited size of the series, the results are not of high statistical significance and there are other weaknesses which the authors appreciate in a retrospective study.

However, digitalis preparations are frequently, if not usually, administered as a "standard" dose. Therefore, the finding of a lesser incidence in the somewhat smaller group of patients (the females) presents added weight to the validity of the study. This new piece of information, coupled with the relatively high rate of toxicity noted particularly among male patients in the study, would indicate that there is still much for us to learn about the actions and usage of digitalis preparations. As for the plus on the female scoreboard, we are becoming used to that.

[From American Academy of General Practice, June 1965]

PHENACETIN AND THE NEPHROLOGISTS

A Food and Drug Administration ruling still requires a printed warning label on over-the-counter preparations containing phenacetin, stating that these products may damage the kidneys when used in large amounts. Despite such official warnings, evidence pointing to the nephrotoxicity of phenacetin is still largely circumstantial.

(Incidentally, the great strides in the understanding and the management of medical renal disease have brought into great prominence the medical specialty now called "nephrology." To be sure, the functional unit of the kidney is the nephron. However, one might consider some of the other terms that would seem equally suitable for labeling this field of study. Why not "renology"? Of course, "urology" does not seem acceptable to the "salt and water" doctor.)

Back to phenacetin. Several years ago, Schreiner queried many nephrologists on the relationship of phenacetin to kidney disease. More than half of 74 nephrologists reported that they had never seen a case of nephritis related to phenacetin.

Now, Strickler suggests that phenacetin may have been singled out unjustly. He cites the conflicting findings in the clinical investigative literature. It is possible that "phenacetin nephritis" is in reality chronic pyelonephritis. The problem still has not been studied in systematic fashion.

[From American Academy of General Practice, September 1967]

DRUG REMOVAL

Suicidal or accidental ingestion of potentially lethal drugs continues to represent an important clinical problem. Two recent trends have been of interest in this regard. The first is the variety of new drugs involved in overdosage situa-

tions. Tranquilizers and antibiotics of various sorts are a case in point. The clinical pharmacology and, indeed, methods for measuring blood levels are not available in every instance. The second trend deals with improved methods of drug removal, particularly by hemodialysis.

Maher and Schreiner have recently reviewed some of these methods in the *Transactions of the American Society for Artificial Internal Organs* for 1967. Several drug removal rates are given, using the well-established figures for hemodialysis into an aqueous bath as the basis of comparison. For example, in the case of lipid soluble poisons, e.g., glutethimide (Doriden®), it is possible to greatly accelerate removal by hemodialysis against a lipid (soybean oil) bath and this has been successfully used clinically. A newer development is hemoperfusion through an activated charcoal column which appears to be superior even to lipid dialysis in removing glutethimide from experimentally poisoned animals. Peritoneal dialysis with various modifications of the dialyzing fluid is appropriate for certain barbiturate poisonings. Further, there may be a significant increase in the rate of drug removal in the patient's own urine by alkalization and forced diuresis.

Drugs of the same class, e.g., barbiturates, differ from one another in response to these therapeutic measures and the clinician must acquaint himself with their individual characteristics. Calcium can be removed by hemodialysis but if the stimulus to hypercalcemia is strong enough, e.g., hyperparathyroidism, there may be no change in blood level. The phenothiazines and chlorthalidone (Librium®) illustrate two types of nondialyzable poisons for which no removal procedure is yet available. Information on drug removal is slowly accumulating and will continue to be important as long as chemical or physiologic methods of treating a poisoned patient remain unavailable.

[From American Academy of General Practice, April 1969]

ACROSS THE MEDICAL EDITOR'S DESK

ANOTHER LOOK AT IMMUNIZATIONS

Mass immunization programs have become a way of life in this country within the past few years. When the oral poliovirus vaccine first became widely available, many communities instituted programs for administering the vaccine to any citizen desiring it. In a number of localities, the development of a successful vaccine against measles was the signal for another mass immunization program for school-age children. The pattern may be expected to continue. New vaccines are appearing on the scene almost yearly—this year, mumps vaccine; next year, rubella vaccine, and so on.

Operation Head Start provides a further example of how long-standing immunization programs (DPT) are coming in for their share of popularity. Particularly in this socioeconomic group, parental recollection of past immunizations is often hazy. In any socioeconomic group, many families which frequently change residence do not take records with them.

Whether speaking of mass immunizing programs or those directed toward patients seen in private practice, the proved efficacy of most vaccines and the relatively low incidence of adverse reactions often have led private and public medical resources into some rather slipshod practices. Is it too much to inquire whether the child has had measles before administering the vaccine? Should we not have immediate prior evidence of a negative tuberculin test?

Recent examples from the medical literature further highlights the problem: Children who have received *inactivated* measles vaccine, when subsequently exposed to measles, may develop a severe illness characterized by high fever, prostration and a maculovesicular rash beginning on the lower extremities and progressing cephalad. Other children who have received inactivated vaccine, when subsequently given live attenuated vaccine, may develop severe local reactions at the site of injection (Nader et al., *Journal of Pediatrics*, January 1968, p. 22).

In this country, morbidity from smallpox vaccination now exceeds that from the naturally occurring disease. In one survey of reports from more than 4,000 physicians in four states, generalized vaccinia and eczema vaccination occurred at a frequency of 238 and 80 per million primary vaccinations respectively (Neff et al., *Pediatrics*, June 1967, p. 916). Complications occurred disproportionately during the first year of life, suggesting that vaccination should be deferred beyond this period.

Current recommendations call for booster doses of tetanus toxoid at 3, 6 and 12 years of age, despite evidence indicating that 96 percent of children receiving a primary immunizing series have tetanus antitoxin titers well above the protective level after 12 years. In older individuals receiving repeated injections of tetanus toxoid, a 1 to 3 percent morbidity may be expected, consisting of urticaria with or without angioneurotic edema or localized vascular injury (Steigman, *Journal of Pediatrics*, May 1968, p. 753).

Still unresolved are questions of subtle, long-term hazards of "overimmunization." In addition to local Arthus-type reactions resulting from tetanus toxoid injections, for example, there is evidence that a delayed hypersensitivity can occur. This involves the toxoid antigen portion of the complex with its homologous antibody.

These are early straws in the wind. American medicine increasingly is moving from a curative to a preventative approach. As one consequence, the underlying mechanisms of patient morbidity from immunizing procedures will need continual reassessment.

AMERICAN FAMILY PHYSICIAN INCOME AND EXPENSE ANALYSIS, NOV. 30, 1968

	Period ending Nov. 30, 1968	Month of November 1968
Income:		
Gross advertising sales.....	\$407,623.00	\$37,121.50
Less:		
Discounts to advertising agencies (15 percent).....	68,955.85	5,568.29
Discounts to advertising agencies (2 percent).....	6,857.05	525.18
Net advertising sales.....	331,810.10	31,028.03
Other income:		
Subscription income.....	422.66	27.72
Single copy sales.....	65.60	0
Total income.....	332,298.36	31,065.75
Expense:		
Editorial:		
Art.....	1,761.07	190.91
Engraving.....	1,106.77	111.77
Total, editorial.....	2,867.84	302.68
Circulation:		
Postage.....	37,992.18	3,188.58
Directory service.....	7,183.85	588.07
Total, circulation.....	45,176.03	3,776.65
Production:		
Authors' alterations and plate changes.....	837.35	30.76
Composition.....	6,124.61	511.83
Electrotypes and foundry.....	6,399.85	417.02
Freight and express.....	1,615.76	134.91
Paper.....	61,142.15	4,113.70
Printing and binding.....	170,432.47	12,403.27
Salaries.....	12,808.34	1,091.66
Total, production.....	259,360.53	18,703.15
General expense: copyright fee.....	72.00	6.00
Total expense.....	307,476.40	22,788.48
Profit or (loss).....	24,821.96	8,277.27

4782 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

AMERICAN FAMILY PHYSICIAN INCOME AND EXPENSE ANALYSIS, NOV. 30, 1967

	Year ending Nov. 30, 1967	Month of November 1967
Income:		
Gross advertising sales.....	\$541,802.00	\$51,536.00
Less discounts to advertising agencies (15 percent).....	173,376.65	16,491.52
Net advertising sales.....	368,425.35	35,044.48
Other income:		
Subscription income.....	263.64	33.72
Single-copy sales.....	81.93	3.88
Total income.....	368,770.92	35,082.08
Expense:		
Editorial:		
Art.....	1,516.59	167.61
Engraving.....	1,133.87	113.42
Total editorial.....	2,650.46	281.03
Circulation:		
Postage.....	49,867.22	4,622.41
Directory service.....	7,797.09	1,626.42
Total circulation.....	57,673.31	6,248.83
Production:		
Authors' alterations and plate changes.....	3,294.38	49.49
Composition.....	4,403.17	539.70
Electrotypes and foundry.....	12,515.21	421.30
Freight and express.....	3,106.68	494.84
Paper.....	77,805.61	7,954.89
Printing and binding.....	203,624.10	19,302.67
Salaries.....	5,000.00	1,000.00
Total production.....	309,749.15	29,762.89
General expense: Copyright fee.....	66.00	6.00
Total expense.....	370,138.92	36,298.75
Profit or (loss).....	(1,368.00)	(1,216.67)

AMERICAN FAMILY PHYSICIAN INCOME AND EXPENSE ANALYSIS, DEC. 31, 1966

	Period ending Dec. 31, 1966	Year ending December 1966
Income:		
Gross advertising sales.....	\$345,291.50	\$40,659.50
Less discounts to advertising agencies.....	110,190.68	12,922.64
Net advertising sales.....	235,100.82	27,736.86
Other income:		
Subscription income.....	232.84	21.64
Single copy sales.....	4.09	0
Total, income.....	235,337.75	27,758.50
Expense:		
Editorial:		
Art.....	2,012.12	397.53
Engraving.....	1,344.92	117.50
Total, editorial.....	3,357.04	515.03
Circulation:		
Postage.....	40,824.10	4,217.67
Directory service.....	7,252.55	0
Total, circulation.....	48,076.65	4,217.67
Production:		
Authors' alterations and plate changes.....	2,884.34	203.55
Composition.....	2,087.55	291.85
Electrotypes and foundry.....	15,344.02	1,770.15
Freight and express.....	914.08	41.27
Paper.....	59,630.21	6,044.13
Printing and binding.....	197,837.89	17,094.94
Total, production.....	278,698.09	25,445.89
General expense: Copyright fee.....	72.00	6.00
Total, expense.....	330,203.78	30,184.59
Excess expense over income.....	94,866.03	2,426.09

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

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AMERICAN FAMILY PHYSICIAN INCOME AND EXPENSE ANALYSIS, DEC. 31, 1965

	Period ending Dec. 31, 1965	Month of December 1965
Income:		
Gross advertising sales.....	\$303,559.50	\$24,313.00
Less discounts to advertising agencies.....	97,139.04	7,780.16
Net advertising sales.....	206,420.46	16,532.84
Other income:		
Subscription income.....	213.06	67.32
Single-copy sales.....	109.00	
Total income.....	206,742.52	16,600.16
Expense:		
Advertising: Advertising promotion.....	1,036.76	(246.54)
Circulation:		
Postage.....	40,912.83	3,087.05
Directory service.....	8,806.01	851.72
Total circulation.....	49,718.84	3,938.77
Production:		
Art.....	1,655.69	162.47
Engraving.....	1,637.34	107.20
Paper.....	60,185.93	4,696.98
Printing and binding.....	199,964.20	15,538.66
Composition.....	2,626.87	467.80
Authors' alterations.....	2,190.13	223.50
Freight and express.....	878.91	65.64
Electrotypes and foundry.....	10,621.60	714.30
Total production.....	279,763.67	21,976.55
General expense: Copyright fee.....	50.00	6.00
Total expense.....	330,566.27	25,674.78
Excess expense over income.....	123,823.75	9,074.62

AMERICAN FAMILY PHYSICIAN INCOME AND EXPENSE ANALYSIS, DEC. 31, 1964

	Period ending Dec. 31, 1964	Month of December 1964
Income:		
Gross advertising sales.....	\$241,382.50	\$25,807.50
Less discount to advertising agencies.....	76,983.15	8,201.45
Net advertising sales.....	164,399.35	17,606.05
Other income:		
Single-copy sale.....	18.85	18.85
Subscription income.....	163.31	64.91
Total other income.....	182.16	83.76
Total, income.....	164,581.51	17,689.81
Expense:		
Advertising: Advertising promotion.....	1,441.00	
Circulation:		
Directory service.....	2,732.41	2,732.41
Postage.....	35,017.19	3,651.57
Total, circulation.....	37,749.60	6,383.98
Production:		
Art.....	2,240.43	395.96
Engraving.....	1,813.20	1,455.29
Paper.....	53,257.01	5,210.21
Printing and binding.....	170,201.82	16,161.19
Composition.....	2,092.45	296.50
Authors' alterations.....	2,332.33	223.86
Freight and express.....	849.11	152.73
Electrotypes and foundry.....	8,491.52	751.53
Total, production.....	241,277.87	24,647.27
General expense:		
Copyright fee.....	48.00	4.00
Fees and dues.....	100.00	
Total, general expense.....	148.00	4.00
Total, expense.....	280,616.47	31,035.25
Excess expense over income.....	116,034.96	13,345.44

AMERICAN FAMILY PHYSICIAN INCOME AND EXPENSE ANALYSIS, DEC. 31, 1963

	Period ending Dec. 31, 1963	Month of December 1963
Income:		
Gross advertising sales.....	\$205,668.40	\$12,563.50
Less discounts to advertising agencies.....	66,376.72	3,972.28
Net advertising sales.....	139,291.68	8,591.22
Subscription income.....	151.69	12.56
Single copy sales.....	8.36	
Total income.....	139,451.73	8,603.78
Expense:		
Advertising		
Sales promotion.....	69.69	
Advertising promotion.....	1,356.88	
Market research service.....	3,000.00	
Total advertising.....	4,426.57	
Circulation:		
Printing and office supplies.....	39.78	
Postage.....	77.76	5.25
Mailing.....	29,912.77	2,657.50
Total circulation.....	30,030.31	2,662.75
Production:		
Art.....	2,369.10	223.37
Engraving.....	1,754.68	
Paper.....	51,528.53	4,413.45
Printing and binding.....	166,135.84	13,146.25
Composition.....	2,287.90	276.75
Alterations and plate changes.....	1,806.64	173.80
Freight and express.....	963.17	70.06
Electrotypes and foundry.....	7,413.21	477.67
Total production.....	234,259.07	18,781.35
General expense:		
Printing and office supplies.....	285.26	
Copyright fee.....	48.00	4.00
Fees.....	80.00	
Total general expense.....	413.26	4.00
Total expense.....	269,129.21	21,448.10
Excess expense over income.....	129,677.48	12,844.32

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

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AMERICAN FAMILY PHYSICIAN INCOME AND EXPENSE ANALYSIS, DEC. 31, 1962

	Period ending Dec. 31, 1962	Month of December 1962
Income:		
Gross advertising sales.....	\$109,947.00	\$9,663.00
Less discounts to advertising agencies.....	34,777.90	3,092.32
Net advertising sales.....	75,169.10	6,570.68
Subscription income.....	76.63	(6.70)
Single copy sales.....	7.00	.50
Total income.....	75,252.73	6,564.48
Expense:		
Advertising:		
Sales promotion.....	167.41	69.18
Printing and office supplies.....	196.50	
Dues and subscriptions.....	500.00	
Advertising promotion.....	6,552.84	62.63
Market research service.....	545.24	
Total advertising.....	7,961.99	131.81
Circulation:		
Circulation promotion.....	161.29	
Printing and office supplies.....	125.97	72.93
Postage.....	171.46	6.12
Mailing.....	28,025.40	2,541.96
Total circulation.....	28,484.12	2,621.01
Production:		
Art.....	2,936.81	481.99
Engraving.....	1,949.97	217.64
Paper.....	45,189.81	4,388.84
Printing and binding.....	141,811.76	14,018.36
Composition.....	2,857.77	295.35
Authors' alterations.....	1,855.28	189.64
Freight and express.....	1,771.53	51.85
Electrotypes and foundry.....	5,471.75	
Total production.....	203,844.68	19,643.67
General expense:		
Printing and office supplies.....	960.04	
Copyright fee.....	40.00	40.00
Total general expense.....	1,000.04	40.00
Total expense.....	241,290.83	22,436.49
Excess, expense over income.....	166,038.10	15,872.01

Family physician income and expense analysis, January through December 1961

Production:	
Salaries.....	\$8,143.24
Art.....	2,493.97
Engraving.....	2,568.19
Paper.....	18,137.62
Printing and binding.....	68,200.62
Composition.....	3,428.75
Authors' alterations.....	478.85
Authors' reprints.....	433.04
Freight and express.....	529.27
Electrotypes and foundry.....	3,910.36
Printing and office supplies.....	345.72
Total.....	108,669.63

4786 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

Family physician income and expense analysis, January through December 1961—Continued

General:

Printing and office supplies.....	2, 655. 29
Office equipment.....	617. 10
Total	3, 272. 39
Total expense.....	161, 144. 94
Excess expense over income.....	113, 169. 92

Income:

Gross advertising sales—98½ pages.....	62, 189. 19
Less: Discounts to advertising agencies.....	14, 217. 49
Net advertising sales.....	47, 971. 70
Subscription income.....	2. 82
Single copy sales.....	. 50
Total income.....	47, 975. 02

Expense:

Accounting:	
Salaries	1, 359. 42
Printing and office supplies.....	9. 38
Total	1, 368. 80
Administration and publishing: Salaries and commissions.....	1, 000. 00

Advertising:

Salaries and commissions.....	4, 225. 73
Printing and office supplies.....	470. 49
Market research.....	3, 638. 29
Sales promotion.....	3, 852. 31
Advertising promotion.....	7, 975. 28
Total	20, 162. 10

Circulation:

Salaries	1, 427. 35
Mailing	11, 856. 96
Postage	28. 12
Promotion	1, 000. 00
Printing and office supplies.....	2, 395. 39
Part time personnel.....	537. 06
Total	17, 244. 88

Editorial:

Salaries	9, 374. 64
Printing and office supplies.....	52. 50
Total	9, 427. 14

BIOGRAPHICAL SKETCH OF MAYNARD I. SHAPIRO, M.D.

DR. SHAPIRO TAKES HELM

Dr. Maynard Irwin Shapiro of Chicago will be installed tonight as the Academy's 21st president, during his 20th anniversary year as an AAGP member. The 53-year-old Chicago native becomes chief spokesman for the Academy after a steady rise from the ranks which triggered his election to the Board of Directors in 1963.

While a director, Dr. Shapiro served as chairman of the Commission on Membership and Credentials and the Commission on Education. Upon completing a three-year term on the Board, he was elected vice president and then became

president-elect last year in Dallas. This past year he has been on the Executive Committee, the Residency Review Committee for General Practice and the Family Health Care Services Committee.

Many key honors have come to Dr. Shapiro during the year. He was named a member of the HEW Medical Assistance Advisory Council and a trustee of the Family Health Foundation of America. In Illinois, he became a member of the Task Force on Health Manpower of the Illinois Regional Medical Program and a consultant in the Family Health Care Project of Illinois Masonic Hospital.

In his home state, Dr. Shapiro has held every elective office of the Illinois chapter, culminating in the presidency in 1961-62. He has been on innumerable committees and commissions and continues to serve in the Illinois Congress of Delegates.

He has served his regional chapter in many capacities and was president in 1955. He was co-chairman for the inception of the postgraduate school which has continued to be recognized as a model.

Dr. Shapiro also has remained active in the Cook County Medical Society, including his local branch, and the Illinois State Medical Society. Currently, he is chairman of the industrial committee of the South Chicago Branch of the CCMS, on the committee on careers in medicine and allied sciences of CCMS and on ISMS advisory committee to the Illinois Medical Assistants Association. He is a consultant to the ISMS advisory committee to the Health Careers Council of Illinois, and continues as a member of the house of delegates of the ISMS.

Dr. Shapiro has worked as a member or co-chairman of several committees of the AMA and currently is serving as alternate delegate from the Section on General Practice and as a member of the Council on Health Manpower. He also is a national advisor to the Student American Medical Association.

He is on the active surgical staff of Jackson Park Hospital, where he also is director of the Department of Physical Medicine and Rehabilitation, director of medical education and director of the Summer Student Program, as well as a member of the Executive and Credentials committees.

Previous hospital affiliations were as clinical assistant in surgery at Mt. Sinai Hospital and as medical-surgical consultant to the Neurological Hospital in Chicago.

In addition to teaching both undergraduate and graduate medical students in the community hospital setting, he is a visiting lecturer in the graduate program in hospital administration in the Graduate School of Business of the University of Chicago.

He is a fellow of the Industrial Medical Association, Central States Society of Industrial Medical and Surgery, Academy of Psychosomatic Medicine and the American Geriatrics Society. He also holds memberships in the Chicago Society of Industrial Medicine and Surgery (he is a past member of the board of governors), American Congress of Rehabilitation Medicine, Mid-America Society (and Illinois division) of Physical Medicine and Rehabilitation, Association of Hospital Directors of Medical Education and the Association of American Medical Colleges.

His civic activities have been equally varied. He served in the city and state venereal disease campaigns, as well as on a medical advisory committee to the city, culminating in the presentation of a citation of service plaque. He currently is president of the Health Careers Council of Illinois (he was elected to an unprecedented third term), on the advisory board of the Health Improvement Foundation of the Illinois Health Improvement Association, a director of the Illinois Social Hygiene League and a member of the professional advisory council of the National Easter Seal Society for Crippled Children and Adults.

Dr. Shapiro is a life member of Phi Delta Epsilon medical fraternity, a member of Scottish rite and Medinah Temple (Shrine) and a member of Beth Am Synagogue and Men's Club.

He was born in Chicago on December 18, 1914. He has remained there, with his residence currently at 8911 South Chappel Ave., and office for full general practice in the Jackson Park Hospital.

Dr. Shapiro received his premedical training at Crane Junior College and Central YMCA College, Chicago. He was graduated from the University of Illinois College of Medicine in 1939 and served his internship and residency at Mt. Sinai Hospital in Chicago.

His military service was with the Army Medical Corps on active duty from 1941-46 in the South Pacific, rising in rank to lieutenant colonel.

Dr. Shapiro and his wife, the former Lenore Martha Gold of Providence, R.I., have one daughter, Juli Ann, 16.

BIOGRAPHICAL SKETCH OF MAC F. CAHAL, J.D.

Mac F. Cahal, Executive Director and General Counsel of the American Academy of General Practice, Publisher of the Academy's medical publications, *GP* and the *American Family Physician*, and Secretary-Treasurer of the AAGP Foundation, Kansas City, Missouri; born March 28, 1907, Kiowa, Kansas; son of Frank B. and Carrie (Fullerton) Cahal; A.B. University of Kansas School of Journalism, 1931; J. D. (Doctor of Jurisprudence) De Paul University College of Law, Chicago, 1935; attended Northwestern University 1937-38; married Wilma Marshall, June 1, 1935; one daughter Carolyn, and son William Marshall.

Doctor Cahal began his work with organized medicine as Executive Secretary of the Sedgwick County Medical Society (Wichita), Kansas, in 1932. In 1937 he became Executive Secretary and General Counsel of the American College of Radiology. During a leave of absence in 1944 he served as Executive Vice-President of the Southwestern Medical Foundation in Dallas. In 1948 he resigned from the American College of Radiology to become General Counsel and Executive Secretary of the American Academy of General Practice.

He is an associate Fellow of the American Medical Association, a member of the American Bar Association and the Chicago Bar Association, an Honorary Member of the Sedgwick County Medical Society, and a member of numerous clubs and societies.

Doctor Cahal was founder and president in 1948 of the Medical Society Executives Association. He is a past president of the Association of Medical and Allied Publications, and serves on the Board of Directors of the American Society of Association Executives. He is the author of numerous monographs on the social, economic, and legal aspects of medicine, published in both the medical and legal literature. He has been a frequent speaker before medical and lay audiences on the above subjects and has testified on several occasions before government boards and committees in Washington.

His home is at 6610 Indian Lane, Mission Hills, Kansas.

BIOGRAPHICAL SKETCH OF WALTER H. KEMP

Mr. Kemp is managing editor of *GP* and *American Family Physician* magazines, both published monthly by the American Academy of General Practice. He is also secretary of the Academy's Commission on Legislation and Public Policy and has previously served as advertising sales manager, director of public relations and director of the Communications Division. He holds B.S. and B.A. degrees in psychology and economics from Northwestern University and is the son of Dr. and Mrs. Howard M. Kemp (both deceased) of Greenfield and Shelburne, Mass.

Mr. Kemp was earlier employed by Armour Research Foundation and the American Medical Association in Chicago. He was a police reporter and special features writer on the *Greenfield (Mass.) Recorder-Gazette*. He is a member of Beta Theta Pi, DERU (seniormen's honorary society) and Sigma Delta Chi. During World War II, he served in the airborne infantry and was honorably discharged after being wounded during the Normandy and subsequent campaigns.

Mr. and Mrs. Kemp have three children and reside at 9332 Catalina Drive, Shawnee Mission, Kansas 66207.

(Whereupon, at 12 o'clock, the Subcommittee on Monopoly of the Select Committee on Small Business was adjourned, to reconvene subject to the call of the Chair.)

APPENDIXES

APPENDIX I

[From the Virginia Medical Monthly, vol. 94, Feb. 1967, pp. 110-114]

THE IMAGE OF THE DRUG INDUSTRY, AS SEEN BY TOWN AND GOWN

(By William J. Hagood, Jr., M.D., Clover, Virginia, John A. Owen, Jr., M.D., Charlottesville, Virginia)

(Presented before the Public Relations Section of the Pharmaceutical Manufacturers Association, Sixth Annual Meeting, Hot Springs, Virginia, October 4-7, 1964.—From the Division of Clinical Pharmacology, Department of Internal Medicine, University of Virginia School of Medicine, Charlottesville. Aided by Training Grant HE 5544 from the U.S. Public Health Service.)

Results of a questionnaire with regard to the pharmaceutical industry and products are presented.

During the last several years the pharmaceutical industry has repeatedly made headlines—not always to its advantage. Perhaps for this reason, the Public Relations Section of the Pharmaceutical Manufacturer's Association included in its 1964 convention program a panel discussion on the industry's image in the eyes of the physician. In preparing our independent presentations for this program we distributed two questionnaires: one to 200 general practitioners in the rural areas and small towns of Virginia and the other to the medical students, interns, and residents of the University of Virginia Medical Center. The contrasting responses from the two groups have given rise to some discussion and conclusions which may be of interest.

THE GENERAL PRACTITIONERS' QUESTIONNAIRE

There were five general questions on this list, as follows:

1. What is your impression of the pharmaceutical industry? Why do you have the opinion you have expressed?
2. What influences you to use a drug company's product? Why do you think the influences you have expressed are important?
3. Do you favor the continuing use of the medical service-representatives or "detail men" by the drug companies? Why?
4. Do you think the cost of drugs is too high, too low, or about right? What would you suggest the pharmaceutical industry do to better inform the patients why drugs cost what they do?
5. What is your opinion of the apparently growing practice of physicians gaining a financial interest in pharmacies and drug distribution firms? Why do you have this opinion?

Of the 200 physicians queried, 80 (40%) responded; these 80 resided in 55 of Virginia's 99 counties and had practiced medicine from three to 61 years in offices located either in open rural country or in villages ranging in population up to 4200. In the following paragraphs, percentage figures will be based on the 80 responses.

In reply to the first question, 64 physicians (80%) affirmed that they have a good impression of the pharmaceutical industry, based primarily on the industry's extensive research programs and high ethical relations. Another 9% were non-committal. Only nine physicians (11%) actually criticized the industry because of exorbitant prices, pushy and garrulous detail men, or excessive advertising.

As reasons for using a specific company's product, 40% claimed to be guided mainly by previous results with the product, 33% by the positive influence of de-

tail men, 28% by the over-all integrity of the company, 21% by medical journals, and 14% each cited the research behind the drug and the relative cost of the drug as being crucial to their decision. There were in all 17 reasons given, the least popular (1 physician, 1%) being the evaluation of the drug by the *Medical Letter*.

Regarding the utility of the detail man, 85% of general practitioners gave him a strong vote of confidence, because his new drug information was valuable to them and he could order drugs directly for dispensing physicians. The other 15% felt that in view of the abundant available literature his services could be eliminated and the resultant savings be passed on to the patient.

Questioned about drug prices, 51% of general practitioners thought that they were "about right," and 45% thought that they were "too high"; none considered them "too low." Furthermore, 24% urged a better public relations attempt to help the layman understand why drugs cost what they do. However, one physician urged the opposite course: "reduce the cost instead of spending more money to tell the patient why drugs are expensive."

Finally, the general practitioners were definitely opposed (75%) to the practice of physicians gaining a financial interest in pharmacies and drug distribution firms.

THE MEDICAL CENTER QUESTIONNAIRE

Questions 1 and 2 required a listing of material gifts from drug companies and stock ownership in them. Questions 3-5 asked for a graded evaluation of the pharmaceutical industry on its (1) record in the development and testing of new drugs, (2) margin of profit in prescription drugs, and (3) performance in disseminating information about new drugs. Questions 6 and 7 tried to assess the impact of the new Food and Drug Administration regulations concerning clinical trials in terms of general awareness and reaction. In question 8, each person was asked to compare and rate the following over-all sources of comprehensive information about new drugs: faculty and house staff, scientific meetings, scientific articles, advertisement in medical journals, mail literature from drug companies, detail men, the "Physician's Desk Reference," the *Medical Letter* and drug inserts. Question 9 asked for a correct matching of both the generic names and the therapeutic effects to the trade names of twenty common drugs.

Question 10 was multiple choice: "The pharmaceutical industry could better serve the medical profession by (1) continuing just as it is; (2) cutting prices; (3) developing more new drugs at a faster rate; (4) sponsoring more post-graduate courses; (5) distributing more educational material; (6) changing its advertising policy as follows; (7) changing its drug development policy as follows; (8) changing its detail man program as follows; (9) changing its drug sample policy as follows; or (10) other." Question 11 asked each person to assign a grade rank to the following factors as strongly affecting his opinion (good or bad) of a specific drug company: "(1) advertisements; (2) experience with its products; (3) gifts and services to you; (4) research support; (5) assistance in post-graduate and medical educational programs; (6) detail men; and (7) other."

Returns from this questionnaire were scattered, ranging from a 7% response from the second-year class to a 30% response from the fourth-year class. There were 73 questionnaires completed and returned from the 384 persons polled, an over-all 19% response.

Almost everyone had received some sort of gift from one of the drug companies. Eli Lilly and Company had donated 57 pen lights, 46 medical bags, 45 percussion hammers, 35 stethoscopes, 30 pocket notebooks, 28 tuning forks, 19 pen knives, and 18 tape measures, as well as sundry other diagnostic aids, to the 73 persons polled. Burroughs Wellcome & Company had given 18 pocket notebooks, Ciba Pharmaceutical Company had distributed 11 subscriptions to the *Ciba Symposia*, and Wyeth Laboratories had given 10 pen lights. In all, 19 drug companies were listed as donors, some only once, of generally minor and inexpensive gifts.

Of the 73 polled, six owned stock in one or more drug companies and 58 of the nonowners considered such stock to be a good financial investment.

Most answers rated the pharmaceutical industry's record in development and testing of new drugs as good (41, or 56%), its margin of profit in prescription drugs as wide (35, or 48%), and its performance in disseminating information about new drugs as good (39, or 54%). Most of the other answers were equally divided between the two evaluations nearest the mode ("very good," and "fair").

Knowledge of the current Food and Drug Administration regulations regarding clinical drug trials seemed to be greater among residents than medical students: 26 out of 35 students had at most a vague cognizance of them; 17 out of 32 residents had a fairly good or exact knowledge. Most medical students felt they were "necessary and reasonable", but the residents were divided equally between this viewpoint and "necessary and unreasonable". In addition, five residents felt them to be "unnecessary and unreasonable", and three "highly commendable and long over-due".

The ratings of best sources of comprehensive information about new drugs are shown in Table I. The influence of faculty and house staff rises to a peak during the intern year and then progressively declines. Articles in medical journals appear to be the most consistently respected authority throughout, with the *Medical Letter* running a close second during the post-graduate period. Advertisements, mailed literature and the detail man are usually at the bottom of the list, although the latter performs better during senior residency years.

TABLE I

Q. 8. Which do you believe to be the best overall source for comprehensive information about new drugs?

M. S. 2	M. S. 3	M. S. 4	I.	R. 1	R. 2	R. 3	R. 4
Insert Journ FachS. Meets. P.D.R. Ads	P.D.R. Journ. FachS. MedLet Meets. Mail Insert Detail Ads	Journ. FachS. P.D.R. Insert MedLet Meets. Meets. Mail Ads Detail	FachS. Journ. P.D.R. Insert MedLet Meets. Insert Ads Mail Detail	Journ. MedLet FachS. Meets. P.D.R. Insert Ads Detail Mail	Journ. MedLet FachS. Insert P.D.R. Meets. Mail Ads Detail	Journ. MedLet Insert FachS. Detail P.D.R. Meets. Mail Ads	Journ. MedLet Meets. FachS. Detail P.D.R.

Legend: M.S.—medical student; I.—intern; R.—resident. Numbers indicate years of training. Abbreviations for sources self-explanatory.

In the matching quiz, some generic names were almost as familiar as their corresponding trade names but there were some impressive discrepancies: 60 persons correctly described Elavil (Merck Sharpe and Dohme) as a mood elevator but only 14 of these knew that its generic name was amitriptyline; 60 persons knew the therapeutic action of Dulcolax (Geigy) but only 23 knew its generic name.

The last two questions produced the most spontaneous responses. The suggestions for the pharmaceutical industry are summarized in Table II. The same general sentiments are reflected in the responses to the last question, illustrated in Table III. The same three sources of dissatisfaction (detail men, advertisements, and gifts) are again apparent.

TABLE II

Q. 10. The drug industry could best serve the medical profession by—

Sponsoring more post-graduate courses.....	18
Distributing more educational material.....	18
Cutting prices.....	16
Changing its advertising policy.....	15
Changing its drug sample policy.....	15
Changing its detail man policy.....	14
Developing more new drugs at a faster rate.....	7
Changing its drug development policy.....	7
Continuing just as it is.....	5

TABLE III

Q. 11. Your opinion (good or bad) of a specific drug company is most strongly affected by:

Factor	Total response	Favorable	Unfavorable	Either
Experience with products.....	57	9	-----	1
Detail men.....	32	1	12	1
Advertisements.....	23	2	7	3
Personal gifts, etc.....	19	6	3	-----
Postgraduate education support.....	17	8	-----	-----
Research support.....	14	8	-----	-----

COMMENT

It would be imprudent to attempt multiple interpretations of the responses to two different questionnaires, distributed to two different and heterogeneous groups, with such a variable percentage of replies. However, the following similarities deserve emphasis.

1. There is general appreciation for and satisfaction with the over-all performance of the pharmaceutical industry.

2. A feeling that drug costs are too high or profits too wide is evident in 45% of the answers from the general practitioners and in 48% of those from the Medical Center.

3. Most doctors judge a drug company by the efficacy of its products, with the activities of the detail man receiving second place in consideration.

In addition, one may ask what is the comparative efficacy of the three forms of advertising: direct mailing, medical journal ads, and the detail man? The physician has a built-in bias against them all, knowing that none is likely to give him what he wants: a carefully balanced comparison of the product vs. (a) older, simpler substances, (b) new products of competitors, and (c) no treatment at all. Also, to make best use of his limited reading time he gladly dispenses with all save the most authoritative sources of information. So it is unlikely that mail literature and journal advertising have any lasting impact; both could probably be curtailed completely without much effect on the practice of medicine.

This is true because in their absence the detail man could serve the same functions. Conversely it is hard to see how impersonal mailings and glossy advertisements could take the place of an ideal detail man: cheerful, helpful, disarmingly proprietary, willing to listen and happy to debate. Although the physician spends time with him, he spends it as he chooses; he can in effect carry on a conversation with a person, with a drug company, or with the entire pharmaceutical industry.

If the ideal detail man exists, he is clearly outnumbered by his imperfect brethren who reportedly interrupt the office routine, parrot stereotyped enconiums, hawk their wares in a truculent manner, and talk without listening. This confrontation destroys the one thing the physician wants: a chance to learn some valid information. Since the physician is unlikely to change his attitude, the pharmaceutical industry must become more information-oriented. This metamorphosis cannot occur spontaneously but requires active and vocal effort on the part of the physician. The following avenues of information have been worked out at many teaching medical centers:

1. A hospital policy for detail men requires that any "detail visit" (five minutes) to any physician be scheduled through a central office.

2. A similar policy encourages drug companies to work through a central office in arranging clinical trials of new drugs, thus bringing together the most promising drug and the best-qualified investigator.

3. Books, films or other educational material can be useful in both medical and post-graduate education; courses and lectureships, research fellowships and honoraria for visiting speakers have been deeply appreciated gifts from the pharmaceutical industry.

4. Occasionally the drug company may support an entire laboratory or clinical research area, where patients are hospitalized for study by all the newer techniques of clinical pharmacology.

Implicit in all of these programs is the presence of a professional person or persons who maintains a liaison with the drug house representatives and arranges these collaborative efforts. At every opportunity such a person works toward one specific goal—to help bring the best information available from the drug houses to the physicians.

Whenever the physician works actively in cooperation with the pharmaceutical industry in these areas, he appreciates anew its scientific contributions and puts aside his built-in resistance to its commercial aspects. Thus these possible approaches to a closer working relations, while sometimes apparently restrictive, cannot fail to increase the physician's appreciation of the industry—a reservoir of good will which is a powerful reality and capable of even greater enhancement. The medical profession and the pharmaceutical industry, working together, should bend themselves to that task.

APPENDIX II

[From the Virginia Medical Monthly, vol. 93, August 1966, pp. 459-461]

TEACHING THE EVALUATION OF DRUG ADVERTISING TO MEDICAL STUDENTS

(By D. R. H. Gourley, Ph. D., professor of pharmacology, University of Virginia School of Medicine, Charlottesville, Va.)

Physicians until the present have developed their own methods for evaluating the advertising of pharmaceutical manufacturers. Now a course is being given in medical school to prepare the student for this task.

From time to time, spokesmen for the pharmaceutical industry have attempted to justify the expenditure of heavy sums for the advertising of prescription drugs to a limited group as "postgraduate education of the doctor." The character of drug advertising in the United States today under regulation by the Food and Drug Administration(6) has improved considerably since the abuses described by May(5) and others. However, there is reason to believe that many physicians in private practice have been introduced to a large proportion of the drugs they are now prescribing by communications from the pharmaceutical manufacturers. Baehr(1) noted that many general practitioners and specialists in his experience were motivated to shift from one drug to another by the persuasive propaganda of advertising literature and by visiting representatives of manufacturers.

It is clearly desirable for the physician to have a set of guidelines by which he can evaluate the claims that will be made for drugs introduced to the therapeutic scene in the years following graduation from medical school. The course in pharmacology appears to be a logical place to begin to introduce such guidelines and studies of the evaluation of drug advertising have been initiated in the pharmacology courses in some medical schools.(2,3) Typically, a program of drug advertising evaluation is modified in some details from year to year, but the principles can be illustrated by a description of the program most recently undertaken with second year medical students in the Department of Pharmacology at the University of Virginia School of Medicine.

The objectives of the evaluation of drug advertising (EDA) program were: (1) to develop in the medical student a skeptical attitude towards advertising claims for new drugs; (2) to provide the medical student with training and experience in the evaluation of these claims and with some knowledge of the reliability of various authorities. The practical exercise of the EDA program was limited to direct mail advertising although it is recognized that this is only one of several channels through which drugs are advertised. To obtain the necessary material, three cooperating physicians saved all of the drug advertisements and samples received through the mail during the three-month period immediately preceding the project. The program was scheduled during the latter part of the pharmacology course after the students had completed their study of drugs which affect the central nervous system, autonomic nervous system, cardiovascular system and kidney. The mass of accumulated mail was gleaned for material advertising drugs in these general categories. Most of the drugs were relatively new but a few older agents were included for balance. Advertised material that included literature references was selected in preference to poorly documented brochures. Although this bias favored the advertising material, it was a necessary concession in order to provide the students with certain leads.

The class was divided into 18 groups of four students each. Therefore, 18 drugs were chosen. All of the available direct mail advertising for one drug was given to one group for their analysis.

At a preliminary session, the students were given their assignment and instructions for the program. The peculiar features of drug advertising and the relative role of direct mail advertising in overall drug promotion were discussed. The volume of drug samples received through the mail during the collection period was dramatized by emptying a large galvanized can containing the drug

samples on the lecture table. A considerable portion of the introductory session was devoted to methods for assessing reports of drug trials. The criteria outlined by Mahon and Daniel(4) were emphasized. The method consists of the stepwise application of the following criteria: (1) the presence of adequate controls, including the effects of a placebo preparation as well as standard therapy; (2) randomization of treatments; (3) objective assessment of drug effects, including the principle of the double-blind trial to avoid biased evaluation; and (4) statistical analysis of results. The students were instructed to determine how many of the cited references were actually available in the Medical Library (which has 1250 scientific journals on the subscription list) and what proportion of those available were adequate according to the above minimal criteria. Attention was also directed to other source material such as the Medical Letter, the A.M.A. Council on Drugs reports, New Drugs, etc.

It was not an objective of this program to criticize or rate individual drug manufacturers. The important role of the pharmaceutical industry is emphasized in many ways in this course. During the EDA program, for example, a one-day visit to a nearby pharmaceutical firm was arranged. In addition to seeing the excellent pharmacological and medicinal chemical research and the manufacturing and packaging functions of this firm, the students were addressed by an executive officer of the firm who, by prearrangement, presented much valuable additional material on drug advertising from a viewpoint somewhat different from that of the instructors.

Each group of students was assigned a clinical advisor, usually a physician who had had considerable clinical experience with the assigned drug. The students were instructed to discuss their assignments with their advisor following the introductory session and from time to time during the progress of the program in regard to questions relative to the evaluation of the drug, the other drugs available for comparable therapy, and the state of knowledge in the field for which the particular drug is intended. They were urged to obtain as many opinions on these questions as possible by also consulting other clinical instructors and to consult several pharmacists regarding available preparations and relative costs to the patient of equivalent doses of the assigned drug and of other comparable drugs. Students were offered secretarial assistance if they wished to write to pharmaceutical firms for additional information.

The students were allowed eight hours of laboratory time over a three-week period to work on the EDA program. At the end of the program, each group submitted a written report of their study and each member of the group was prepared to present an oral 10-minute report. The oral reports were presented to the class and discussed by the class advisors and departmental staff. The person chosen from each group to present the oral report was not announced in advance.

The staff of instructors and the clinical advisors report that the students rapidly developed a skeptical attitude towards the particular advertising claims which they studied. The students were particularly impressed with the number of quoted "references" which were not available even in a good medical library. Many groups found that of the references they could find in the literature only about 5% fulfilled all of the criteria for a satisfactory clinical trial of a new drug, which is in general agreement with results of the large study reported by Mahon and Daniel. (4).

At the end of the pharmacology course, student opinion of various aspects of the pharmacology course was polled in an unsigned questionnaire. The class was unanimous in its belief that a study of drug advertising belonged in a medical pharmacology course. Ninety-five per cent of the class thought that the project outlined in this report was a valuable learning experience and 85% thought that the time allotted to the project was "about right". Further polls of the same class will be sought just before graduation and after a period of time in practice to determine whether attitudes towards drug advertising and reports of clinical trials of new drugs developed as a result of this teaching exercise have been maintained. In the meantime the enthusiasm of the students and the members of the faculty who participated is ample justification for continuing the project with modifications designed to improve the attainment of the objectives or to better suit further developments in drug advertising and regulations of the Food and Drug Administration.

Acknowledgements: It is a pleasure to acknowledge the contributions to the success of this program of the A. H. Robins Co., Inc., Richmond, and the following members of the faculty of the University of Virginia School of Medicine: Drs. A. J. Bollet, E. D. Brand, G. Goldstein, C. D. Green, J. I. Kitay, C. M. Kunin, D. N. Mohler, J. A. Owen, Jr., L. E. Rudolf, O. A. Thorup, Jr., and F. B. Westervelt, Jr.

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APPENDIX III

APRIL 22, 1969.

Dr. W. J. Hagood, Jr.,
Little Retreat Clinic,
Clover, Va.

DEAR DR. HAGOOD: When you appeared before our Subcommittee on February 19th, you stated that you had prescribed the drug combination, Signemycin to one of your patients.

I am enclosing copies of two drug efficacy studies by the National Academy of Sciences which may be of interest to you. The NAS/NRC appraisal of this drug applies to every dosage form.

I would appreciate any comments you might have.

Sincerely,

GAYLORD NELSON,

Chairman, Monopoly Subcommittee.

(No reply was received from Dr. Hagood.)

NATIONAL ACADEMY OF SCIENCES—NATIONAL RESEARCH COUNCIL

Division of Medical Sciences

DRUG EFFICACY STUDY

Form A

(To be submitted in duplicate by applicant)

Reg. No. 146c.231
 1. NDA Number _____ 2. Date Originally Approved 4/21/58 3. Rx ☒ OTC ☐
 4. Brand Name Signemycin Capsules 125 mg. and 250 mg., Signemycin 375 Capsules
 5. Applicant's Name Chas. Pfizer & Co., Inc.
 and Address 235 East 42nd Street, New York, New York 10017

6. Quantitative Formula

Established (Non-Proprietary) Name of Active Ingredients (in case known on label)

Amount (per tablet, per ml., etc.)

Signemycin Capsules 125 mg.

Signemycin 125 mg. (83 mg. of tetracycline hydrochloride, 42 mg. of oleandomycin as triacetyloleandomycin)

Signemycin Capsules 250 mg.

Signemycin 250 mg. (167 mg. of tetracycline hydrochloride, 83 mg. of oleandomycin as triacetyloleandomycin)

Signemycin 375 Capsules

Signemycin 375 mg. (250 mg. of tetracycline hydrochloride, 125 mg. of oleandomycin as triacetyloleandomycin)

7. Dosage Form (tablets, etc.) Capsules8. Route of Adm. (Oral, etc. Where a new drug application covers different routes of administration, separate forms should be used.) Oral

9. Therapeutic Claims—Attach 10 labels and 10 package inserts (if used) to original Form A (blue) and 1 copy to duplicate Form A (white).

10. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, the package insert, or brochure. Approximately 5 to 10 key references are requested, if available. (Attach 10 copies to original Form A (blue) and 1 copy to duplicate Form A (white).)

11. The applicant is invited, if he so desires, to submit any unpublished material that is pertinent to the evaluation of the drug by the Academy—Research Council. This supplementary material should be packaged with Form A (white). A single copy of this material is requested.

12. In this space, please list and describe briefly the supplementary material that is submitted with Form A (white).

PANEL ON ANTI-INFECTIVE DRUGS (III)

INDICATIONS

I. Signemycin is indicated in the therapy of acute severe infections caused by susceptible organisms and primarily by bacteria more sensitive to the combination than to either component alone.

Evaluation: Ineffective as a fixed combination.

Comments: Although either tetracycline or oleandomycin is effective in the treatment of some infections, there are serious objections to the use of the combination as formulated. Oleandomycin is present in insufficient amounts for effective treatment. If sufficient oleandomycin is administered for effective treatment, tetracycline overdosage results.

The Panel is not aware of infections caused by bacteria more sensitive to this combination than to either of its components.

Establishing efficacy would involve demonstrating that the clinical response to the combination is greater than to either agent used alone. No such evidence is available. *In vitro* studies of this combination have given variable results. The effects may be antagonistic, additive, or synergistic, and are unpredictable for any particular organism.

Thus, there is no evidence that each of the active ingredients contributes to the effect as claimed.

Documentation :

1. Jones, W. F., Jr., R. L. Nichols, and M. Finland. Development of resistance and cross resistance *in vitro* to erythromycin, carbomycin, spiramycin, oleandomycin and streptogramin. *Proc. Soc. Exper. Biol. & Med.* 93 :388-393, 1956.

2. Jones, W. F., and M. Finland. Antibiotic combinations. Tetracycline, erythromycin, oleandomycin, and apiromycin, and combinations of tetracycline with each of the other three agnts.—Comparison of activity *in vitro* and antibacterial action of blood after oral administration. *New Eng. J. Med.* 257 :482-491, 536-547, 1957.

3. Fofar, J. O., and A. F. Maccabe. Erythromycin, spiramycin and oleandomycin. *Brit. Med. J.* 1 :581, 1957.

4. Editorial. Erythromycin, oleandomycin and spiramycin—and their combinations with tetracycline. *New Eng. J. Med.* 257 :525-526, 1957.

II. Favorable clinical response to Signemycin has been observed in the following categories and indications: infections of the respiratory tract and related structures and the genitourinary system, surgical infections, and miscellaneous (amebiasis and lymphogranuloma venereum have been found responsive to Signemycin). Dental infections caused by susceptible organisms are candidates for Signemycin therapy.

Evaluation : Ineffective as a fixed combination.

Comments : There is no evidence that each of the drugs present in this combination contributes to the effect as claimed. Although case reports can be found indicating favorable response, this response is similar to that expected following administration of tetracycline alone or, more rarely, oleandomycin.

Documentation : Informed judgment of the Panel.

III. In streptococcal infections, therapy should be continued for 10 days to minimize the possibility of the development of rheumatic fever or glomerulonephritis.

Evaluation : Ineffective as a fixed combination.

Comments : The Panel is not aware of convincing evidence that treatment with Signemycin will prevent either of these conditions, regardless of the duration of therapy. More effective drugs are available for therapy of streptococcal infections.

Documentation : Informed judgment of the Panel.

Approved by WM. KIRBY,
Chairman.

NATIONAL ACADEMY OF SCIENCES—NATIONAL RESEARCH COUNCIL

Division of Medical Sciences

DRUG EFFICACY STUDY

Form A

(To be submitted in duplicate by applicant)

2418
2111

1. NDA Number: 146c.231 2. Date Originally Approved: October 4, 1956 3. Rx ☒ .OTC ☐

4. Brand Name: Sigmamycin (Sigmamycin) Capsules 50, 100 and 250 mg.

5. Applicant's Name: Chas. Pfizer & Co., Inc. (INTERNATIONAL)

and Address: 235 East 42nd Street, New York, New York 10017

6. Quantitative Formula

Established (Non-Proprietary) Name of Active Ingredients (in order shown on label)

Amount (per tablet, per ml., etc.)

50 mg.Tetracycline (HCl)
Oleandomycin (Phosphate)33.3 mg.
16.7 mg.100 mg.Tetracycline (HCl)
Oleandomycin (Phosphate)66.7 mg.
33.3 mg.250 mg.Tetracycline (HCl)
Oleandomycin (Phosphate)167 mg.
83 mg.7. Dosage Form (tablets, etc.) Capsules8. Route of Adm. (Oral, etc. Where a new drug application covers different routes of administration, separate forms should be used.) Oral

9. Therapeutic Claims—Attach 10 labels and 10 package inserts (if used) to original Form A (blue) and 1 copy to duplicate Form A (white).

10. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, the package insert, or brochure. Approximately 5 to 10 key references are requested, if available. (Attach 10 copies to original Form A (blue) and 1 copy to duplicate Form A (white).)

11. The applicant is invited, if he so desires, to submit any unpublished material that is pertinent to the evaluation of the drug by the Academy—Research Council. This supplementary material should be packaged with Form A (white). A single copy of this material is requested.

12. In this space, please list and describe briefly the supplementary material that is submitted with Form A (white).

PANEL ON ANTI-INFECTION DRUGS (III)

INDICATIONS

I. Sigmamycin is indicated in the therapy of acute severe infections caused by susceptible organisms and primarily by bacteria more sensitive to the combination than to either component alone.

Evaluation: Ineffective as a fixed combination.

Comments: Although either tetracycline or oleandomycin is effective in the treatment of some infections, there are serious objections to the use of the combination as formulated. Oleandomycin is present in insufficient amounts for effective treatment. If sufficient oleandomycin is administered for effective treatment, tetracycline overdosage results.

The Panel is not aware of infections caused by bacteria more sensitive to this combination than to either of its components.

Establishing efficacy would involve demonstrating that the clinical response to the combination is greater than to either agent used alone. No such evidence is available. *In vitro* studies of this combination have given variable results. The effects may be antagonistic, additive, or synergistic, and are unpredictable for any particular organism.

Thus, there is no evidence that each of the active ingredients contributes to the effect as claimed.

Documentation :

1. Erythromycin, oleandomycin and spiramycin—and their combinations with tetracycline. *New Eng. J. Med.* 257: 525-526, 1957. (Editorial)

2. Forfar, J. O., and A. F. MacCabe. Erythromycin, spiramycin, and oleandomycin. *Britt. Med. J.* 1: 581, 1957. (Correspondence)

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4. Jones, W. F., Jr., R. L. Nichols, and M. Finland. Development of resistance and cross-resistance *in vitro* to erythromycin, carbomycin, spiramycin, oleandomycin and streptogramin. *Proc. Soc. Exp. Biol. Med.* 93: 388-393, 1956.

II. Favorable clinical response to Sigmamycin has been observed in the following categories and indications: infections of the respiratory tract and related structures and the genitourinary system, surgical infections, and miscellaneous (amebiasis and lymphogranuloma venereum have been found responsive to Sigmamycin). Dental infections caused by susceptible organisms are candidates for Sigmamycin therapy.

Evaluation : Ineffective as a fixed combination.

Comments : There is no evidence that each of the drugs present in this combination contributes to the effect as claimed. Although case reports can be found indicating favorable response, this response is similar to that expected following administration of tetracycline alone or, more rarely, oleandomycin.

Documentation : Informed judgment of the Panel.

III. In streptococcal infections, therapy should be continued for 10 days to minimize the possibility of the development of rheumatic fever or glomerulonephritis.

Evaluation : Ineffective as a fixed combination.

Comments : The Panel is not aware of convincing evidence that treatment with Sigmamycin will prevent either of these conditions, regardless of the duration of therapy. More effective drugs are available for therapy of streptococcal infections.

Documentation : Informed judgment of the Panel.

Approved by WM. KIRBY,
Chairman.

APPENDIX IV

[From the *New England Journal of Medicine*, vol. 261, No. 26, Dec. 24, 1959, pp. 1318-1321]

FATAL CIRCULATORY COLLAPSE IN PREMATURE INFANTS RECEIVING CHLORAMPHENICOL *

(By Lafayette E. Burns, M.D.,† Joan E. Hodgman, M.D.,‡ and Alonzo B. Cass, M.D.,§ Los Angeles, Calif.)

A survey was made of premature infants born twenty-four hours or longer after spontaneous rupture of the fetal membranes, because of a higher mortality

*From the Premature Center of the Los Angeles County Hospital and the departments of Pediatrics, University of Southern California School of Medicine and College of Medical Evangelists School of Medicine.

†Assistant in pediatrics, University of Southern California School of Medicine.

‡Assistant professor of pediatrics, University of Southern California School of Medicine.

§Associate clinical professor of pediatrics, College of Medical Evangelists School of Medicine.

in this group than in the premature infants whose membranes had ruptured at birth. Routinely, these infants had been placed on antibiotics shortly after birth because of assumed exposure to infection. The role of antibiotics in this higher mortality was questioned. A comparative study of these infants on different treatment schedules was conducted from March, 1958, to February, 1959. This is a report of that study.

METHOD

All premature infants delivered in the birth suites of the Los Angeles County Hospital after spontaneous rupture on the fetal membranes for twenty-four hours or more were assigned to one of four groups according to the time of admission to the premature center. Group 1 received no antibiotics. Group 2 received chloramphenicol,[¶] 100 to 165 mg. per kilogram of body weight per day intramuscularly. Group 3 received procaine penicillin, 150,000 to 600,000 units per day, and streptomycin, 50 mg. per kilogram of body weight per day. Group 4 received all three antibiotics in the same dosage previously mentioned. Half of the daily dose of each antibiotic was given intramuscularly every twelve hours.

RESULTS

Table 1 lists the results of the study. The mortality rates in the nontreated group and the group treated with penicillin and streptomycin are similar. The mortality in both groups given chloramphenicol is strikingly higher than that in the groups not receiving it. The higher mortality is most obvious in the infants weighing 2001 to 2500 gm., that of the babies given chloramphenicol being 45 per cent and that in those not given it 2.5 per cent.

TABLE 1.—COMPARISON OF MORTALITY

Birth weight (grams)	Group 1 (no treatment)		Group 2 (chloramphenicol)		Group 3 (penicillin and streptomycin)		Group 4 (penicillin and streptomycin and chloramphenicol)	
	Total infants	Percent- age who died	Total infants	Percent- age who died	Total infants	Percent- age who died	Total infants	Percent- age who died
<1,000.....	1	100.0	0	0	3	100	1	100
1,001-1,500.....	5	40.0	5	100	2	0	4	100
1,501-2,000.....	9	22.0	9	67	4	75	11	90
2,001-2,500.....	17	5.9	16	50	24	0	15	40
Total.....	32		30		33		31	
Average.....		19.0		60		18		68

The general care of the babies in this study followed the established routine for the nursery. All babies came from the socioeconomic group cared for by the county hospital. All babies had ruptured fetal membranes for twenty-four hours or longer before delivery. Analysis for sex and race showed no significant difference among the groups.

CLINICAL STUDY

The clinical histories of the infants were reviewed. Figure 1 lists the common physical signs and symptoms and presents the percentage in each group who were symptomatic. The two groups given chloramphenicol were similar and were combined to simplify the presentation. All the signs and symptoms but jaundice were present in markedly increased numbers in the babies receiving chloramphenicol. The higher number of gastrointestinal symptoms in the infants treated with penicillin and streptomycin as compared to the nontreated group should be noted. The clinical courses of the chloramphenicol-treated babies who died were strikingly similar. The symptoms appeared in a typical order. Figure 1 lists the average age at onset of each symptom for the chloramphenicol-treated groups.

[¶]In the form of Chloromycetin Intramuscular, Parke, Davis and Company, Detroit, Mich.

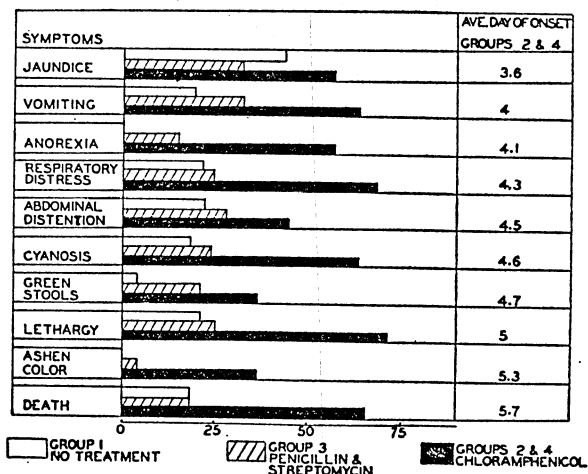


FIGURE 1.—Comparison of Symptoms.

Treatment was started in all cases within twelve hours of birth. The infant's condition at forty-eight hours of age was generally satisfactory. The first evidence of toxicity was vomiting or regurgitation of feedings, which appeared from two to nine days after the start of treatment, with an average onset at four days of age. Refusal to suck followed shortly. Respiratory distress, manifested by irregular, rapid respirations, appeared within a few hours, followed by abdominal distention, periods of cyanosis and passage of loose, green stools. By twenty-four hours after the onset of symptoms these infants were seriously ill. Progression of symptoms continued rapidly, with the appearance of flaccidity, ashen color and a drop in temperature during the next twelve hours. Death usually occurred late in the fifth day of life. Fifty-eight per cent of the babies who survived ran a similar course, recovering twenty-four to thirty-six hours after the chloramphenicol was stopped. These infants appeared normal at the time of discharge.

Of the 126 infants studied, blood cultures were taken on admission to the nursery in 99, and again at death in 27. In no case was there any agreement between the admission and terminal blood cultures. The pathological findings at autopsy correlated with the organism recovered from the blood culture in only 1 case. This infant had a negative blood culture on admission to the nursery. *Escherichia coli* was recovered from the terminal culture. He received no treatment, becoming sick on the fifth day and dying three days later. Autopsy revealed subarachnoid hemorrhage and meningitis.

Cultures of the gastric contents were taken on admission to the nursery in 89 infants. Thirty-nine of the cultures showed no growth. From the remaining cultures, the following organisms were recovered: *Staphylococcus albus*, 17; *Bacillus subtilis*, 12; *Esch. coli*, 6; coliform organisms, 10; gamma-hemolytic streptococcus, 5; beta-hemolytic streptococcus, 3; *Staph. aureus*, 1; and diphtheroids, 1. There was no correlation between the organisms recovered and the clinical course of the infants. Random throat, urine and stool cultures were equally nonspecific.

Blood chemical studies were done in some of the infants. All the infants studied had an elevated non-protein nitrogen. As their condition deteriorated, the serum carbon dioxide fell, and the serum potassium rose. Spinal-fluid chemical findings in 2 of the infants were normal. White-cell counts ranged from 6000 to 30,000.

Autopsies were done on 34 infants, or 68 per cent of the deaths. Gross findings were not remarkable in 25 of them, the cause of death being obscure. Of the remainder 2 had bronchopneumonia, 5 had cerebral hemorrhage, and 2 died after surgical correction of a tracheoesophageal fistula and a duodenal stenosis. Microscopical findings will be reported in detail in a later paper.

Chloramphenicol blood levels were obtained in 2 of the infants. The levels were determined by testing for aromatic nitro compounds after the method of

Glazko et al., (1, 2) which includes both the active and the inactive metabolites of chloramphenicol. Figure 2 shows the levels in the babies. Both infants died within four hours of the last blood level indicated. Autopsy showed intraventricular hemorrhage in baby E. No autopsy was done on baby J.

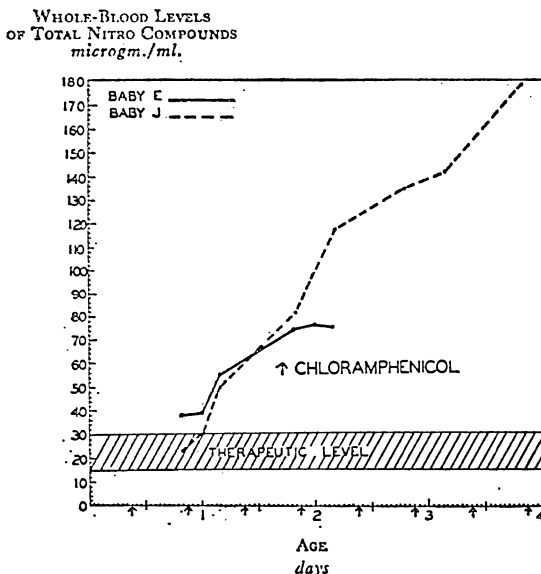


FIGURE 2.—Chloramphenicol Blood Levels.

Although the groups were small, there was no increase in mortality in infants who received 140 to 165 mg. of chloramphenicol per kilogram of body weight as compared to those given 110 to 140 mg. per kilogram per day.

DISCUSSION

Physiologic studies have shown that liver and kidney functions are poor in the premature infant as compared to the adult. Potter and Thierstein (3) found histologically immature kidneys in almost all premature infants weighing 2000 mg. or less. The volume of urine excreted is small, and the ability to concentrate it is poor. Glomerular filtration, as measured by urea and inulin clearance, and tubular excretion, as measured by iodopyracet compound and para-amino-hippurate excretion, are markedly reduced. (4-6) Deficiency in the glucuronide conjugation of bilirubin in the premature liver has been well established. (7-9) This deficiency is thought to be due to a lack of conjugating enzyme. (10) In adults, Glazko and his associates (11) demonstrated that chloramphenicol is detoxified in the liver and excreted by the kidney. They found that detoxification is mainly by glucuronide conjugation. They were able to recover 90 per cent of a given dose from the urine of adults. (12) The bulk of the excreted drug was in the form of an inactive glucuronide conjugate. Less than 10 per cent was excreted unchanged. Renal plasma-clearance studies in adults suggest that the active form is filtered by the glomerulus, and the inactive form is excreted by the tubules.

The toxicity of chloramphenicol has been extensively studied in animals. Smith et al. (13) found that the LD_{50} for chloramphenicol given by mouth to adult mice was 245 mg. per kilogram of body weight. Smaller doses caused tremors and prostration followed by recovery. They also found that dogs given chloramphenicol intravenously responded with a fall in blood pressure. With the use of high doses, the bloodpressure fall was followed by respiratory failure and death.

Several reports in the European literature describe fatal circulatory collapse in patients with typhoid fever treated with chloramphenicol, the shocklike state appearing three to five days after the start of medication. (14-18)

Sutherland and his co-workers (19,20) recently reported 5 cases of fatal circulatory collapse in newborn and premature infants that they believed to be due to chloramphenicol toxicity. (19,20) Their findings clinically and at autopsy were similar to our findings. They postulated that the high blood levels demonstrated were due to poor absorption, poor excretion or failure of conjugation. Dorn and Smith (21) reported prolonged blood levels in the newborn and the premature infant after a single dose of chloramphenicol.

SUMMARY AND CONCLUSIONS

Premature babies delivered after rupture of the fetal membranes for twenty-four hours or longer were assigned to one of four treatment groups. Group 1 received no antibiotic, Group 2 received chloramphenicol alone, Group 3 received penicillin and streptomycin, and Group 4 received all three. The mortality of the group treated with penicillin and streptomycin was the same as that of the untreated group, but a higher number of the treated babies had gastrointestinal symptoms.

The mortality rates of the two groups given chloramphenicol were significantly higher than those of the other two groups.

The babies receiving chloramphenicol followed a typical clinical course. Gastrointestinal symptoms appeared first, followed by circulatory collapse and death. Blood levels of chloramphenicol showed a continuous rise. Removal of the drug stopped the progression of symptoms. Recovery left no sequelae.

Since the administration of chloramphenicol was the only factor common to the two groups having the high mortality, and the absence of chloramphenicol the only factor common to the two groups with the low mortality, chloramphenicol in the dosage used must have been responsible for the increase in mortality observed. Poor liver function, especially in the glucuronide conjugation system, as well as decreased kidney function, allowed normally safe doses to accumulate to toxic levels. This toxicity manifested itself by a characteristic picture of circulatory collapse.

If toxicity is partially due to failure of glucuronide conjugation, other drugs using this pathway of metabolism should be evaluated for use in the premature infant.

No benefit to the infants from administration of penicillin or streptomycin could be demonstrated. Since there were more symptoms in the group treated with penicillin and streptomycin than in the non-treated group, these drugs may not be harmless. Therefore, the use of prophylactic antibiotics has been discontinued in this nursery.

We are indebted to the Pediatric Attending and House Staff of the Los Angeles County Hospital for help with this study, to Dr. Frederick Moore, who prepared the statistical analysis, to Drs. Charles F. Weiss and A. J. Glazko, Parke, Davis and Company, who did the assays on blood levels, and to Mary Finley, R.N., and the nursing personnel of the Premature Center.

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APPENDIX V

[From American Journal of Diseases of Children, vol. 101, February 1961, pp. 140-148]

SAFE AND EFFECTIVE CHLORAMPHENICOL DOSAGES FOR PREMATURE INFANTS

(By Joan E. Hodgman, M.D. and Lafayette E. Burns, M.D., Los Angeles)

Infections are a significant cause of death in premature infants. Arey and Dent(1) reported, in 1953, a survey of 102 neonatal deaths of which 84 were premature. They listed infection as the major cause of death in 13 (15.4%) of the prematures. Six years later Branton,(2) in a report of 176 consecutive newborn deaths, of which 136 were prematures, attributed death to infection in 20 (14.7%) of the prematures. He reported gram-negative coliform bacilli in 5 of 6 positive blood cultures. Infection also plays a significant role in the mortality at the Premature Center of Los Angeles County Hospital, which cares for over 1,200 premature infants yearly. The main organisms cultured from infections have been gram-negative coliform bacilli, particularly *E. coli* and *Klebsiella aerogenes* group. Studies have indicated that these organisms are most consistently sensitive to chloramphenicol. The toxicity of chloramphenicol to premature infants in doses over 100 mg/kg is well documented (3-6). Reported studies have correlated this toxicity with high blood levels of chloramphenicol. Prophylaxis with chloramphenicol as well as other antibiotics has been discontinued at the Premature Center, since in a controlled study they did not lower the mortality rate(3). Chloramphenicol would still be useful for the treatment of infected prematures if a safe dosage schedule were established.

This paper is a report of studies of blood-level responses to intramuscular and intravenous chloramphenicol made to determine whether lower doses would give therapeutic blood levels without toxicity.

METHOD

Premature infants of varying weights and ages were given microcrystalline or the succinate ester of chloramphenicol intramuscularly and intravenously, according to planned dosage schedules. Blood levels of total nitro compounds were

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NOTE.—Numbered references at end of article.

determined by analyzing capillary blood according to the method of Glazko (7).^{*} This method measures both active and inactive metabolites of chloramphenicol as total nitro compounds.

Timed urine specimens were collected by plastic bags from some of the infants. These were analyzed for chloramphenicol content by microbiologic assay against *Shigella sonnei* (8), as well as by chemical determination for total nitro compounds.^{*}

Microchemical analyses for serum sugar, BUN, and potassium levels were performed at the start of treatment, at 24 hours, and at 96 hours in the group of infants receiving chloramphenicol 25 mg/kg/day. Serum bilirubin determinations were done on any infant who developed jaundice.

MICROCRYSTALLINE CHLORAMPHENICOL†

Figure 1 shows the average blood level of total nitro compounds obtained in premature infants 1 to 6 days old given microcrystalline chloramphenicol, 10 mg/kg every 12 hours intramuscularly. The average level is low and probably inadequate for 12 to 24 hours after the start of treatment. From then on, it gradually rises as the nitro compounds accumulate. A tendency for the level to plateau may be noted during the fourth day of treatment. Of the 13 babies studied, 11 reached therapeutic levels of 10–20 $\mu\text{g}/\text{cc}$ (9), and showed no toxic symptoms. One infant failed to reach a therapeutic blood level. One infant accumulated nitro compounds to high levels and developed symptoms of chloramphenicol toxicity.

This infant was 3 days old at the start of treatment and weighed 1,980 gm. On the third day of treatment, he was noted to be voiding very little. During the next 24 hours he became limp and lethargic, at which time his blood level of nitro compounds had risen to 78 $\mu\text{g}/\text{cc}$. Following the omission of one dose, the blood level fell to 52, and his symptoms became less severe. Treatment was continued for 3 more days, during which time he was anorexic and somewhat listless. His symptoms disappeared 3 days after treatment was stopped.

Figure 1 also shows the average blood level of nitro compounds in 5 premature infants 12 to 67 days old on the same dosage schedule, 10 mg/kg every 12 hours intramuscularly. Of the 5 infants, 4 had been tested previously in the 1- to 6-day-old group. The absence of accumulation in this group is clearly demonstrated. None of these infants reached adequate blood levels on this dosage.

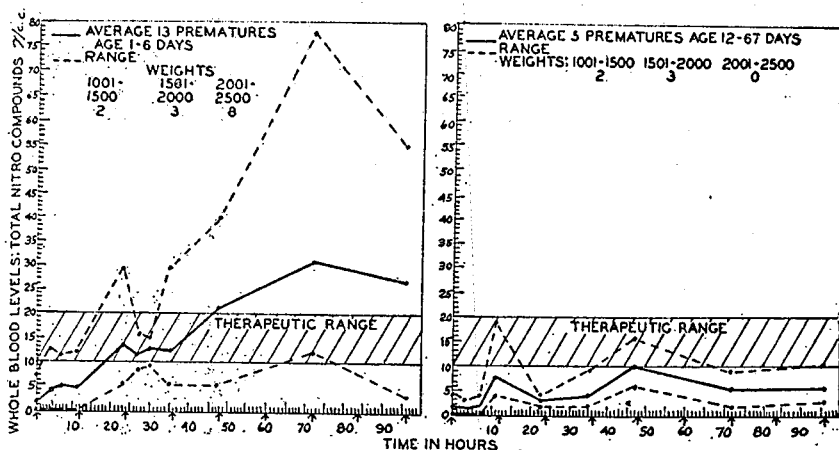


FIGURE 1.—Blood levels during treatment with microcrystalline chloramphenicol 10 mg/kg every 12 hours i.m.

^{*} Analyses were done by the Parke, Davis & Company Laboratories.

† Chloromycetin Intramuscular.

The average blood level for 15 premature infants, 1 to 2 days old, given a single injection of microcrystalline chloramphenicol, 50 mg/kg intramuscularly, is shown in Figure 2. Adequate blood levels were attained within 7 hours in all but 2 infants. The peak was reached at the 23-hour sample, followed by a gradual fall. The half-life of the administered dose was 28 to 44 hours as compared to a half-life in adults of 15 to 24 hours. (10) Two premature infants 8 and 9 days old were given the same dose. The blood levels as shown in Figure 2 were lower than in the younger babies, and the fall in level was more rapid. The birth weights of the infants tested are grouped on the charts. There was no correlation between birth weights and blood levels.

Further studies were carried out on week-long dosage schedules. Premature infants, ages 1 to 4 days, were given microcrystalline chloramphenicol, 50 mg/kg intramuscularly, every 48 hours. Of 12 infants tested, 8 had adequate levels but with marked fluctuations. Only 1 of 4 prematures, ages 13 to 27 days, similarly tested, had adequate levels. Using a schedule of 25 mg/kg given once daily, all of 12 infants tested had adequate levels in the 1- to 6-day-old group, but only 2 of 8 in the 14- to 23-day-old group. Given 50 mg/kg once daily to premature infants 9 to 36 days old produced adequate levels in all 8 infants tested without toxic symptoms.

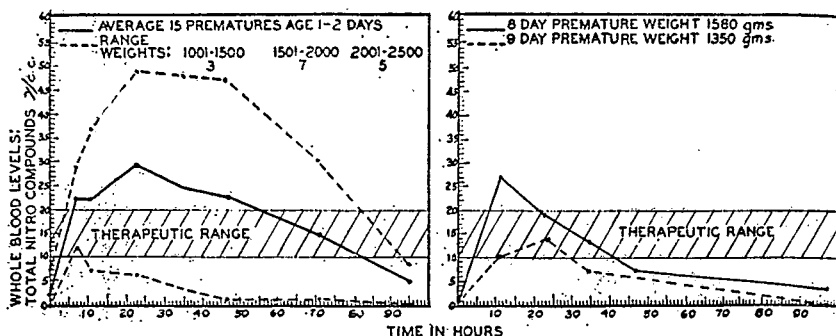


FIGURE 2.—Blood levels following a single dose of microcrystalline chloramphenicol 50 mg/kg I.M.

CHLORAMPHENICOL SODIUM SUCCINATE†

Chloramphenicol sodium succinate is a recently introduced ester of chloramphenicol which is highly water soluble and hence more readily absorbed than the micronized form. (11) Figure 3 shows the average blood level of nitro com-

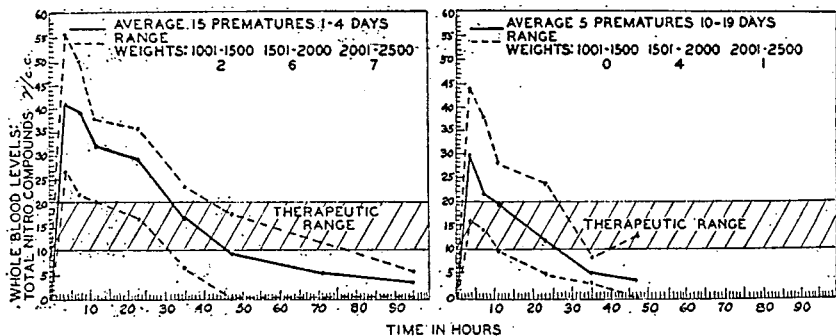


FIGURE 3.—Blood levels following a single dose of chloramphenicol sodium succinate 50 mg/kg I.M.

†Chloromycetin Succinate.

pounds following a single 50 mg/kg intramuscular injection of the succinate ester in 15 prematures 1 to 4 days old. Peak levels were obtained within 3 hours, clearly showing rapid absorption. Adequate levels were present for over 48 hours, but fell more rapidly, the half-life being 24 hours, as compared with a half-life of 28-44 hours with the microcrystalline form. Levels fall even more rapidly in older children, the half-life being 4 hours in 5-year-olds given the succinate ester. (1,10) Figure 3 shows the average blood level found in 5 prematures, 10 to 19 days old, given the same dose. Absorption was again rapid, and here, too, excretion was more rapid than with the younger prematures. The half-life was 14 hours with adequate levels maintained for 12 to 18 hours.

Eight premature infants, 2 to 4 days old, given chloramphenicol sodium succinate, 25 mg/kg intramuscularly once daily, after an initial dose of 50 mg/kg, had adequate levels for the week they were treated. One infant accumulated nitro compounds on this schedule, the blood level on the third day reaching 56 $\mu\text{g}/\text{cc}$. At this time the infant's abdomen was distended; he had liquid stools and grunting respirations. The infant recovered, and the blood levels dropped without stopping the drug. Although the symptoms disappeared while treatment was continued, they may represent a toxic reaction.

Three prematures, 12 to 22 days old, had inadequate levels when given 25 mg/kg/day intramuscularly. Five prematures, ages 10 to 18 days, had good levels on 50 mg/kg/day without toxic symptoms. Again, no correlation between birth weights and blood levels was found.

Chloramphenicol sodium succinate given intravenously to premature infants was also slowly excreted, as shown in Figure 4. Three 1-day-old infants were given 25 mg/kg in 50 cc. 5% glucose in water over a 5-hour period. Blood levels remained in the therapeutic range for 18 to 24 hours following completion of the infusion; the half-life was 15 to 22 hours. Two infants, 13 and 23 days old, were given 50 mg/kg over a 3-hour period. Again, adequate levels persisted for the succeeding 12 and 21 hours, with a half-life of 8 and 15 hours, respectively. One infant developed ashen gray pallor and lethargy within 1 hour after starting the infusion, when his blood level was 72 $\mu\text{g}/\text{cc}$. The symptoms disappeared in the next 3 hours coincident with the fall in blood level to 53 $\mu\text{g}/\text{cc}$.

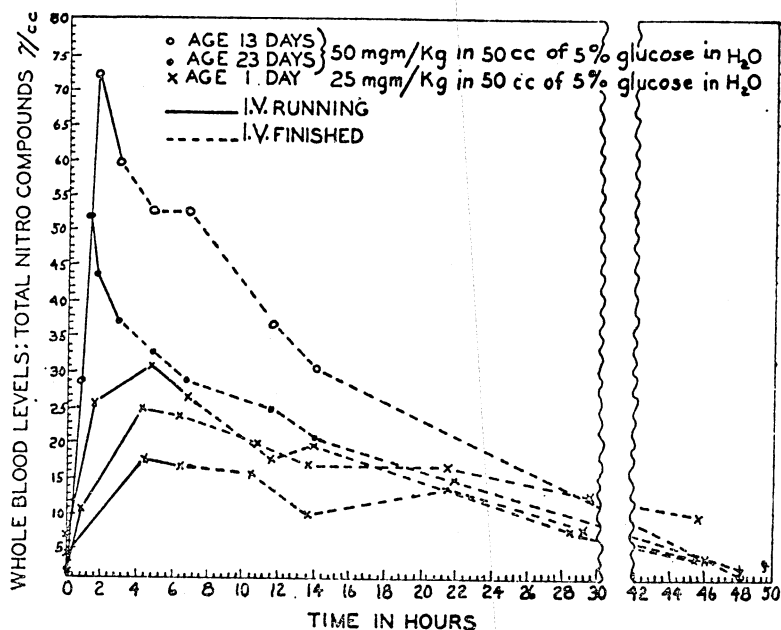


FIGURE 4.—Blood levels following I.V. administration of chloramphenicol sodium succinate.

URINE STUDIES

Twenty-four-hour excretion studies of microcrystalline chloramphenicol were made. In a study of 19 premature infants under 7 days old, an average of 20% of the daily dose was recovered (range 5%-52%). A higher average, 33%, was recovered from 5 infants over 10 days old (range 1.4%-50%). In similar studies on adults Glazko (12) was able to recover 90% of the daily dose, of which 5%-10% was excreted as the active form. In our studies on 8 premature infants under 7 days old, 7.7% of a dose was excreted in the active form, in older prematures, 9.2%.

BLOOD CHEMISTRIES

Blood chemistry determinations taken at the start of treatment, 24 hours later, and at 96 hours, were studied in 32 1- to 2-day-old premature infants on chloramphenicol injections of 25 mg/kg daily. BUN levels ranged from 8 to 30 mg%, except for 3 infants whose levels were 37, 53, and 89 mg%. The 2 infants with levels of 37 and 53 mg% had the lowest levels of nitro compounds in their respective test groups. The remaining infant, whose blood urea nitrogen level at the start of treatment was 89 mg% and at 24 hours was 85 mg%, gradually accumulated nitro compound levels to 56 µg/cc at 72 hours.

This infant, who weighed 1,162 gm. at birth, was 4 days old and in apparently good condition at the start of treatment with 25 mg/kg/day of microcrystalline chloramphenicol. Except for mild dehydration, his clinical condition remained good until the fifth day of treatment when he developed lethargy, respiratory distress, and abdominal distention. The chloramphenicol was discontinued, but the baby's symptoms progressed until death 48 hours later. A white blood cell count on the day before death was 29,500, with 74 segmented forms, 5 band forms, and 21 lymphocytes. A blood culture before death grew *E. coli*, sensitive only to polymyxin. Autopsy revealed pulmonary hemorrhage.

With the exception of the infant mentioned above, there was no consistent correlation between the BUN and nitro compound levels. Of 8 infants who had BUN levels between 25 and 30 mg%, 7 had nitro compound levels similar to others in their test groups. BUN levels below 10 mg% were not accompanied by low nitro compound levels.

Serum potassium levels were under 7 mEq/L in all except 3 infants. Two of these had low blood nitro compounds levels. The third was the infant mentioned above with elevated BUN levels, who died.

Blood sugar levels ranged between 26 and 107 mg%, except for the infant described above whose level was 144 mg% initially, and 126 mg% at 24 hours.

There was no correlation between serum bilirubin levels and levels of nitro compounds in 30 infants tested. For example, one infant had high blood nitro compound levels and a bilirubin level of 17 mg%. Another had a bilirubin of 16.8 mg% and low nitro compound levels. Infants receiving chloramphenicol had no increase in incidence of jaundice.

MORTALITY

Tests were performed on 126 premature infants. Six infants died during or after treatment. In general, infants in good condition were selected for study, making the mortality rate in this group meaningless. The clinical course of one of the infants who died is outlined above. A brief résumé of the histories of the remaining 5 infants follows:

Baby, birth weight 2,180 gm., demonstrated webbing of the neck and minor skeletal anomalies, but was in good general condition at the start of treatment with 50 mg/kg/48 hours of microcrystalline chloramphenicol. At 10 days of age, following 7 days of treatment, the infant died suddenly. Autopsy revealed infantile coarctation of the aorta. Blood levels of nitro compounds were consistently low.

Baby, birth weight 1,280 gm., died at 2 days of age after 1 injection of 50 mg/kg. Blood level at 24 hours was 40 µg/cc. Autopsy revealed intraventricular cerebral hemorrhage.

Baby, birth weight 1,920 gm., was in good condition at 4 days of age when treatment with mg/kg/48 hours of microcrystalline chloramphenicol was started. The baby developed lethargy, cyanosis, abdominal distention, and apnea at the start of treatment. Blood and spinal fluid cultures grew an organism of the *Klebsiella-Aerobacter* group, sensitive to chloramphenicol. Treatment was continued but the infant died at 6 days. Autopsy confirmed the diagnosis of purulent meningitis.

Baby, birth weight 1,420 gm., was started on treatment of 50 mg/kg/48 hours of microcrystalline chloramphenicol at 4 days of age. Forty-eight hours later, the infant developed vomiting, followed by loose yellow stools, lethargy, ashen gray pallor, apnea, and death at 8 days of age. Blood levels reached a peak at $54\mu\text{g/cc}$ 24 hours following the start of the treatment, dropped to $40\mu\text{g/cc}$ at 48 hours when symptoms appeared, fell to $25\mu\text{g/cc}$ at 72 hours, and rose again to $50\mu\text{g/cc}$ at 96 hours. Death occurred 14 hours after the last blood level noted. Blood culture drawn at death was sterile. No autopsy was permitted.

Baby, birth weight 1,990 gm., was started on treatment of 50 mg/kg/48 hours of microcrystalline chloramphenicol on the first day of life. Respiratory distress was present from birth. Tremors appeared on the third day, followed by distention of the abdomen, lethargy, ashen gray pallor, apnea, and death on the sixth day. Blood levels were $41\mu\text{g/cc}$ at 24 hours, and $38\mu\text{g/cc}$ at 48 hours. Blood culture drawn at death was sterile. No autopsy was permitted.

COMMENT

The normal metabolic pathway for chloramphenicol is absorption, conjugation with glucuronic acid in the liver, and excretion by the kidney tubules. (12) Some active chloramphenicol is removed from the circulation by glomerular filtration. (13) Accumulation of chloramphenicol in the premature infant must be due to differences in one or more of these factors.

Single-dose studies of the microcrystalline form of chloramphenicol clearly demonstrate its slow absorption, the peak level not being attained for 24 hours. Considering the low solubility of this form of the drug, a depot effect could be anticipated. Single-dose studies of chloramphenicol sodium succinate showed rapid absorption with a peak within 4 hours, but also gave prolonged levels with half-lives 2 to 3 times those of adults. Half-lives of the succinate ester given intravenously were much longer than those reported for adults, eliminating slow absorption as the explanation for the prolonged levels. Decreased kidney function in the premature is well established. (14-16). The glucuronide conjugated, or inactive, chloramphenicol is excreted by the renal tubules while the active form is filtered by the glomerules. Tubular excretion is quantitatively the most important excretory pathway, as 90% of the chloramphenicol in the urine is in the conjugated form in both the adult and premature. (12). However, the adult excretes 90% of a daily dose, in contrast to 1.4%-52% in the premature. Therefore, a decrease in tubular excretion in the premature must be one of the factors accounting for prolongation of blood levels.

A deficiency in conjugation by the liver must also be present to explain the prolonged levels of active chloramphenicol. If hepatic conjugation were normal with poor kidney function, only the inactive form would accumulate. This is seen clinically in anuric adults, where a renal defect only is present, the conjugated form alone accumulates to high levels and patients exhibit no toxicity. (17) In the premature, however, only 35% of the circulating chloramphenicol is in the inactive form. (5,10) A deficiency of the glucuronidase in the liver of the newborn has been documented. (18,19). The accumulation of active chloramphenicol in the premature can be explained by this deficiency. The finding that blood levels plateau on the third and fourth day, plus the correlation of levels with chronological age rather than birth weight, lend support to the idea that enzymatic deficiencies, which improve as the infant matures, are responsible for the prolonged blood levels.

As chloramphenicol and bilirubin apparently follow the same metabolic pathway, some correlation between blood levels of bilirubin and chloramphenicol could be expected. No correlation was demonstrated. In a previous study, there was no increase in the incidence of jaundice among premature infants receiving chloramphenicol compared with a similar group not receiving it. (3) In the same study, autopsies on infants who died with chloramphenicol toxicity did not reveal kernicterus.

There was no correlation between the levels of nitro compounds and a BUN of 53 mg% or less. One infant with a BUN of 89 mg% at the start of treatment accumulated nitro compounds, as did another infant with a low renal output for 24 hours. Infants with a BUN above 60 mg%, or other signs of defective renal function should be treated cautiously with a reduced dosage.

Premature infants were tested in all weight groups over 1,000 grams. No correlation between birth weight and blood levels was found. A definite correlation between age and blood levels was demonstrated. Tendency to accumulate nitro compounds in the blood stream was most marked during the first 4 days

of life. None of the infants tested after 7 days of age showed accumulation of nitro compounds in the blood. The majority of these older infants failed to maintain levels in the therapeutic range on 25 mg/kg/day, whereas doses of 50 mg/kg/day produced therapeutic levels without toxic symptoms. Premature infants over 1 week of age can be treated with 1 daily dose of 50 mg/kg of chloramphenicol with reasonable safety.

The young infants also showed greater variability of levels on a given dosage than did premature infants over 7 days of age. This is well demonstrated in Figure 1, representing 1-4-day-old infants given microcrystalline chloramphenicol, 10 mg/kg every 12 hours. On this dose, one infant accumulated nitro compounds to toxic levels, while another failed to reach therapeutic levels.

The young infants tested on low doses of microcrystalline chloramphenicol given twice daily accumulated nitro compounds more rapidly than when a larger dose was given once a day. Since adequate levels are maintained for 24 hours after a single injection of both types of chloramphenicol tested, the total dose should be given once daily.

The symptoms of chloramphenicol toxicity in the premature infant have been reported by several authors. (3-6) The time necessary for symptoms to appear depends on the dose used. When 125-165 mg/kg/day were given intramuscularly, the earliest symptoms appeared from 48 to 96 hours after the start of treatment and involved the gastrointestinal tract. (3) The infants refused to nurse, began to regurgitate formula, their abdomens became distended, and they developed loose green stools. Within 24 hours after the appearance of toxic symptoms, they became ashen gray, lethargic, and developed rapid, shallow respirations. Death, when it occurred, followed within an additional 24 hours. The infants who recovered had no demonstrable sequelae on discharge from the nursery.

Of the 126 infants tested during this study, 6 developed symptoms similar to those described. One infant was receiving intravenous medication, and the correlation between symptoms and blood levels seems clear cut. Lethargy and grayish pallor appeared within an hour of starting the intravenous medication, when the blood level was 72 μ g/cc. and the symptoms disappeared rapidly coincident with a fall in level to 53 μ g/cc. The accumulation of nitro compounds in this baby was caused by too rapid an intravenous infusion, and the symptoms could have been prevented by slower administration. This is a precaution that must be carefully observed when giving chloramphenicol intravenously.

Two infants, both under 4 days of age, developed symptoms of chloramphenicol toxicity on intramuscular medication, but recovered. In both of these infants the symptoms appeared on the third day of treatment, when their blood levels were over 50 μ g/cc. and the symptoms disappeared as the levels fell. In the 3 surviving infants, toxic symptoms seemed to be correlated directly with elevation in blood levels of nitro compounds. The blood levels varied from 53 μ g/cc to 73 μ g/cc at the time symptoms appeared.

Three infants died while receiving chloramphenicol, with symptoms similar to those described above. The symptomatology of septicemia is very similar to that of chloramphenicol toxicity. One case had abnormal blood chemistries at the start of treatment, and a chloramphenicol-resistant organism was grown from blood culture taken before death. Symptoms appeared after 5 days of treatment, when the infant was 9 days old. This death was probably due to infection, but may represent a toxic reaction to chloramphenicol. Autopsies were not performed on the remaining 2 infants, and blood cultures taken at the time of death were sterile. The levels of chloramphenicol in these infants were never over 54 μ g/cc. A definite cause of death could not be determined on the basis of the clinical findings. Unexplained deaths, particularly without autopsy, are too common on a premature service to definitely assign these deaths to chloramphenicol toxicity; however, it is possible that these 3 infants represent a toxic reaction at relatively low blood levels. It is perhaps important that these babies were under one week of age at the start of treatment.

If chloramphenicol is used for young premature infants, it should be given in a dosage of 25 mg/kg once daily. If toxic symptoms appear, the drug should be discontinued immediately and blood levels determined where possible. Blood levels can be determined by following the method of Glazko et al. (11).§ The determination requires 0.2 cc. of whole blood, which can be obtained from a heel puncture. The method is a relatively simple colorimetric comparison, which could be performed by the average hospital laboratory.

§Detailed procedure available from Parke, Davis & Company.

Of the 5 infants exhibiting toxicity on intramuscular medication, 4 were given microcrystalline chloramphenicol. This preparation has the disadvantage of slow absorption, resulting in low initial blood levels and greater tendency to accumulation with repeated dosage. In treatment of the premature infant, the more rapidly absorbed chloramphenicol sodium succinate would be preferred.

SUMMARY

Recent investigations have documented chloramphenicol toxicity in premature infants given doses over 100 mg/kg/day. Toxicity was shown to have a correlation with elevated blood levels of chloramphenicol. In order to establish whether lower doses would result in therapeutic levels without toxicity, we determined blood nitro compounds in premature infants after intramuscular and intravenous administration of 20 to 50 mg/kg/day.

Initial levels were lower and toxic reactions occurred more commonly with microcrystalline chloramphenicol than with the sodium succinate ester. The latter form should be preferred for treatment of the premature infant. A tendency to accumulate chloramphenicol in the blood was observed only in the young infants, regardless of birth weight.

Two infants under 4 days of age accumulated blood levels over 50 µg/cc and developed toxic symptoms after daily doses of 25 mg/kg intramuscularly. Two infants died with blood levels below 50 µg/cc without clinical explanation of their death. Two of the infants with toxic symptoms had clinical or laboratory evidence of reduced renal function. Such infants should be treated cautiously with a smaller dose.

Premature infants 7 days of age or less maintained blood levels in the therapeutic range when given 25 mg/kg of chloramphenicol sodium succinate intramuscularly once daily. Premature infants over 7 days of age failed to maintain therapeutic levels on this dose, but developed adequate levels without toxic symptoms when given 50 mg/kg intramuscularly once daily of the same drug. The same doses of chloramphenicol sodium succinate in each age group, given intravenously, gave adequate levels for 24 hours. This form of the drug must be infused slowly over a period of 3 to 5 hours to prevent accumulation of chloramphenicol to toxic levels.

All premature infants, especially those in the first week of life or with evidence of reduced renal function, should be carefully watched for the development of abdominal distention, lethargy, respiratory distress, and gray cyanosis. The drug should be discontinued promptly if these symptoms appear.

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EDITORIAL COMMENT

This report documents the considerable variability of chloramphenicol blood levels achieved in individual prematures even when the intravenous or intramuscular route of administration is used. Observe that several less than week old infants showed signs and symptoms of toxicity while receiving doses currently recommended. Also note the frequent failure to achieve blood levels claimed to be therapeutic when the "cautious" dose is used after the first week. The suspected inability of newborns to absorb adequately the palmitate form of the drug when given by mouth is not dealt with here.

APPENDIX VI

[From *Annals New York Academy of Sciences*, 1967, pp. 488-498]

BACTERIAL MENINGITIS*

(By Paul F. Wehrle, Allen W. Mathies, John M. Leedom and Daniel Ivler, Departments of Pediatrics and Medicine, University of Southern California and the Communicable Disease Service, Los Angeles County General Hospital, Los Angeles, Calif.)

INTRODUCTION

Bacterial infections of the central nervous system still constitute serious medical emergencies, despite the availability of numerous effective antimicrobial agents. Death occurs in at least 10% of these patients, and serious sequelae are frequently seen among those who survive. In spite of the serious nature of these

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infections and the significant disability among many of those who survive, the various therapeutic regimens proposed have not been evaluated as thoroughly as is desirable.

Some of the problems that complicate analysis of the various therapeutic routines advocated in the past are readily apparent. The incidence of bacterial meningitis infections is not great, and the relative etiologic importance of particular bacterial species varies with the age group considered. Rates of bacterial meningitis approach 1:1000 live births during the neonatal period. The rates fall rapidly during infancy and childhood. This progressive decline in age specific rates continues until the fifth decade. It then rises slightly with the increase in pneumococcal infections among older persons. Because of these low rates, relatively few patients are available for study in any single hospital. In addition, the diagnosis of these infections is often made in hospitals other than those providing definitive treatment. Referral for definitive treatment may be made after some form of treatment has been initiated. This referral is usually to other hospitals on the basis of age group, economic status, or other selective determinants. These factors make the interpretation of experience within a single hospital, unless carefully controlled, subject to serious errors. It is also obvious that experience in different hospitals with different routines cannot be compared, yet several attempts to do so have been made. As yet, no well controlled cooperative study has been attempted, involving several large institutions, to evaluate the management of this type of infection, although such an effort might yield useful data. If such a study were contemplated, these and still other factors must be properly controlled.

The severity of the illness and the progressive nature of the disease often introduce additional variables with respect to supportive therapy. This support, dependent upon experienced nursing and medical personnel, is necessary if the patient is to survive long enough for an antimicrobial drug to have any benefit. This situation is further complicated by a fixed and mystical belief that if one antimicrobial agent is good, two must be better, and three even more efficacious, despite evidence to the contrary. (1)

It is the purpose of this paper to examine some of the characteristics of bacterial meningitis and the factors important in survival. In addition, the results of treatment with ampicillin alone and ampicillin plus chloramphenicol supplemented by two days of streptomycin therapy will be presented.

If one examines the case fatality rates for a particular type of bacterial meningitis on our service during successive years, it is interesting to note the substantial variation in mortality. If one contrasts selected years, this variation is greater than expected by chance alone. As yet, we have no explanation for these variations. This pattern is clearly illustrated by meningococcal infections treated on our service during the past six years, as shown in Table 1. During this time, Type B meningococci have been predominant, and approximately one-third of the strains tested have been resistant to sulfadiazine ($MIC \geq 10$ mg/100 ml). (2)

NATURAL VARIATION IN CASE FATALITY RATES

TABLE 1.—MENINGOCOCCAL DISEASE, CASE FATALITY RATIOS BY YEAR, LOS ANGELES COUNTY GENERAL HOSPITAL

Year of treatment	Outcome of patient		Total cases	Case fatality (percent)
	Survived	Died		
1961.....	34	4	38	10.5
1962.....	64	6	70	8.6
1963.....	67	6	73	8.2
1964.....	85	14	99	14.1
1965.....	88	3	91	13.3
1966 ²	86	6	92	6.5
Total.....	424	39	463	(8.4)

¹ $\chi^2 = 6.74$; $p < 0.01$.

² Through October 1966.

NOTE.—Numbered references at end of article.

No changes in staffing pattern have been made, and the level of experience of the staff directly concerned with patient care has been similar during each of these years. During this period, any patient reaching the hospital with a detectable heart beat, regardless of the need for respiratory assistance has been included.

The contrast between 1964 and 1965 is apparent. Fourteen deaths occurred among 99 patients treated during 1964, while only three deaths occurred among 91 patients treated during 1965. If one uses standard techniques to calculate the probability of the difference between these years occurring by chance alone, $\chi^2=6.74$; $p<0.01$. Furthermore, if one examines the trend over the years as is illustrated in figures 1 and 2, it is apparent that clustering of both cases and deaths occurs during several intervals over these years. It is also apparent that a substantial influx of patients occurred during the weeks immediately subsequent to the influenza outbreak in late February of 1966.

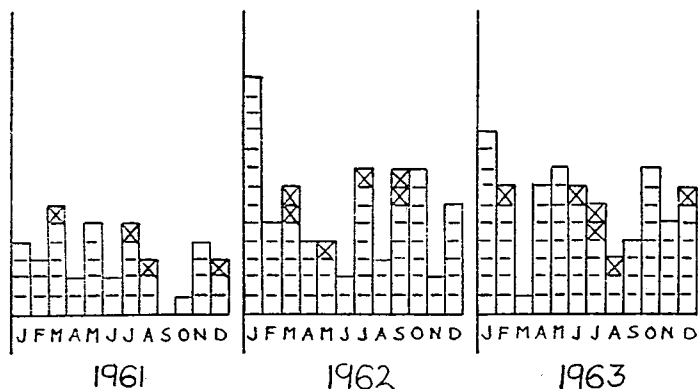


FIGURE 1. Meningococcal disease, Los Angeles County General Hospital.

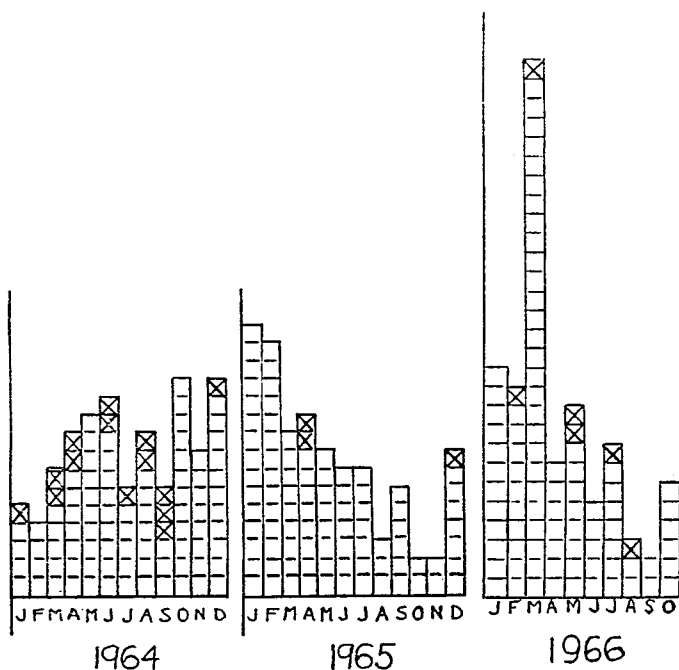


FIGURE 2.—Meningococcal disease, Los Angeles County General Hospital.

These variations are not limited to meningococcal infection, since *Hemophilus influenzae* infections have similar variations. As noted in table 2, two deaths occurred among 96 patients treated in 1962, while nine deaths occurred among the 91 cases admitted during 1963. These differences are substantial ($X^2=5.30$; $p<.02$).

The contrast between these two types of infection during these four years is even more interesting, since the difference in meningococcal case fatality rates occurred in years characterized by a relatively stable (8.3 and 6.9) case fatality ratios for *H. influenzae* infections. The converse was also true, since 1962 and 1963 were characterized by stable (8.6 and 8.2) ratios for meningococcal disease. This independent variation of case fatality rates by etiologic agent provides assurance that alteration in the mechanics of the service were not important in the variation seen, but that the difference was due to other factors. These fluctuations are unlike the consistently low case fatality rates reported during World War II when Group A meningococcal disease was epidemic (3).

TABLE 2.—"HEMOPHILUS INFLUENZAE" MENINGITIS CASE FATALITY RATIOS, BY YEAR, LOS ANGELES COUNTY HOSPITAL

Year of treatment	Outcome of patient		Total cases	Case fatality (percent)
	Survived	Died		
1961.....	89	8	97	8.2
1962.....	94	2	96	2.1
1963.....	82	9	91	9.8
1964.....	110	10	120	8.3
1965.....	94	7	101	6.9
1966 ¹	68	5	73	6.8
Total.....	537	41	578	(7)

¹ Through October 1966.

² $\rightarrow X^2=5.30$; $p<.02$.

Whether these variations in the proportion of fatal cases reflect concomitant infections with other agents intermittently operative in the community, or whether they simply represent the extremes of chance variation is impossible to determine at this time. However, these variations do serve as a warning to those evaluating various forms of therapy unless observations are carefully controlled and made simultaneously.

Evaluation of the outcome of pneumococcal infections of the central nervous system is particularly difficult, since several recognizable factors are operative. The relatively low mortality seen with subsequent attacks in patients with repeated episodes of disease has been recognized for many years, as has the better prognosis with pneumococcal meningitis following otitis media or skull fracture, and the extremely high risk of the alcoholic and the elderly person. Particular hospitals, by virtue of serving skid-row populations may have case fatality ratios several times higher than those catering to younger or less debilitated populations.

Some of the problems in analysis of pneumococcal meningitis data are illustrated in Table 3. Here, one sees not only the variation by age, but also by severity of illness at the time of admission to the hospital. If one treated only younger patients, or excluded the severe cases requiring artificial respiration to maintain life during transfer to the definitive hospital and those with a fulminant course of a few hours duration, one would have quite a different case fatality ratio.

It is apparent from these data that if any rational comparison between hospitals or between treatment routines is contemplated, many factors must be carefully controlled. Analysis of the severity of illness at the time of admission to the hospital is essential, as is a strict random alternation of patients for various treatment routines. In addition, care must be taken in interpretation of results to avoid bias in regard to portal of entry, age of the patient, and the general state of health.

EVALUATION OF THERAPEUTIC REGIMENS

In an attempt to clarify the relative effectiveness of various currently advocated treatment routines, the activity of several antibiotics was determined against *Hemophilus influenzae*, Type B., *Neisseria meningitidis*, and *Diplococcus pneumoniae* isolated from spinal fluid. It became apparent that ampicillin, on the basis

of *in vitro* studies, was at least as active as chloramphenicol against *H. influenzae*, and as penicillin G against the meningococcus and the pneumococcus. After initial *in vitro* studies of many isolates of *H. influenzae*, Type B, ampicillin was administered cautiously to patients with meningitis due to this organism who had been partially treated with chloramphenicol. Later, ampicillin was used as initial therapy in individuals not critically ill, providing satisfactory assurance of clinical efficacy and data concerning the diffusion of this drug into spinal fluid. (4,5) Concomitant and subsequent trials indicated that the clinical efficacy was similar to penicillin G in the treatment of both pneumococcal and meningococcal infections, and at least equivalent to chloramphenicol in *H. influenzae* Type B infections. (6,7,8,)

TABLE 3.—PNEUMOCOCCAL MENINGITIS—OUTCOME BY AGE AND SEVERITY OF ILLNESS, LOS ANGELES COUNTY GENERAL HOSPITAL, JULY 1963 TO JUNE 1966

Age group, years	Severity ¹ on admission to hospital						Total patients studied		
	Severe		Moderate ²		Mild ³				
	Total	Fatal	Total	Fatal	Total	Fatal	Cases	Deaths	Percent fatal
Under 1.....	8	1	7	3	10	0	25	4	16.0
1 to 15.....	14	6	0	0	23	0	38	6	15.8
15 to 29.....	5	0	1	0	7	0	13	0	0
30 to 44.....	15	10	2	1	6	1	23	12	52.2
45 to 59.....	24	9	0	0	9	1	33	10	30.3
60 plus.....	34	17	1	0	6	0	41	17	41.5
Total.....	101	43	11	4	61	2	173	49	28.3

¹ Severe equals coma, semicoma, significant hypotension or definite shock.

² Moderate equals convulsions.

³ Mild equals none of the above.

The present study includes patients admitted to our service between July 1st, 1965, and July 5, 1966. Therapy was provided using ampicillin in an initial rapid I.V. infusion of 50 mg per kg, followed by 150 mg per kg per day in six divided four-hourly rapid infusions. Alternate patients, selected on the basis of chart number, received two additional antimicrobial agents. These were chloramphenicol, 100 mg per kg per day, to a maximum of four grams each day for the total duration of therapy, and streptomycin, 40 mg kg per day (to a maximum of two grams) for the initial two days of treatment. The administration of each dose of chloramphenicol was delayed until 30 minutes after ampicillin had been administered in an effort to avoid antibiotic interference. Chloramphenicol was given by rapid I.V. infusion like the ampicillin. Streptomycin was given I.M. Both ampicillin and chloramphenicol were sometimes given I.M. at the I.V. dosage level to convalescent patients.

In table 4, the patients included in this evaluation are recorded by age group and by severity of illness at the time of admission to the hospital. In addition to the patients recorded in the table, a total of 15 infants less than two months of age were admitted during the study period. These infants have been excluded from analysis, since the organisms differed and initial treatment for meningitis in this age group was with either penicillin G or ampicillin plus kanamycin. This latter combination provides optimal initial therapy for organisms responsible for neonatal infections during recent years in our hospital.

Response to therapy for the two treatment routines is contrasted in table 5. The response to ampicillin given as a single agent was excellent, with only 6 deaths among 145 patients treated, giving an overall case fatality rate of 4.1%. There were 14 deaths among 123 patients given multiple antibiotic treatment, a case fatality ratio of 11.4%. This difference is significant, ($X^2=5.01$: $p \cong 0.02$). Although a few more patients receiving ampicillin were randomly included in the mild disease category, this chance shift is insufficient to explain the substantial difference in outcome observed.

TABLE 4.—CASES OF ACUTE BACTERIAL MENINGITIS, EXCLUDING NEONATES,¹ BY AGE GROUP, SEVERITY, AND OUTCOME, LOS ANGELES COUNTY GENERAL HOSPITAL, 1 YEAR EXPERIENCE TO JULY 1966

Age group	Severity ² on admission to hospital							
	Mild		Moderate		Severe		Total	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
2 to 11 months.....	48	1	18	0	15	5	81	6
1 to 14 years.....	103	0	11	0	14	2	128	2
15 to 44 years.....	28	0	0	0	21	4	49	4
45 to 59 years.....	10	1	0	0	17	7	27	8
60 years and over.....	6	0	0	0	17	8	23	8
Total.....	195	2	29	0	84	26	308	28

¹ 15 infants up to 2 months of age treated, with 6 deaths.² Severe—coma, semicoma, significant hypotension, or definite shock; moderate—convulsions; mild—none of the above.

TABLE 5.—SINGLE VERSUS MULTIPLE ANTIMICROBIAL THERAPY IN PATIENTS MORE THAN 2 MONTHS OF AGE WITH ACUTE BACTERIAL MENINGITIS, BY SEVERITY OF ILLNESS, LOS ANGELES COUNTY GENERAL HOSPITAL (1 YEAR EXPERIENCE TO JULY 1966)

Severity of illness on admission	Therapeutic regimen selected								
	Ampicillin alone			Ampicillin plus chloramphenicol plus streptomycin			Total patients treated ¹		
	Cases	Deaths	Percent	Cases	Deaths	Percent	Cases	Deaths	Percent
Mild.....	100	1	1.0	76	0	-----	176	1	0.6
Moderate.....	14	0	-----	10	0	-----	24	0	0
Severe.....	31	5	16.1	37	14	37.8	68	19	27.8
Total.....	145	6	4.1	123	14	11.4	268	20	7.5

¹ Patients excluded: unusual organisms, 15; error in treatment assignment or penicillin allergy, 17; endocarditis, mechanical defect, etc., 6; inadequate records, 2; total exclusions, 40, with 8 deaths.

Table 6 demonstrates the positive correlation of increasing age with an increasing proportion of deaths. It is important, however, to note that the increased fatality in the multiple drug regimen occurred at all ages, and was not limited to infants, as in the "grey syndrome" associated with chloramphenicol (9), nor did it involve the elderly or the alcoholic exclusively.

When one examines the response recorded in Table 7 to single vs. multiple therapy by category of disease, no single category predominates in the excess mortality found among patients receiving multiple drug therapy.

It is apparent from these data that adding other antimicrobial agents to a single effective bactericidal drug in the therapy of the common types of acute bacterial meningitis may be detrimental. The reasons for this difference are obscure. Perhaps this is the one time in 50 ($p=0.02$) in which this difference could have occurred by chance alone. On the other hand, it seems entirely possible that interference between chloramphenicol and ampicillin may have occurred (1). In addition, the toxicity of chloramphenicol may be sufficient, in the critically ill person, to have an adverse effect upon survival. In any event, careful investigative work is needed for further evaluation of our present antibiotics in the management of bacterial meningitis.

A recently described antimicrobial agent, hetacillin, offers promise of efficacy similar to that of ampicillin for the treatment of these infections. *In vitro* activity appears to be similar to that of ampicillin, as is shown in Figures 3, 4 and 5. These data were derived using standard procedures with 25 strains of pneumococci and meningococci, and 25 strains of *Hemophilus influenzae* Type B recently isolated from spinal fluid.* These data, together with the demonstrably greater peak serum levels obtained after injection of equivalent doses (10), suggest that hetacillin deserves careful evaluation in the treatment of meningitis.

*Curves of rate of killing of a few strains of meningococci are similar for ampicillin, penicillin G and hetacillin.

TABLE 6.—SINGLE VERSUS MULTIPLE ANTIMICROBIAL THERAPY IN ACUTE BACTERIAL MENINGITIS BY AGE GROUP OF PATIENT, LOS ANGELES COUNTY GENERAL HOSPITAL

[1 year experience to July 1965]

Age group of patients	Therapeutic regimen selected					
	Ampicillin alone		Ampicillin+chlor- amphenicol+ streptomycin		Total patients treated ¹	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
2 to 11 months.....	35	1	30	2	65	3
1 to 14 yr.....	63	0	55	1	118	1
15 to 44 yr.....	22	1	19	2	41	3
45 to 59 yr.....	17	4	8	3	25	7
60-plus years.....	8	0	11	6	19	6
Total.....	129	5	111	13	268	20
Case fatality (percent).....	4.1		11.4		7.5	

¹ Patients excluded; unusual organisms, 15; error in treatment assignment or penicillin allergy, 17; endocarditis, mechanical defect, etc., 6; inadequate records, 2; total exclusions, 40 with 8 deaths.

TABLE 7.—SINGLES VERSUS MULTIPLE ANTIMICROBIAL THERAPY IN PATIENTS MORE THAN 2 MONTHS OF AGE WITH ACUTE BACTERIAL MENINGITIS¹ BY DISEASE CATEGORY, LOS ANGELES COUNTY GENERAL HOSPITAL

[1 year experience to July 1966]

Type of bacteria isolated	Therapeutic regimen selected						
	Ampicillin alone		Ampicillin + chlor- amphenicol + streptomycin		Total patients treated ¹		
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Per cent
Meningococci.....	53	1	39	3	92	4	4.3
H. influenzae.....	37	0	38	2	75	2	2.7
Pneumococci.....	27	4	27	7	54	11	20.4
Purulent, non isolated.....	28	1	19	2	47	3	6.4
Total.....	145	6	123	14	268	20	7.5
Case fatality (percent).....	4.1		11.4		7.5		

¹ Patients excluded: unusual organisms, 15; error in treatment assignment or penicillin allergy, 173; endocarditis, mechanical defect, etc., 6; inadequate records, 2; total exclusions, 40 with 8 deaths.

ACTIVITY OF FOUR ANTIBIOTICS AGAINST TWENTY-FIVE STRAINS OF
D. PNEUMONIAE

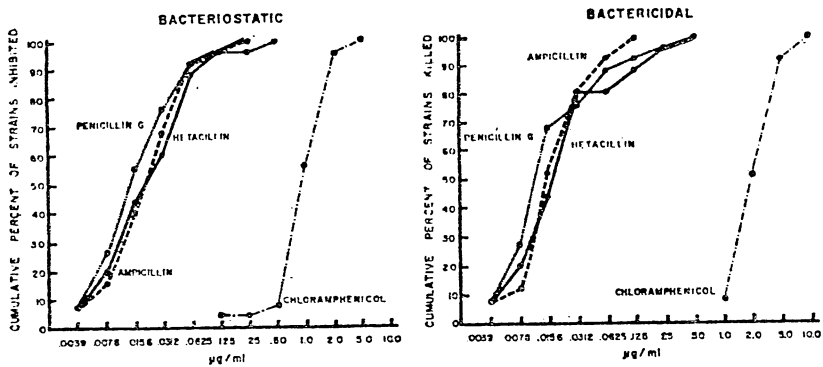


FIGURE 3.—Activity of four antibiotics against 25 strains of *D. pneumoniae*.

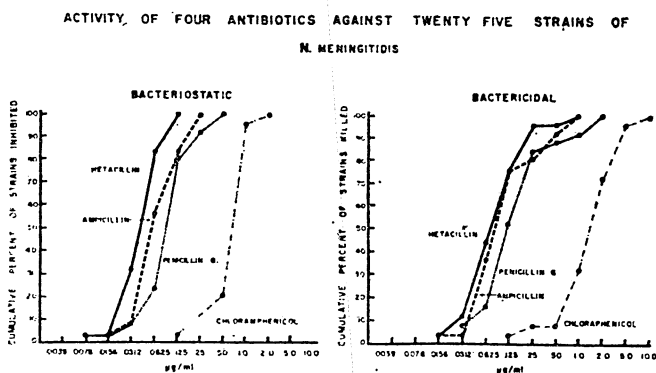


FIGURE 4. Activity of four antibiotics against 25 strains of *N. meningitidis*.

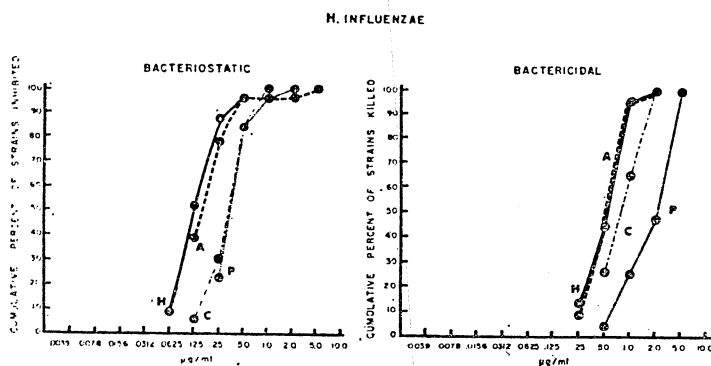


FIGURE 5.—Activity of four antibiotics against 25 strains of *H. influenzae*. H=hetacillin; A=ampicillin; C=chloramphenicol; P=penicillin G.

CONCLUSION

Acute bacterial meningitis remains a serious problem, and despite the availability of numerous effective antimicrobial agents, it carries a substantial risk of death or significant disability. The prompt administration of a specific antimicrobial agent substantially reduces mortality and morbidity. At present, the efficacy of ampicillin alone in the treatment of the common types of bacterial meningitis appears to be established. Hetacillin, a recently developed antibiotic closely related to ampicillin, deserves evaluation in these infections.

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APPENDIX VII

[From *Clinical Neurosurgery*, vol. 14, pp. 72–85]

Chapter IV

MANAGEMENT OF BACTERIAL MENINGITIS *

(By Paul F. Wehrle, M.D., Allen W. Mathies, Jr., M.D., Ph. D., and John M. Leedom, M.D.)

Acute bacterial central nervous system infections represent, particularly in early infancy, true medical emergencies. Before the advent of modern antibacterial therapy, these infections were usually associated with death or serious disability. At the present time, the case fatality rate remains relatively high, approximately 10 per cent. Higher case fatality rates occur after pneumococcal meningitis, particularly among older individuals, with somewhat lower mortality accompanying disease due to *Hemophilus influenzae*, Type B, and *Neisseria meningitidis*. Infections seen among newborn and young infants are most frequently caused by enteric organisms and result in a mortality rate of at least 50 per cent. Serious neurological sequelae, an important problem at any age, occur in at least 50 per cent of those cured bacteriologically.

Infancy and childhood are the ages of greatest incidence of these infections. Table IV.I shows data from the Los Angeles County General Hospital during a 12-month period ending in July 1966. During that year, 285 patients representing all age groups, all socioeconomic levels, and all geographic areas within the county were treated. Some 69 per cent of all our patients were less than 15 years of age, and 84 (or 29 per cent) were infants less than 1 year old. These data also clearly show the substantial increase in severity of infection associated with older age groups and the higher mortality at the extremes of life. Only two of six (33 per cent) of the patients less than 2 months old who died were placed in the severe category at the time of admission. In contrast, 21 of the 23 (91.3 per cent) older patients who died were judged to be severely ill on admission. These data suggest the relative difficulty of assessing the severity of the illness in young infants.

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NOTE.—Numbered references at end of article.

TABLE IV.1.—CASES OF ACUTE BACTERIAL MENINGITIS¹

Age group	Severity ² on admission to hospital							
	Mild		Moderate		Severe		Total	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Death
<2 months.....	10	3	2	1	3	2	15	6
2 to 11 months.....	42	1	14	0	13	4	69	5
1 to 14 years.....	91	0	11	0	12	1	114	1
15 to 44 years.....	25	0	0	0	17	2	42	2
45 to 59 years.....	9	1	0	0	16	7	25	8
60+ years.....	4	0	0	0	16	7	20	7
Total.....	181	5	27	1	77	23	285	29

¹ Los Angeles County General Hospital, 1 year experience to July 1966, by age group, severity, and outcome.

² Severe: coma, semicoma, significant hypotension, or definite shock. Moderate: convulsions. Mild: none of the above. See references 3, 9, and 12.)

Optimal management of the medical and, at times, surgical emergencies which are seen in patients with acute bacterial central nervous system disease requires careful attention to certain key principles of diagnosis and therapy. With observation of these principles, described below, and the use of newer techniques for monitoring the illness, morbidity and mortality may be reduced below current levels in most hospitals.

EVALUATION OF THE TOTAL PATIENT

Critical and rapid clinical evaluation of the patient is essential to determine the general condition, the presence of actual or impending shock, underlying defects, associated complicating disease (such as brain abscess or bacterial endocarditis), and the state of hydration.

Nearly 10 per cent of our patients arrive at the hospital in definite or impending shock. Recognition of this problem and prompt expansion of the intravascular fluid volume are essential if life is to be maintained. Inasmuch as the great majority of deaths occur within the first few hours after arrival in the hospital, nonspecific measures such as administration of blood, plasma, and electrolyte solutions must be instituted. Use of a central venous catheter provides continuous information regarding venous return and cardiac output if shock is present. Attention to the airway, with tracheostomy if necessary, is most important during this stage. Because even the most effective antibacterial therapy requires some time to arrest the progress of the disease, the importance of these supportive measures cannot be overemphasized.

During the initial evaluation of the patient, the clinician must be alert for evidence of associated disease such as brain abscess or localized cerebritis which may require attention later. It should be noted that nearly 2 per cent of patients admitted to our service with central nervous system infections have concomitant bacterial endocarditis. These patients are particularly likely to have localized neurological changes and brain abscesses.

Patients older than 2 months of age almost invariably have infections with *H. influenzae*, Type B, *N. meningitidis*, or *Diplococcus pneumoniae*, in descending order of frequency. However, the presence of a dermal sinus tract, concurrent or preceding endocarditis, and prior multiple lumbar punctures, neurosurgical procedures (particularly with entry of the dura), or the presence of a ventricular shunt should alert the physician to the substantially greater likelihood of the presence of unusual organisms. Initial antimicrobial therapy, discussed below, may require alteration if any of these conditions is present. In any event, the group of organisms encountered in these situations is so heterogeneous that laboratory guidance is absolutely essential for the final selection of definitive antimicrobial treatment.

In obtaining spinal fluid, it is important that examination of the eye grounds should precede lumbar puncture. If choked discs are seen, small diameter needles should be used and minimal quantities of fluid should be removed slowly. The bevel of the needle should be parallel with the trunk in order to minimize dural tear. A dry tap should alert the physician to the possibility of epidural abscess or other obstruction. Because of penetration of the nucleus pulposus instead of the dural sac, gelatinous fluid with few elliptical cells is occasionally seen in young infants when spinal fluid is obtained by relatively inexperienced physicians. It is important that pressure be recorded and flow carefully controlled during the collection of fluid.

DETERMINATION OF THE TYPE OF INFECTION

Immediate spinal fluid examination in the clinical and bacteriological laboratories should provide rapid and accurate information regarding the general type of central nervous system disease. It is almost always possible to determine whether infection exists, and, if so, whether it is bacterial or viral in origin or is one of the chronic meningitides.

The importance of the clinical and bacteriological laboratories in aiding the physician in deciding whether the infection is bacterial or viral, and, if it is bacterial, in giving a presumptive diagnosis of the specific agent, cannot be overestimated. Bacterial infections characteristically have marked cellular responses, which are predominantly polymorphonuclear in type. Although viral central nervous system infections are occasionally associated with spinal fluid cell counts as high as 2000 cells, most are below 200 cells, and there is usually monocytic predominance. Spinal fluid glucose determinations, most useful in distinguishing between viral and tuberculosis or mycotic infections, are also helpful adjuncts in identifying bacterial infections.

Fulminant meningococcal disease at any age or pneumococcal infections, particularly at the extremes of life may not be associated with appreciable cellular response at the time the patient is first seen. At times, cloudy spinal fluid has been seen in the young infant or in the elderly alcoholic with absolutely no increase in spinal fluid cell count, the cloudiness representing huge numbers of organisms in the fluid. This type of response suggests that Gram-stained spinal fluid sediment must be carefully examined in all patients suspected of central nervous system infection if serious errors are to be avoided.

With bacterial infections, an accurate diagnosis of the specific etiological agent is possible in more than half of the patients within minutes after the fluid reaches the laboratory. In most cases in which organisms are visible, a simple Gram-stain of the centrifuged sediment of the cerebrospinal fluid (CSF) yields accurate etiological information on morphological grounds. Fluorescent antibody techniques and the quelling reaction for *H. influenzae*, Type B, performed on freshly obtained spinal fluid may yield immediate, precise etiological confirmation.

It should be noted, however, that in our experience only 10 per cent more specific diagnoses may be made by including fluorescent antibody staining of the spinal fluid sediment with conventional smear and culture routines. As fluorescent antibody techniques are perfected further, they can be expected to be particularly useful in the neonatal group and in those patients in whom unusual organisms may be anticipated on the basis of the clinical evaluation.

SELECTION OF SPECIFIC THERAPY

In most instances, proper and rational selection of the bactericidal drug or drugs of greatest efficacy is possible at the time of admission. More than one antibiotic is seldom desirable, because specific therapy provides effective treatment with fewer complications and reactions.

The selection of an antimicrobial agent is dependent on rational review of the activity and spectrum of each of the various agents currently available. It seems obvious that, at least on theoretical grounds, bactericidal rather than bacteriostatic agents should be selected. Inasmuch as impaired circulation may result in delayed absorption from intramuscular sites, the intravenous route should be used when possible in order to assure maximal serum and CSF levels. Therapy should be as specific as possible because apparent antibiotic interference, a phenomenon suggested by Jawetz, was seen in at least one prospective study (5). Due consideration must be paid, however, to the uncertainties concerning the specific agent in the neonatal period or in patients with particular types of

underlying disease or complications as noted above. Because of its effectiveness and lack of toxicity, penicillin G represents the agent of choice in known meningococcal and pneumococcal infections. Penicillin, when given alone and in adequate doses, clearly provides as effective a response as sulfonamides (6). Even though sulfonamides were previously recommended for meningococcal disease, the prevalence of sulfonamide-resistant meningococci in civilian populations (33 per cent among our patients) during the last 3 years has made reliance upon these agents impossible for optimal therapy of meningococcal disease (4).

On the basis of both *in vitro* and *in vivo* data (3, 7), ampicillin is at least as effective against *H. influenzae*, Type B, as is chloramphenicol, and shares with penicillin G its bactericidal activity against both the meningococcus and pneumococcus (3). This activity, with its concomitant lack of toxicity, makes ampicillin a logical choice for initial therapy in the patient older than 2 months of age when there is no evidence suggesting that an unusual organism may be present.

Early laboratory and clinical trials with ampicillin in acute bacterial meningitis due to *H. influenzae* were begun in 1962. It was immediately apparent that ampicillin was bactericidal *in vitro* against strains of *H. influenzae*, Type B, which were isolated from spinal fluid at levels easily attainable in the patient (3). No resistant strains of the organism have been identified, although disc sensitivity tests have frequently been misleading. The disc sensitivity of *H. influenzae*, Type B, against ampicillin may suggest that the organism is resistant, but careful tube dilution tests have confirmed the uniform sensitivity of these organisms to date.

After initial *in vitro* studies of many isolates, ampicillin was administered cautiously to patients with meningitis due to *H. influenzae* who had been partially treated with chloramphenicol. After this, ampicillin was cautiously used as initial therapy in individuals not critically ill, and it seemed at least equivalent to chloramphenicol. Concomitant cautious early trials seemed to indicate that ampicillin was also at least as effective as penicillin G in the treatment of pneumococcal and meningococcal meningitis. At that time, an alternate patient study, which compared ampicillin therapy with conventional therapy as used in many hospitals throughout the world, was instituted in patients older than 2 months. The results of the initial steps in this evaluation confirmed the effectiveness of ampicillin (3, 9, 12, 13).

TABLE IV.2.—SINGLE VERSUS MULTIPLE ANTIMICROBIAL THERAPY IN ACUTE BACTERIAL MENINGITIS¹

Severity ² of illness on admission	Therapeutic regimen selected								
	Ampicillin alone			Ampicillin+chloramphenicol+streptomycin			Total patients treated		
	Cases	Deaths	Percent	Cases	Deaths	Percent	Cases	Deaths	Percent
Mild.....	88	1	1.1	67	0	-----	155	1	0.6
Moderate.....	13	0	-----	9	0	-----	22	0	0
Severe.....	28	4	14.3	35	13	37.2	63	17	27.0
Total.....	129	5	3.9	111	13	11.7	240	18	7.5

¹ Patients excluded: infants <2 months of age, 15; unusual organisms, 15; error in treatment assignment, 9; endocarditis, mechanical defect, etc., 6; total exclusions, 45 with 11 deaths. Table was computed by severity of illness. Los Angeles County General Hospital, 1 year experience to July 1956.

² See footnote 1 to table IV.1.

TABLE IV.3.—SINGLE VERSUS MULTIPLE ANTIMICROBIAL THERAPY IN ACUTE BACTERIAL MENINGITIS ¹

Age group of patients	Therapeutic regimen selected					
	Ampicillin alone		Ampicillin+chloramphenicol+streptomycin		Total patients treated ²	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
2 to 11 months.....	35	1	25	2	60	3
1 to 14 years.....	57	0	49	1	106	1
15 to 44 years.....	16	0	19	1	35	1
45 to 59 years.....	15	4	8	3	23	7
60-plus years.....	6	0	10	6	16	6
Total.....	129	5	111	13	240	18
Case fatality (percent).....	3.9		11.7		7.5	

¹ Table computed by age group of patients. Los Angeles County General Hospital, 1-year experience to July 1966.

² Patients excluded: infants >2 months of age, 15; unusual organisms, 15; error in treatment assignment, 9; endocarditis, mechanical defect, 6; total exclusions, 45 with 11 deaths.

Additional data from our most recent study of the treatment of meningitis in patients older than 2 months of age are shown in Tables IV.2, IV.3, and IV.4. Therapy consisted of ampicillin alone in an initial intravenous push dose of 50 mg. per kg., followed by 150 mg. per kg. per day in six divided push doses at 4-hour intervals, and contrasted ampicillin alone with ampicillin plus two other drugs. Alternate patients received therapy consisting of a combination of the same dose of ampicillin plus chloramphenicol at 100 mg. per kg. per day, to a maximum of 4 gm. each day for the total duration of therapy, and streptomycin at 40 mg. per kg. per day (to a maximum of 2 gm.) for the initial 2 days of treatment. Administration of chloramphenicol was delayed until 30 min. after ampicillin had been administered in an effort to avoid antibiotic interference.

As noted in Table IV.2, the response to ampicillin was excellent, with only five deaths among 129 patients treated or an over-all mortality of 3.9 per cent. Multiple antibiotic treatment yielded 13 deaths among 111 patients, a mortality rate of 11.7 percent. The difference is statistically significant ($\chi^2=5.33$; $p<0.02$). Although a slight chance variation is seen in that more patients with milder disease were randomly included in the ampicillin category, this shift is not sufficient to explain the difference observed.

In Table IV.3 the effect of increasing age on mortality is shown. However, it is important to note that the excess mortality seen with the multiple drug regimen included all ages and was not caused by the chance assignment of the elderly alcoholic with his associated high mortality rate to this treatment group.

When the responses of patients, in specific etiological categories, to treatment with ampicillin alone or to the multiple routine were compared (Table IV.4), no single type of infection seemed to contribute excessively to the higher mortality among the patients in the multiple drug group.

It is apparent from these data that there is no advantage, and a possible disadvantage, to using more than a single agent in the therapy of the common types of acute bacterial central nervous system infections. Whenever possible, we believe that therapy should be specific.

Acute bacterial central nervous system disease during the first 60 days of life, particularly in the newborn, represents a totally different problem. At this age, enteric organisms are much more frequently encountered, and their antimicrobial sensitivities are impossible to predict accurately. The organisms isolated from patients in our hospital with neonatal meningitis during the past 5 years are listed in Table IV.5. No single antimicrobial agent is optimally effective against more than two-thirds of these organisms, although, on the basis of *in vitro* data, a combination of either penicillin or ampicillin plus kanamycin is effective in more than 95 percent. The importance of repeated spinal fluid examinations to determine the course of the disease for guidance of therapy is extremely important at this age. Even antimicrobial agents selected on the basis of careful *in vitro* testing may be ineffective when given in the usual dosage.

TABLE IV.4.—SINGLE VERSUS MULTIPLE ANTIMICROBIAL THERAPY IN ACUTE BACTERIAL MENINGITIS¹

Type of bacteria isolated	Therapeutic regimen selected						
	Ampicillin alone		Ampicillin+chloramphenicol+streptomycin		Total patients treated ²		
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Percent
Meningococci.....	45	1	35	3	80	4	5
H. influenzae.....	36	0	32	2	68	2	3
Pneumococci.....	23	4	25	6	48	10	21
Purulent, unknown.....	25	0	19	2	44	2	5
Total.....	129	5	111	13	240	18	
Case fatality (percent).....	3.9		11.7		7.5		

¹ Table was computed by type of causative organism. Los Angeles County General Hospital, 1 year experience to July 1966.

² Patients excluded: infants <2 months of age, 15; unusual organisms, 15; error in treatment assignment, 9; endocarditis, mechanical defect, 6; total exclusions, 45 with 11 deaths.

TABLE IV.5—NEONATAL MENINGITIS¹

[Distribution of etiology]

Gram-negative.....	45	Gram-positive.....	13
Escherichia coli.....	19	Streptococci.....	6
Paracolon.....	12	α.....	1
Klebsiella-Aerobacter.....	6	β.....	3
Proteus.....	3	γ.....	2
Salmonella.....	2	Listeria.....	4
Mimae.....	1	Diplococcus pneumoniae.....	1
Hemophilus influenzae.....	1	Staphylococcus albus.....	2
Pseudomonas.....	1		

Unknown: 13

¹ Los Angeles County General Hospital, 1961-65.

While sensitivity studies are pending, the above antimicrobial agents should be administered in doses of 75 to 150 mg. per kg. i.v. per day of ampicillin and 15 mg. per kg. per day of kanamycin given intramuscularly. Occasionally, intrathecal therapy with polymyxin or kanamycin is necessary; this route is invariably required when polymyxin is the agent selected. Although ampicillin should be given by the intravenous route, it is not advisable to use this route for kanamycin. At times, dosages in excess of those mentioned above may be necessary, but careful attention to signs of renal toxicity and full awareness of the potential ototoxicity of kanamycin are necessary. It is reassuring to note that the latter agent, contrary to expectations, has not been associated with appreciable ototoxicity in the newborn period when used carefully within accepted dosage limits (2).

OTHER THERAPEUTIC CONSIDERATIONS

The use of proper methods of monitoring the patient's condition (such as indwelling central venous catheters and frequent blood pressure determinations in shock), during the course of the infection, is essential. Attention should be paid to complications of both disease and therapy. An important, but often overlooked, procedure is a second spinal fluid examination after 24 or 36 hours of therapy. This is the only method of adequately evaluating proper *in vivo* response to the particular antimicrobial agent selected. With the exception of infections in the newborn period, no organisms should be seen after 24 hours. Provided that effective antimicrobial therapy has been selected and proper dosage given, cultures obtained after 24 to 36 hours of treatment should be sterile, even in cases of neonatal infection.

Although enzymes of various types have been advocated for intrathecal use in patients with unusually purulent spinal fluid, we believe that there are insufficient experimental data available at present to justify their general use, even in the presence of grossly purulent spinal fluid.

Intrathecal administration of antibiotics has also been advocated, although, with the exception of polymyxin which does not reach the spinal fluid in therapeutic concentration after intramuscular administration, there is no evidence that mortality or morbidity is decreased by the use of this route.

Acute cerebral edema represents a serious problem, and, although urea (0.5 gm. per kg. i.v. in 12 hours) or Mannitol (2.0 gm. per kg. i.v. in 30 min.) has been advocated for its control, these are not as effective in inflammatory central nervous system disease as they are in cases of acute trauma to the brain. If either of these agents is used, and they may be tried if indicated, electrolytes and blood urea nitrogen should be followed carefully.

Persistent fever is usually due to subdural effusion, the formation and persistence of a brain abscess, lateral sinus thrombosis, sinusitis or mastoiditis, a urinary tract infection, phlebitis with superinfection, pneumonitis, or drug fever. The last of these is, in our experience, the most deceptive and the most frequently overlooked of these several possibilities.

SURGICAL CONSIDERATIONS

If the physician is alert for their symptoms and signs, the common surgical problems associated with central nervous system infections are relatively easily recognized. Approximately 10 per cent of infants have associated symptomatic subdural effusions. Although removal of subdural fluid may not be essential for recovery, we prefer to remove any such accumulation with daily subdural taps and will remove a maximum volume of 15cc. from each side of the fontanel daily. Fluid should be permitted to drip freely; if it reaccumulates without obvious diminution after 2 weeks, surgical intervention is indicated and should be performed approximately 3 weeks after recognition of the effusion. Surgery is required in about 2 per cent of patients. Antimicrobial therapy should be continued until after surgical correction of the lesion, inasmuch as infection may be reactivated when the surgeon enters the walled off subdural cavity.

If brain abscess is suspected, cerebral angiograms are indicated, provided that the patient's condition permits. Occasionally, the echoencephalogram is helpful in lateralizing the lesion. Surgical treatment should be delayed, if possible, until the disease has reached the subacute stage and the abscess has been well localized. Abscess with meningitis secondary to acute mastoiditis should be managed in a similar fashion, and occasionally is associated with lateral sinus thrombosis.

Repeated episodes of meningitis, usually of pneumococcal etiology, suggest a prior skull fracture with spinal fluid leakage. Surgical correction is possible in many cases, but the sinus tract should be identified before correction is attempted.

REHABILITATION

An extremely important, although frequently overlooked, requirement for total therapy for a patient with acute bacterial central nervous system disease lies in planning proper rehabilitation measures during and after convalescence from the acute infection. It is important to note that motor impairment is seen in nearly 20 per cent of patients surviving the acute illness, and intellectual or hearing impairments or both are seen with approximately the same frequency. Also, it is important to remember that these defects occur with much greater frequency among infants than they do in the older child or adult. Fully 50 per cent of neonates recovering from bacterial meningitis may be expected to exhibit either motor or intellectual impairment (1, 8, 10, 11). Even though many of these defects are not severe, or may not even be recognized in the hospital prior to discharge, it is apparent that the patient must be evaluated carefully during convalescence and must have repeated evaluations during the succeeding months or years. This is particularly important in the young infant inasmuch as intellectual impairment may not be apparent or recognized until school entry unless special evaluations are performed. Proper counselling and attention to defects, when they are recognized, will do much to diminish the impact of these defects upon the developing individual and his family.

CONCLUSIONS

Recognition and management of acute bacterial meningitis remain important problems. Prompt administration of an appropriate and specific antimicrobial agent, with attention to supportive measures and potential complications, can substantially reduce mortality and morbidity. Careful evaluation of the patient during convalescence is of utmost importance if optimal rehabilitation is to be achieved.

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QUESTIONS AND ANSWERS

QUESTION: What do you consider adequate treatment when: (1) an organism is not found on the initial spinal fluid examination, and (2) the patient is not responding to treatment started elsewhere, also without having isolated the organism?

DR. WEHRLE: This is a situation that we face in about one-third of the patients who come to us for treatment. In 50 to 60 per cent of the patients we can identify the organism at the time of admission to the hospital with a direct Gram stain. This figure may be increased slightly when one adds to the Gram stain the results of the fluorescent antibody technique. This leaves a substantial portion who must be treated without a definite diagnosis since only about 10 per cent of patients with no organisms identified on smear will have a positive culture.

We have studied a standard approach in two different age groups. For those cases from birth through 2 months of age, we start with either penicillin or ampicillin in doses equivalent to about 75 mg. per kg. per day of ampicillin after an initial loading dose of one-third of that and kanamycin at a dose of 15 mg. per kg. per day. In these very young infants there are a great many different organisms that may be causing the infection, and in our experience about 95 to 97 per cent of all of these organisms are inhibited by this particular combination.

In patients 2 months of age and older who do not have a dermal sinus, endocarditis, previous neurosurgical procedures, ventriculovenous shunt, or other factors that might be associated with an unusual organism, ampicillin alone appears to be more effective than the combination of chloramphenicol and penicillin with or without the addition of streptomycin.

It should be noted that the mortality rate in patients in whom you do not see the organism on smear is lower than in those where the organism is identified. The only exception to this is the Waterhouse-Friderichsen syndrome in meningococcal infection. Also, the very young or very old individual with a fulminant

pneumococcal meningitis may have little or no appreciable cellular response. Organisms may be seen in the spinal fluid, although if an antibiotic has been given this may prevent cultural identification of the organism.

QUESTION: What criteria do you use for discontinuing antibiotic therapy?

Dr. WEHRLE: Our procedure is to treat intensively with full dosage of antibiotics for the required period. We do not reduce dosage during the course of therapy. We continue full dosage until the patient has been afebrile for about 5 days, which is usually about 2 weeks after treatment is started. At that point a repeat spinal puncture is done and if the cell count is less than 30 white blood cells per cm., and, if the protein is less than 50 mg. per cent, we discontinue antimicrobial therapy, watch the patient for 2 days in the hospital, and then send him home. We do not believe that low dosage of antibiotics over an additional 1- to 2-week period or longer does anything other than to mask those infections that have not been treated adequately. With young infants we do not discontinue therapy until at least 3 weeks have gone by. If the protein or cell count remains up, even though there are no neurological changes, treatment should be continued.

Relapses occur in two or three kinds of situations. One is with a Gram-negative infection either in young infants or in individuals whose immune defenses are impaired regardless of age. In several hundred meningococcal infections we have yet to see a relapse. A relapse after pneumococcal meningitis is extremely rare, and if relapse occurs it is usually associated with mastoiditis or abscess. Occasionally *Hemophilus influenzae* infections will recur, particularly in the very young infant.

QUESTION: How do you explain the lower mortality rate with ampicillin alone compared with combination antibiotic therapy?

Dr. WEHRLE: There are three possibilities that might explain this. It could be a chance variation. This study was an alternate control using odd and even chart numbers. The (χ^2) is 6 with a p value of nearly 0.01 so that maybe this is the one change in 100. The second possibility is that the toxicity of chloramphenicol when used in an already sick patient caused an adverse effect. Certainly this drug has been amply shown to cause serious difficulties in young infants, and it was responsible, at least in part, for the increased mortality rate in infants during the wave of the staphylococcal problem when large doses of chloramphenicol were being used. The third possibility is that there may be some kind of interference between the drugs. However, antimicrobial interference between a primarily bacteriostatic drug such as chloramphenicol or tetracycline and a primary bactericidal drug such as penicillin has certainly not been important in clinical medicine. We are still puzzled by this finding and will continue to investigate it.

QUESTION: What drugs are now given intrathecally?

Dr. WEHRLE: We consider three drugs as the only ones that we will use by this route: kanamycin, on occasion; polymyxin, invariably if you must use polymyxin for therapy in *Pseudomonas* infection or on the basis of the particular sensitivity of an unusual organism; and amphotericin. I would like to emphasize that there is no purpose in giving intrathecal medication, if the spinal fluid culture and Gram stain are negative 24 to 36 hours after you put the patient on therapy, because you are achieving an adequate suppressant effect with the particular systemic antimicrobial agent used.

QUESTION: What is the place of prophylactic antibiotics in basal skull fracture?

Dr. WEHRLE: I would like to state here one concern that I have with regard to prophylaxis. One can cause a shift in the nasopharyngeal flora to Gram-negative organisms including *Escherichia coli*, *Pseudomonas*, *Klebsiella-Aerobacter*, or a number of other organisms in the nasopharynxes of individuals who are receiving penicillin or other prophylactic antibiotics at a level at which they would be expected to eradicate the pneumococcus and really be effective prophylactic therapy. I see no value in this type of therapy.

QUESTION: What central nervous system dysfunction has been seen with ECHO viruses?

Dr. WEHRLE: We have confirmation in some patients that ECHO viruses have been associated with definite muscle weakness with a relatively mild poliomyelitis-type pattern of anterior horn cell disease. We have tried to reproduce this disease in monkeys, not successfully as yet, but we plan to go further with this. Only certain strains of ECHO viruses 4, 6, and 9 have been clearly implicated. Acute cerebellar ataxia has also been associated with ECHO-9 infection.

APPENDIX VIII

[From Antimicrobial Agents and Chemotherapy, 1967, pp. 218-224]

ANTIBIOTIC ANTAGONISM IN BACTERIAL MENINGITIS

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In vitro studies have shown that certain antibiotics used in combination may be antagonistic. Few studies have shown this phenomenon in patients. Lepper and Dowling observed an increased case fatality rate in patients with pneumococcal meningitis treated with penicillin and chlortetracycline in comparison to those treated with penicillin alone. From 1 July 1965 through 4 July 1966, 264 patients ≥ 2 months of age were assigned by chart number to treatment with either a single drug (ampicillin, 150 mg/kg daily) or a combination of drugs [ampicillin, 150 mg/kg daily; chloramphenicol, 100 mg/kg daily to a maximum of 4 g/day; and streptomycin, 40 mg/kg to a maximum of 2 g/day (48 hr only)] for acute bacterial meningitis. The groups were comparable in respect to age, severity of disease, and etiology of disease. Of 140 patients treated with the single drug regimen, 6 expired, giving a case fatality rate of 4.3%. There were 13 deaths among 124 patients receiving multiple antibiotic therapy, or a case fatality rate of 10.5%. A similar increased rate of neurological residua was observed in patients treated with multiple drugs. These differences were observed in those patients who were severely ill on admission; however, they were not restricted to one age group or etiological category. Antibiotic antagonism may explain the observed differences in case fatality rates and in rates of neurological residua.

With the development of each new antibiotic, researchers have investigated whether its spectrum of activity could be broadened or enhanced by combination with an existing drug. Although combinations of antimicrobials have proven beneficial in a few instances, the undesirable effects of antibiotic antagonism have also been observed. Antagonism has been observed in vitro in many test situations, leading Jawetz et al. (9) to perform a series of studies which partially systematized the relationships of antimicrobial interaction. Jawetz et al. (9) noted that bacteriostatic antibiotics, such as chloramphenicol and tetracycline, may act antagonistically with those that are bactericidal, such as penicillin, streptomycin, bacitracin, and neomycin. They categorized the former as group II drugs and the latter as group I drugs. This grouping according to in vitro activity, with bactericidal action used as an end point of antimicrobial potency, has been confirmed by other investigators with only minor revisions (6, 14). The antimicrobial agents introduced since the original reports of Jawetz et al. can be categorized similarly, with the Jawetz formula in general holding true (4).

Experimental demonstrations of the phenomenon of antibiotic antagonism have not been limited to in vitro situations. Jawetz et al. (10) found that mice infected experimentally with *Streptococcus pyogenes* had a higher case fatality rate when treated with a single dose of penicillin plus chloramphenicol than with penicillin alone. Ahern, Burnell, and Kirby (1) confirmed these results; however, the same authors (1) found that no interference in antibiotic action could be demonstrated when the same antibiotics, administered for 2 to 3 days, were substituted for the single-dose regimen. Dowling, Lepper, and Jackson (5) studied pneumococcal infections in mice treated with combinations of chlortetracycline and penicillin. By varying the doses of penicillin, they were able to confirm the observations of both Jawetz et al. (10) and Ahern, Burnell, and Kirby (1), and they concluded that the discrepancy between these authors' observations was apparently due to the "comparative dosages of antibiotics used and not to maintenance of antibiotic blood levels for two or three days." The fact that one study could confirm two opposite viewpoints supported the concept held by many physicians that antibiotic antagonism was a laboratory phenomenon which had no relevance to clinical medicine.

At the same time the original in vitro studies (9) were reported, Lepper and Dowling (11) observed that a group of patients with pneumococcal meningitis who received penicillin plus chlortetracycline had a much higher case fatality

NOTE.—Numbered references at end of article.

rate than did a similar group treated with penicillin alone. These observations were not immediately confirmed, and the lack of demonstration of antibiotic interference in other infections of humans suggested to some that the study of Lepper and Dowling (11) represented an exception and that combination therapy was not detrimental (2).

Multiple-drug therapy is often recommended in bacterial meningitis, even when the etiology is known, despite the repeated demonstration that this entity can be treated satisfactorily with a single drug. The demonstration that ampicillin alone is effective against the three major etiological agents of bacterial meningitis allowed a comparison of a single drug with a combination of drugs in the treatment of bacterial meningitis (3, 8, 15, 20, 22).

MATERIALS AND METHODS

The patients studied included all persons 2 months of age or older admitted to the Communicable Disease Service, Los Angeles County General Hospital, for the treatment of acute bacterial meningitis during the period 1 July 1965 through 4 July 1966. All age groups, both sexes, and diverse socioeconomic groups were represented. Each patient was assigned to a treatment group on the basis of an odd or even chart number. The hospital numbers were assigned by an office in a separate building. Thus, the physicians caring for the patients had no means of influencing allotment of chart numbers, and a random assignment of patients to the two treatment groups was assured. All patients received an initial rapid intravenous infusion of ampicillin at a dose of 50 mg/kg followed by 150 mg/kg daily divided into six equal intravenous doses. Patients with odd hospital numbers received the same dosage schedule of ampicillin plus two other antibiotics. They received a rapid intravenous infusion of 33 mg of chloramphenicol per kg 30 min after the initial dose of ampicillin. Subsequently, chloramphenicol, 100 mg/kg daily to a maximal dosage of 4.0 g/day, was given by rapid intravenous infusion in six equal divided doses. Streptomycin, 20 mg/kg, was given intramuscularly every 12 hr for four doses. No patient received more than 2.0 g of streptomycin per 24-hr period. The administration of each dose of chloramphenicol was delayed until 30 min after the ampicillin had been given in an effort to avoid antibiotic interference. Treatment was continued until the patient was afebrile for 5 days and the cerebrospinal fluid had returned to normal.

RESULTS

Patients studied. During the period of study, 308 patients 2 months of age or older were admitted to the service—44 of these were excluded from the analysis for the following reasons: unusual organisms, 15; error in treatment assignment or penicillin allergy, 21; endocarditis, mechanical defect, etc., 6; inadequate records, 2. There were 9 deaths among the 44 excluded patients. The two treatment groups were comparable with respect to age distribution, severity of illness on admission, and distribution of etiological categories. A preliminary analysis of these patients stressing the outcome of therapy has been reported previously (22).

Frequency of case fatality and neurological sequelae. The results of therapy, as measured by frequency of death or neurological residua, are presented in Table 1. The disadvantage of triple therapy is apparent from increased rates both of case fatalities and of residua. All deaths, except one, occurred in patients categorized as severe on admission. The statistical significance of the difference in case fatality rates hovered about 5%, depending upon the method of analysis. Perhaps more important is an analysis of the combined case fatality and residual rates. The residua included such serious disabilities as hemiparesis, 6 patients; cranial nerve paresis, 6; deafness, 4; seizures, 1; ataxia, 5; hydrocephalus, 1; and mental retardation, 2. By the X^2 technique correcting for continuity, the difference between single and triple therapy with respect to the combined residual and fatality rates was significant at the 4% level.

Other clinical variables. Factors other than death or disability which might have illustrated the advantages of either treatment regimen are listed in Table 2. The duration of fever did not differ significantly by treatment group. Within 7 days after admission, 80% of the patients became afebrile. Fever was more prolonged, in both treatment groups, in patients with pneumococcal and *Haemophilus influenzae* meningitis than in the meningococcal and "purulent unknown" groups.

Subdural effusions, often associated with sequelae, were evenly distributed between the two therapeutic groups, and the excess rate of neurological residua in the triple therapy group could not be attributed to this complication. A preliminary analysis of serial cerebrospinal fluid examinations failed to show any significant differences in the rates of return to normal in the two groups.

The mean hospital stay for both treatment groups was 19 days, with median stays of 16 and 17 days for those in the ampicillin and triple drugs groups, respectively. The prolonged hospital stays of all patients reflect the adherence to a rather stringent set of clinical criteria for the discontinuation of treatment (15).

In contrast to our earlier study (15), the complications of drug therapy were not significantly different in the two treatment groups. The rather high frequencies of rash and phlebitis in each treatment group are probably secondary to the large amounts of ampicillin given intravenously.

Times of death. Analysis of the deaths occurring in each group, by time after treatment was begun, revealed a different distribution in the single-drug group (Table 3). Two-thirds of the deaths (4 of six) in the ampicillin group occurred in the first 48 hr, whereas only 30% (4 of 13) of the deaths in the triple therapy group occurred during the first 2 days. The proportion of early deaths to the total numbers of patients in each group was similar, i.e., 4 of 140 (2.9%) on ampicillin and 4 of 124 (3.3%) on the triple therapy.

TABLE 1.—FREQUENCY OF DEATH AND SEVERE NEUROLOGICAL RESIDUA IN PATIENTS WITH ACUTE BACTERIAL MENINGITIS BY TREATMENT GROUP¹

Treatment regimen assigned	Results of treatment								Total number of patients
	Recovered, no residua		Recovered with residua		Died		Combined fatal-ity and residua		
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	
Ampicillin.....	123	87.9	11	7.8	6	4.3	17	12.1	140
Triple.....	96	77.4	15	12.1	13	10.5	28	22.6	124
Total.....	219	83.0	26	9.8	19	7.2	45	17.0	264

¹ Drug dosages, patients excluded, and type of residua are explained in text.

TABLE 2.—DISTRIBUTION OF COMPLICATIONS OF DISEASE AND RESPONSE TO THERAPY BY TREATMENT GROUP

Problems observed	Treatment regimen			
	Ampicillin		Triple	
	Cases	Percent	Cases	Percent
Persistent fever (100 F[R]>7 days).....	27	20.0	23	21.6
Subdural effusion.....	6	4.5	6	5.4
Prolonged hospital stay (≥19 days).....	47	35.0	36	32.2
Complications of therapy (rash, eosinophilia, phlebitis, etc.).....	38	27.6	30	27.0
Hematological.....	0	0	3	2.7

TABLE 3.—TIME OF DEATH AFTER INITIATION OF THERAPY BY TREATMENT GROUPS IN 2 SEPARATE SERIES OF PATIENTS WITH BACTERIAL MENINGITIS

Source of data	Single drug				Combination of drugs			
	Death		All deaths	Total cases	Death		All deaths	Total cases
	≥48 hr.	>48 hr.			≥48 hr.	>48 hr.		
Lepper and Dowling (11).....	9	4	13	43	3	8	11	14
Percent.....	69	31	100	-----	27.2	72.8	100	-----
Present report.....	4	2	6	140	4	9	13	124
Percent.....	66.7	33.3	100	-----	30.8	69.2	100	-----

DISCUSSION

The data presented support the thesis that antibiotic interference or antagonism can be observed in a clinical situation. The interference of one antibiotic with another may be expressed clinically in several ways, as illustrated in Table 4. As previously mentioned, Lepper and Dowling (11) observed an increased case fatality rate in patients with pneumococcal meningitis treated with penicillin plus chlortetracycline. A similar observation was made by Olsson, Kirby, and Romansky (16) in patients with the same disease. In comparing various treatment regimens, excessive mortality was present only in the treatment group which combined penicillin and a tetracycline (16). Increased case fatality rates are not the only manifestations of antibiotic interference. Lepper, Wehrle, and Blatt (12) observed a slower response to therapy in patients with *H. influenzae* meningitis who received multiple drug therapy; in that series, penicillin was not used, although chlortetracycline was common to each treatment group. Strom (18, 19) reported apparent interference of chlortetracycline and erythromycin with the action of penicillin in streptococcal disease. Antimicrobial antagonism may occur in the treatment of infections with gram-negative enteric bacilli, as illustrated by the report of McCabe and Jackson (13). These authors (13) clearly showed a relationship between in vitro antagonism and clinical outcome, as measured by failure to eradicate bacteriuria. Bacteriological correlations are less apparent in patients with meningitis. Excepting neonates, almost all patients who die with meningitis have negative post-mortem cultures.

TABLE 4.—CLINICAL STUDIES DEMONSTRATING ANTIBIOTIC ANTAGONISM

Reference	Disease	Manifestation	Combination therapy
Lepper and Dowling (11).	Pneumococcal meningitis.	Increased mortality.	Penicillin+chlortetracycline.
Olsson et al. (16).	do.	do.	Penicillin+a tetracycline.
Lepper et al. (12).	Haemophilus influenzae meningitis.	Slower response.	Chlortetracycline+streptomycin+sulfisoxazole.
Strom (18).	Scarlatina.	Persistence of organism.	Penicillin+chlortetracycline.
Strom (19).	do.	Slower response.	Penicillin+erythromycin.
McCabe and Jackson (13).	Urinary tract infection.	Relapse.	Various.
Present study.	Bacterial meningitis.	Increased mortality and residua.	Ampicillin+chloramphenicol+streptomycin.

TABLE 5.—PERSISTENCE OF VIABLE ORGANISMS IN CEREBROSPINAL FLUID AFTER 24 HOURS OF ANTIMICROBIAL THERAPY

Patient	Age	Complications	Initial therapy	Organism	Outcome
C. V.	26 yr.	None	Chloramphenicol+penicillin G.	Haemophilus influenzae	Successful.
D. D.	3 yr.	do.	do.	do.	Do.
M. W.	16 months.	do.	do.	do.	Do.
D. D.	2 yr.	do.	do.	do.	Do.
T. P.	18 months.	do.	do.	do.	Do.
P. H.	7 months.	Subdural.	Chloramphenicol	do.	Residua.
J. A.	64 yr.	None	Penicillin G.	Pneumococci.	Death.
J. M.	32 yr.	do.	do.	do.	Do.

What factors are responsible for the apparent antagonism in bacterial meningitis and its seeming absence in other severe infections requiring antibiotic therapy? The difference probably is due to the lack of surface phagocytosis and other host defense factors which act together with antibiotics to effect recovery (17). In meningitis, a "test-tube" situation is more nearly approximated. Wallace et al. (21) have clearly shown interference of chloramphenicol with the rapid bactericidal action of penicillin in experimental pneumococcal meningitis in dogs. That this situation may pertain in humans is suggested by the data in Table 5. The eight patients listed were observed in a previous study (15); all had viable organisms in the cerebrospinal fluid after 24 hr of antibiotic therapy. One might speculate that the host defenses in patients J.A. and J.M., who died 3 days after admission with pneumococcal meningitis, were totally inadequate because

of age or underlying illness such as alcoholism. Likewise, the persistence of organisms in patent P.H., who had a subdural effusion, might be explained by a drug diffusion problem. In the other five patients, there were no obvious explanations for persistence of viable organisms other than antibiotic interference. These five patients received a rapid intravenous infusion of penicillin and chloramphenicol on admission, followed by a continuous intravenous infusion containing the two antibiotics in our standard dosage (15). In contrast, no ampicillin-treated patients with the usual types of meningitis have had positive cultures after 24 hr of therapy. Similar observations, after 12 to 36 hr of therapy, have also been made by Fleming et al. (7) in a controlled study of the treatment of meningitis.

Lepper and Dowling (11), in comparing the two regimens which they employed, noted that the majority of deaths in the penicillin-treated group occurred within 48 hr of admission, whereas only 3 of the 11 patients who died while receiving combination therapy did so during the first 48 hr. An analysis of our patients revealed the same distribution (Table 3). Our observations would tend to substantiate the view that the effective single-drug and multiple-drug regimens both failed to effect recovery in a certain number of patients. In addition, multiple-drug therapy seems to have failed in potentially salvageable patients, presumably because of antibiotic interference.

It is somewhat surprising that in our study the only obvious difference between the single- and multiple-therapy groups was disability or death. One would have expected other differences, which might have been manifested in cerebrospinal fluid findings, days of fever, or hospital stay. Although no differences were apparent in the large groups, more detailed analyses of subgroups may be fruitful.

CONCLUSIONS

Many investigators have demonstrated the phenomenon of antibiotic antagonism *in vitro* and in experimental animals. Clinical examples of this phenomenon are restricted to a few situations in which the rapid bactericidal action of an antibiotic is apparently necessary for a good response. Bacterial meningitis, particularly that which is severe on admission, appears to be one of the situations in which a combination of bacteriostatic and bactericidal agents is undesirable.

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APPENDIX IX

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AMPICILLIN IN THE TREATMENT OF ACUTE SUPPURATIVE MENINGITIS¹

(By Fred F. Barrett, M.D., Warren A. Eardley, M.D., Martha D. Yow, M.D., and Howard A. Leverett, Houston, Tex.)

During 1963 and 1964 *in vitro* sensitivity studies indicated that ampicillin was effective against the three common etiologic agents of bacterial meningitis in children. Blood and cerebrospinal fluid studies revealed high blood levels and detectable cerebrospinal fluid levels of ampicillin in patients with and without meningeal disease but the mean cerebrospinal fluid/serum ratio was significantly higher in patients with bacterial meningitis. Twenty-eight children with acute bacterial meningitis were treated with ampicillin alone. No significant differences in mortality or complications were noted when the results of this therapy were compared with those in two groups of patients treated with conventional "triple therapy."

Ampicillin, alpha-aminobenzyl penicillin, became available in England in 1961. This semisynthetic penicillin is of particular interest since it is bactericidal against both gram-positive and gram-negative bacteria. Ampicillin has been found to be highly effective *in vitro* against *Diptococcus pneumoniae*, *Neisseria meningitidis*, and *Hemophilus influenzae*, to achieve good blood levels when administered by oral and parenteral routes, and to have a low incidence of side

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effects. (1-7) These characteristics suggested that ampicillin might be an ideal single drug for the treatment of acute suppurative meningitis due to *D. pneumoniae*, *N. meningitidis*, or *H. influenzae*. The parenteral form of ampicillin was released for clinical trials in the United States in 1963. During 1963, Ivler and his associates (8) published a preliminary report of in vitro studies and clinical experiences, in the management of 31 patients with purulent meningitis due to various organisms, including *D. pneumoniae*, *N. meningitidis*, and *H. influenzae*. A more detailed report of the treatment of *H. influenzae* meningitis with ampicillin was presented at the International Conference on Therapy With the New Penicillins (9) in 1964. These investigators found that 126 strains of *H. influenzae* isolated from the cerebrospinal fluid were sensitive to ampicillin. Ninety-one per cent of the strains were killed by 0.4 mcg. per milliliter and only one strain required as much as 1.6 mcg. for bactericidal activity. Ampicillin and penicillin G were both bactericidal at 0.4 mcg. per milliliter for greater than 90 per cent of 72 strains of *N. meningitidis* and 37 of *D. pneumoniae*. Ivler, Thrupp, and co-workers (8, 9) found that ampicillin was comparable to chloramphenicol and equal to penicillin G in efficacy for the treatment of bacterial meningitis. Ampicillin did not appear to have any definite advantages over chloramphenicol other than freedom from hematologic depression.

During 1963 and 1964 similar laboratory and clinical investigations were conducted at the Texas Medical Center in Houston. This report summarizes the results of these investigations. Since the majority of the laboratory studies were performed as a base line for the clinical studies, the laboratory data are presented as Part I and the clinical studies as Part II.

PART I. LABORATORY STUDIES

In vitro sensitivity tests. Prior to the initiation of clinical studies, strains of *D. pneumoniae*, *N. meningitidis* group C, and *H. influenzae* Type B freshly isolated from patients with meningitis in the Houston area were tested for susceptibility to ampicillin,* tetracycline, chloramphenicol, and penicillin G. The two-fold serial tube dilution technique using tryptose phosphate broth and an inoculum of approximately 10^4 organisms was employed for the determination of the minimal bactericidal concentration (MBC) of pneumococci and meningococci. Agar diffusion plates were used in determining the minimal inhibitory concentration (MIC) of *H. influenzae*. Casman's agar base with 10 per cent heated blood was employed as the medium. The plates were inoculated from a 24 hour culture in 5 per cent blood and brain-heart infusion broth with a standard 5 mm. wire loop. All of the strains tested during the preliminary phase of investigation were sensitive in vitro to all four of these antibiotics. Since the results of sensitivity tests of organisms isolated from patients enrolled in the later clinical trials were similar to those obtained in the preliminary studies, the cumulative results are presented in Table I.

TABLE I.—MINIMAL INHIBITORY CONCENTRATIONS OF AMPICILLIN, CHLORAMPHENICOL, PENICILLIN G AND TETRACYCLINE AGAINST HEMOPHILUS INFLUENZAE AND MINIMAL BACTERICIDAL CONCENTRATIONS OF THESE SAME DRUGS AGAINST DIPLOCOCCUS PNEUMONIAE AND NEISSERIA MENINGITIDIS STRAINS ISOLATED FROM PATIENTS WITH MENINGITIS

Antibiotic	Number of strains tested	Antibiotic concentration								
		0.012 (mcg./ml.)	0.025 (mcg./ml.)	0.05 (mcg./ml.)	0.01 (mcg./ml.)	0.20 (mcg./ml.)	0.39 (mcg./ml.)	0.79 (mcg./ml.)	1.56 (mcg./ml.)	3.12 (mcg./ml.)
Hemophilus influenzae:										
Ampicillin	41		2			10	26	3		
Chloramphenicol	24					4	6	4	10	
Penicillin G	15					2	9	1	3	
Tetracycline	27					2	7	7	11	
Diplococcus pneumoniae:										
Ampicillin	12	2	6	4						
Chloramphenicol	11								3	8
Penicillin G	12		5	7						
Tetracycline	11				5	3	2		1	
Neisseria meningitidis:										
Ampicillin	15		1	8	5	1				
Chloramphenicol	7							3	4	
Penicillin G	13		1	4	7	1				
Tetracycline	7						3	4		

*Polycillin (Bristol Laboratories).

A total of 41 strains of *H. influenzae*, 12 of *D. pneumoniae*, and 15 of *N. meningitidis* were tested for their sensitivity to ampicillin. Varying numbers of these same strains were tested for their sensitivity to chloramphenicol, penicillin G, and tetracycline. All of the strains of *H. influenzae* were inhibited by ampicillin in a concentration of 0.78 mc. per milliliter or less, the majority by a concentration of 0.39 mcg. per milliliter. The MBC of ampicillin and penicillin G for pneumococci and meningococci were similar and ranged from 0.012 to 0.05 mcg. per milliliter for pneumococci and from 0.025 to 0.20 for meningococci.

Serum and spinal fluid ampicillin levels. Thirty eight simultaneous serum and spinal fluid samples were obtained one hour after a parenteral dose (intravenously or intramuscularly) of ampicillin. Eight of the paired specimens were from patients with no evidence of meningeal disease, 10 from patients with viral meningitis or encephalitis, and 20 from patients with bacterial meningitis. Ampicillin levels in the serum and spinal fluid were assayed by Bristol Laboratories using the cup-plate method with *Sarcina lutea* as the test organism. The relationship between the dose of ampicillin and the cerebrospinal fluid and serum levels could not be assessed in this series of patients because of variations in dosage and route of administration. However, data are presented to demonstrate the ratios between simultaneous cerebrospinal fluid and serum levels (Tables II and III). The dose employed varied from 25 mg. per kilogram (150 mg. per kilogram per day divided into 6 doses) to 50 mg. per kilogram (250 mg. per kilogram per day divided into 6 doses). The paired samples were obtained one hour after administration of the dose and all patients had been on the drug for a period of 1 to 4 days at the time of sampling.

Satisfactory serum levels were obtained in all instances and ampicillin was detectable in each spinal fluid specimen. However, there was a striking differential between the simultaneous cerebrospinal fluid and serum levels. The highest mean cerebrospinal fluid-to-serum ratio (expressed as percentage) was obtained in patients with bacterial meningitis (11 per cent) while the ratio in the patients with viral meningitis was 9 per cent and in patients without evidence of meningitis was 4 per cent. Although the mean cerebrospinal fluid ampicillin levels in the patients with bacterial meningitis and the group without evidence of meningitis, 1.9 mg. per milliliter and 0.8 mg. per milliliter, are not significantly different ($p > 0.1$), the mean ratios in those two groups of patients, 11 and 4 per cent, respectively, are significantly different ($p < 0.01$.)

TABLE II.—SIMULTANEOUS BLOOD AND CEREOSPINAL FLUID AMPICILLIN LEVELS IN 8 PATIENTS WITH NORMAL MENINGES AND IN 10 PATIENTS WITH VIRAL MENINGOENCEPHALITIS

Route and frequency of administration	CSF level (mcg./ ml.)	Blood level (mcg./ ml.)	Ratio (CSF/ blood)	Total daily dose (mg./ kg./day)	Individual dose (mg./ kg.)	Time of CSF and blood sam- pling after drug given (hour)
Normal meninges:						
Intramuscularly every 6 hours.....	0.1	20.0	0.005	150	38	1
Do.....	.3	29.0	.010	150	38	1
Do.....	.3	25.0	.012	150	38	1
Do.....	.3	14.0	.021	225	56	1
Intramuscularly every 4 hours.....	.8	57.0	.014	150	25	1
Intramuscularly every 6 hours.....	.8	25.0	.032	170	43	1
Intravenously every 4 hours.....	.9	14.0	.064	150	25	1
Do.....	2.9	15.0	.193	150	25	1
Mean.....	.8	24.9	.044			
Percent.....			(4.4)			
Viral meningitis:						
Intramuscularly every 6 hours.....	.2	36.0	.006	150	38	1
Intravenously every 4 hours.....	.4	4.4	.091	150	25	1
Do.....	.5	14.0	.036	150	25	1
Do.....	.5	14.0	.036	150	25	1
Do.....	.5	12.0	.042	150	25	1
Intramuscularly every 6 hours.....	.6	29.0	.021	150	38	1
Do.....	.6	22.0	.027	150	38	1
Intramuscularly every 4 hours.....	1.2	20.0	.060	150	25	1
Intravenously every 4 hours.....	3.7	15.0	.247	150	25	1
Do.....	3.8	11.0	.345	150	25	1
Mean.....	1.2	17.7	.091			
Percent.....			(9.1)			

TABLE III.—SIMULTANEOUS BLOOD AND CEREBROSPINAL FLUID AMPICILLIN LEVELS IN 20 PATIENTS WITH BACTERIAL MENINGITIS

Route and frequency of administration	Total daily dose (mg./Kg./day)	Individual dose (mg./Kg.)	Time of CSF and blood sampling after drug given (hr.)	CSF level (mcg./ml.)	Blood level (mcg./ml.)	Ratio (CSF/blood)
Intravenously every 4 hours.....	150	25	1	0.2	9.0	0.022
Do.....	150	25	1	0.3	10.0	0.030
Do.....	160	27	1	0.5	7.0	0.071
Do.....	160	27	1	0.6	10.0	0.060
Do.....	150	25	1	0.7	15.0	0.047
Do.....	150	25	1	0.7	12.0	0.058
Do.....	150	25	1	0.7	11.0	0.064
Do.....	150	25	1	0.8	15.0	0.053
Do.....	150	25	1	0.9	12.0	0.075
Do.....	150	25	1	1.1	10.0	0.109
Do.....	150	25	1	1.1	9.4	0.117
Do.....	250	42	1	1.2	20.0	0.060
Do.....	160	27	1	1.4	21.0	0.067
Do.....	150	25	1	1.6	15.0	0.107
Do.....	145	24	1	2.1	21.0	0.100
Do.....	150	25	1	2.3	20.0	0.115
Do.....	150	25	1	2.5	14.0	0.179
Do.....	165	28	1	4.1	27.0	0.152
Do.....	150	25	1	6.1	16.0	0.381
Do.....	250	42	1	8.4	27.0	0.311
Mean total.....				1.9	15.0	10.109

¹ 10.9 percent.

TABLE IV.—ETIOLOGY OF ACUTE MENINGITIS: STUDY, MATCHED CONTROL, AND 5-YEAR REVIEW PATIENTS

	Study patients		Matched control patients		5-year review patients	
	Number	Percent	Number	Percent	Number	Percent
<i>H. influenzae</i>	16	57	12	48	88	46
<i>N. meningitidis</i>	8	29	7	28	8	4
<i>D. pneumoniae</i>	1	3	4	16	35	19
Unknown etiology.....	3	11	2	8	59	31
Total.....	28	100	25	100	190	100

PART II. CLINICAL STUDIES

The clinical progress of three groups of patients was evaluated: (1) 28 patients with bacterial meningitis who were treated with ampicillin during 1964 and 1965 (study patients); (2) 25 matched control subjects treated by conventional methods during 1965; (3) 190 patients treated by conventional methods during the 5 year period 1959 through 1963 (5 year review patients).

Description of study patients. During the nine month period from July, 1964, to April, 1965, 28 patients admitted consecutively to Ben Taub General Hospital with the diagnosis of acute bacterial meningitis due to *H. influenzae*, *D. pneumoniae*, *N. meningitidis*, or to an unknown agent were enrolled in a study designed to determine the efficacy and safety of the treatment of meningitis with ampicillin. One case of meningococcemia without meningitis was included in the study before it became apparent that the patient did not have meningitis. The blood culture was positive but the bacteriologic studies of the cerebrospinal fluid were negative. One patient was considered to have definite meningococcemia and meningitis despite negative blood and cerebrospinal fluid cultures. The direct smear of the spinal fluid revealed gram-negative intracellular diplococci and the patient presented the classical clinical picture of meningococcemia and meningitis. The etiologic agent was considered to be *H. influenzae* type B in 16 of the 28 patients, meningococcus in 8, and pneumococcus in 1 (Table IV). Three patients were classified as having meningitis of unknown etiology since a causative agent could not be positively identified in the cerebrospinal fluid or blood. All of the patients were between 3 months and 9 years of age. The ages, sex, and race of the patients are shown in Table V.

TABLE V.—AGE, SEX, AND RACE: STUDY, MATCHED CONTROL, AND 5-YEAR REVIEW PATIENTS

Age (years)	Study patients		Matched control patients		5-year review patients	
	Number	Percent	Number	Percent	Number	Percent
0 to 1.....	14	50	14	56	120	63
1 to 5.....	10	36	10	40	53	28
5 to 10.....	4	14	1	4	12	6
10 to 15.....	0	0	0	0	5	3
Male.....	13	46	16	64	90	47
Female.....	15	54	9	36	100	53
Negro.....	20	71	18	72	148	78
White.....	8	29	7	28	42	22

Description of matched control patients. Twenty-five pediatric patients admitted to Ben Taub General Hospital from April, 1965, to July, 1965, served as matched control subjects. The study and control patients were relatively well matched as to age, sex, race, and etiologic agent (Tables IV, V). Twelve of the 25 patients had *H. influenzae* meningitis, 7 meningococcal disease, 4 pneumococcal meningitis and 2 bacterial meningitis of unknown etiology. As in the study group, there was one patient included in the meningococcal category on the basis of identification of a gram-negative bacterium on a smear of cerebrospinal fluid and compatible clinical illness despite negative blood and spinal fluid cultures. One case of meningococcemia was included before it became apparent that the patient did not have meningeal involvement.

Description of 5 year review patients. In order to establish a base line of mortality and morbidity of bacterial meningitis in our hospital, a review was made of the charts of all pediatric patients (2 months to 14 years) admitted to Ben Taub General Hospital with bacterial meningitis and treated by conventional methods during the 5 year period 1959 through 1963. As in the study and matched control groups, patients under 2 months of age were excluded in order to eliminate cases of meningitis due to organisms which are common etiologic agents in the newborn period (*Escherichia coli*, *Proteus* sp., *Listeria monocytogenes*, and various groups of streptococci). One hundred and ninety patients were suitable for inclusion in the "5 year review group." The etiologic agents isolated from these children are shown in Table V. *H. influenzae* was the causative agent in almost one half of the cases. The etiologic agent could not be determined in approximately one third of the cases although many of these patients had organisms on the direct smear of the cerebrospinal fluid.

Assessment of severity of illness. The severity of the illness on the day of admission to the hospital could be adequately evaluated in the study and the matched control groups, but not in the 5 year review group. A scale of 1+ to 4+ as described by Thrupp and co-workers (9) was used:

- 4+ Coma, shock, semicoma or hypotension.
- 3+ Convulsions without coma or shock.
- 2+ Temperature $>105^{\circ}$ F., symptoms >5 days, or complicating disease.
- 1+ None of the above.

TABLE VI.—SEVERITY OF ILLNESS: STUDY AND MATCHED CONTROL PATIENTS

Severity of illness ¹	Number of study patients				Number of matched control patients			
	4+	3+	2+	1+	4+	3+	2+	1+
<i>H. influenzae</i>	8	2	4	2	7	2	2	1
<i>N. meningitidis</i>	4		3	1	3			4
<i>D. pneumoniae</i>		1				1	1	2
Unknown etiology.....			3				1	
Total patients.....			3			1	1	
Total patients.....	12	3	10	3	10	4	4	7

¹ See text.

As can be seen in Table VI, the severity of the illness was comparable in the study and matched control groups.

The duration of fever prior to admission to the hospital was used as a rough index of the stage of illness (Table VII). There were no outstanding differences in the three groups except for a wide variation in the duration of illness in the "unknown" category.

Bacteriologic studies. Cerebrospinal fluid and blood cultures were obtained from all the study, matched control, and 5 year review patients on admission to the hospital. Repeat spinal fluid cultures were performed on all patients. In the ampicillin-treated and matched control groups the repeat cultures were obtained within 24 to 48 hours after the original culture. Additional cultures were obtained at suitable intervals and prior to discharge. Repeat cultures were also performed on all patients in the "5 year review group" but the time interval was less uniform than in the former two groups. The antibiotic sensitivity tests are described in the previous section on laboratory studies.

TABLE VII.—MEAN DURATION OF FEVER PRIOR TO ADMISSION: STUDY, MATCHED CONTROL, AND 5-YEAR REVIEW PATIENTS

	Study patients (days)	Matched control patients (days)	5-year review patients (days)
<i>H. influenzae</i>	4.9	3.5	3.5
<i>N. meningitidis</i>	1.1	1.6	2.0
<i>D. pneumoniae</i>	2.0	2.3	4.2
Unknown etiology.....	2.3	8.5	5.2

Antibiotic management. The study patients received ampicillin, 150 mg. per kilogram per day divided into 6 intravenous doses for at least 48 hours. The ampicillin was diluted with 5 c.c. of 0.85N saline and given over a period of 60 seconds. Unused portions of ampules were discarded so that each dose was freshly prepared. After 48 hours the intramuscular route was employed except in instances where patients exhibited a slow response to treatment. In these cases, intravenous therapy was continued for longer periods of time. The average total duration of ampicillin therapy was 2 weeks.

The matched control patients and the 5 year review patients received penicillin, chloramphenicol, and sulfadiazine until an etiologic agent had been identified. Thereafter, the appropriate antibiotic was continued and the unnecessary ones discontinued. The dose of penicillin was 4 to 12 million units per day depending on the size of the child, chloramphenicol, 100 mg. per kilogram per day, and sulfadiazine, 150 mg. per kilogram per day.

RESULTS

A summary of the results of treatment in the three groups of patients is presented in Table VIII.

Seventeen of the 28 ampicillin-treated patients recovered completely (61 per cent), 2 died (7 per cent mortality), subdural effusions were demonstrated in 4 (14 per cent), 1 (4 per cent) had severe neurologic sequelae, and 4 (14 per cent) had minor neurologic sequelae which subsequently disappeared.

TABLE VIII.—RESULTS OF THERAPY: STUDY, MATCHED CONTROL, AND 5-YEAR REVIEW PATIENTS

	Study patients		Matched control patients		5-year review patients	
	Number	Percent	Number	Percent	Number	Percent
Satisfactory course.....	17	61	12	48	123	64
Deaths.....	2	7	3	12	18	9
Severe sequelae.....	1	4	1	4	24	13
Subdural effusion.....	4	14	5	20	25	14
Minor sequelae.....	4	14	4	16	(1)	-----
Total.....	28	100	25	100	190	100

¹ Unknown.

Twelve of the 25 matched control patients recovered completely (48 per cent), 3 died (12 per cent mortality), subdural effusions were demonstrated in 5 (20 per cent), 1 (4 per cent) had permanent neurologic sequelae, and 4 (16 per cent) had minor neurologic sequelae which subsequently disappeared.

The mortality in the 5 year review group (9.5 per cent) was strikingly similar to that of the other two groups. Twenty-five of the 190 patients (14 per cent) had subdural effusions. The incidence of permanent neurologic sequelae in this group of patients (13 per cent) was not significantly different from that of the other two groups ($p = < 0.1$). Minor neurologic sequelae could not be adequately evaluated in the 5 year review patients.

All of the deaths in the study and matched control groups occurred in patients who were in coma and/or shock on admission to the hospital. Four of the 5 deaths took place during the first 48 hours of hospitalization. The cerebrospinal fluid was sterile at the time of death in all 5 patients. Table IX presents the mortality figures in relationship to the etiologic agent. The incidence of subdural effusion and severe neurologic sequelae according to etiologic agent is shown in Table X.

TABLE IX.—MORTALITY RATE: STUDY, MATCHED CONTROL, AND 5-YEAR REVIEW PATIENTS

	Study patients		Matched control patients		5-year review patients	
	Number	Percent	Number	Percent	Number	Percent
H. influenzae.....	1/16	3.5	2/12	8	9/88	4.7
N. meningitidis.....	1/8	3.5	1/7	4	0/8	0
D. pneumoniae.....	0/1	0	0/4	0	7/35	3.7
Unknown etiology.....	0/3	0	0/2	0	2/59	1.1
Overall mortality.....	2/28	7	3/25	12	18/190	9.5

TABLE X.—INCIDENCE OF SUBDURAL EFFUSION AND SEVERE NEUROLOGIC SEQUELAE ACCORDING TO ETIOLOGY: STUDY, MATCHED CONTROL, AND 5-YEAR REVIEW PATIENTS

Etiologic agent	Study patients				Matched control patients				5-year review patients			
	Subdural effusion		Severe neuro-sequelae		Subdural effusion		Severe neuro-sequelae		Subdural effusion		Severe neuro-sequelae	
	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent	Num-ber	Per-cent
H. influenzae.....	3/16	19	1/16	6	4/12	33	1/12	8	14/88	16	8/88	9
N. meningitidis.....	0/8	-----	0/8	-----	0/7	-----	0/7	-----	0/8	-----	0/8	-----
D. pneumoniae.....	1/1	100	0/1	-----	1/4	25	0/4	-----	7/35	20	7/35	20
Unknown etiology.....	0/3	-----	0/3	-----	0/2	-----	0/2	-----	4/59	7	9/59	15
Total.....	4/28	14	1/28	4	5/25	20	1/25	4	25/190	13	24/190	13

TABLE XI.—MEAN DURATION OF FEVER AFTER INITIATION OF THERAPY: STUDY, MATCHED CONTROL, AND 5-YEAR REVIEW PATIENTS

	Study patients (days)	Matched control patients (days)	5-year review patients (days)
H. influenzae.....	6.9	8.5	7.0
N. meningitidis.....	6.3	6.3	4.0
D. pneumoniae.....	5.0	2.5	5.2
Unknown etiology.....	3.0	2.0	2.9

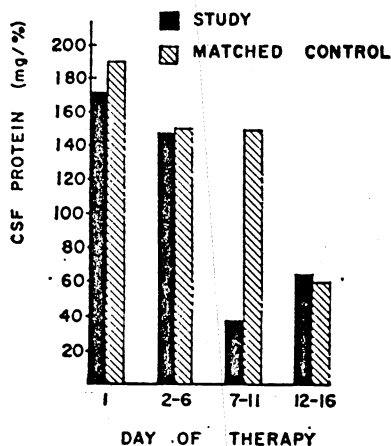


FIGURE 1.—Mean cerebrospinal fluid cell counts of study and matched control patients.

RANGE OF CEREBROSPINAL FLUID PROTEIN VALUES IN MILLIGRAMS PERCENT

	Day 1	Days 2-6	Days 7-11	Days 12-16
Study group.....	13-480	30-970	14-76	23-120
Control group.....	22-684	34-571	21-1,400	20-140

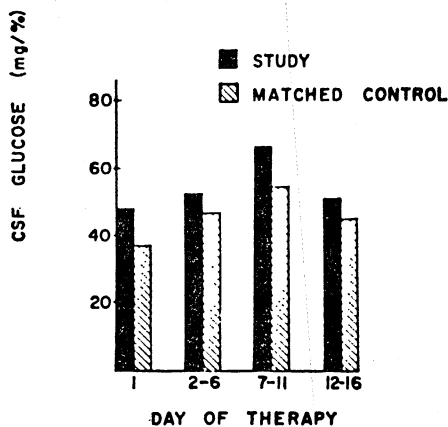


FIGURE 2.—Mean cerebrospinal fluid glucose values of study and matched control patients.

RANGE OF CEREBROSPINAL FLUID GLUCOSE VALUES IN MILLIGRAMS PERCENT

	10-92	20-98	50-94	30-80
Study group.....	10-78	20-95	35-75	28-58
Control group.....				

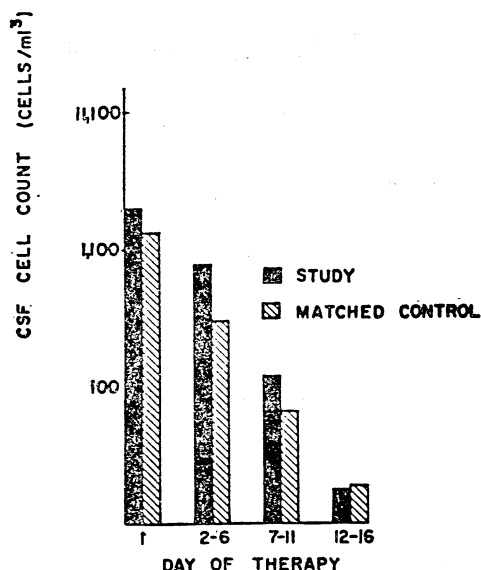


FIGURE 3.—Mean cerebrospinal fluid protein values of study and matched control patients.

RANGE OF CEREOSPINAL FLUID CELL COUNTS PER CUBIC MILLILITER

Study group.....	90-19,500	3-6,000	2-237	0-103
Control group.....	52-11,000	3-4,150	0-182	0-115

In addition to mortality figures and neurologic sequelae, other criteria used to assess the efficacy of antibiotic therapy were: duration of fever after initiation of therapy; eradication of bacteria from the spinal fluid, and return of the spinal fluid cell count, sugar, and protein to normal values. The duration of fever in the ampicillin-treated patients, the matched control patients and the 5 year review patients is shown in Table XI. There does not appear to be any significant difference in the time of defervescence in the three groups. The bacteriologic response to antibiotic therapy was rapid in the groups of patients studied in 1964 and 1965 (study and matched controls). There were no positive cultures within 48 hours after initiation of therapy in either of these two groups. There were insufficient data to evaluate the rapidity of bacteriologic response in the 190 patients receiving conventional therapy during the last 5 years.

The cerebrospinal fluid findings of the study and matched control groups are presented in Figs. 1 to 3. No significant differences in the initial cerebrospinal fluid cell count, protein, and sugar values are apparent in the two groups. These values returned to normal at the same rate in the two groups. The difference in protein values at 7 to 11 days may be a reflection of the small number of lumbar punctures done during that phase of the illness. There were insufficient data to evaluate the cerebrospinal fluid findings in the 5 year review group.

The incidence of drug hypersensitivity and toxicity could be evaluated in the study and matched control patients but not in the 5 year review group. No skin manifestations of hypersensitivity developed in the ampicillin-treated patients. Eosinophilia was observed in 8 patients. The serum glutamic oxaloacetic transaminase (SGOT) was slightly elevated in 8 patients. Three patients developed mild diarrhea which may have been related to ampicillin therapy. The eosinophilia and diarrhea cleared spontaneously in every case, usually without discontinuation of drug therapy. The SGOT returned to normal after cessation of therapy in all patients in whom repeat values were obtained. No hematologic abnormalities developed in the study patients. None of the patients in the matched control group developed evidence of penicillin allergy. Four patients with

Hemophilus influenzae meningitis developed anemia and/or absolute neutropenia while on chloramphenicol therapy. One patient with pneumococcal meningitis developed anemia while on triple antibiotic therapy. In all instances the anemia and neutropenia resolved spontaneously with cessation of chloramphenicol therapy.

SUMMARY AND CONCLUSIONS

During 1963–1965, strains of *H. influenzae*, *D. pneumoniae*, and *N. meningitidis* isolated from patients with purulent meningitis were tested for in vitro sensitivity to ampicillin, chloramphenicol, penicillin G, and tetracycline. These studies indicated that, in vitro, ampicillin was as effective or slightly more effective than chloramphenicol, penicillin G, and tetracycline against *H. influenzae* and was equally effective in vitro as penicillin G against *D. pneumoniae* and *N. meningitidis*.

Simultaneous serum and cerebrospinal fluid ampicillin levels were determined in 8 patients with no evidence of meningeal disease, 10 patients with viral meningitis or encephalitis, and 20 patients with bacterial meningitis. High blood levels were achieved in all three groups. The drug was detectable in the cerebrospinal fluid of patients with normal meninges as well as patients with inflamed meninges. The mean cerebrospinal fluid/serum ratio, however, was significantly higher in patients with bacterial meningitis than in those with no evidence of meningeal disease.

Twenty-eight patients admitted consecutively to Ben Taub General Hospital from July, 1964, to April, 1965, with the diagnosis of acute bacterial meningitis received single drug therapy with ampicillin (study group). Twenty-five patients admitted from April, 1965, to July, 1965, received conventional antibiotic therapy and served as a matched control group. In order to establish a base line of mortality and morbidity of bacterial meningitis in our hospital, the charts of 190 children (2 months to 14 years of age) who received conventional antibiotic therapy for bacterial meningitis from 1959 through 1963 were reviewed (5 year review group).

The mortality rate and the incidence of severe neurologic sequelae were not significantly different in the three groups of patients studied. The incidence of subdural effusion was approximately equal in the three groups of patients, and the incidence of minor neurologic sequelae was approximately the same in the study and matched control groups.

The rapidity of response to therapy as measured by: (1) the duration of fever after the institution of antibiotic treatment in the three groups studied and (2) the return of the cerebrospinal fluid values to normal in the study and matched control groups indicated no significant difference between therapy with ampicillin and conventional drugs.

No serious drug reactions occurred in the ampicillin-treated patients. Eosinophilia, diarrhea, or slight elevation of the SGOT were encountered in a few patients but these often subsided without cessation of therapy. Five patients in the matched control group developed anemia and/or absolute neutropenia while on chloramphenicol therapy. In all instances, the anemia and neutropenia resolved with cessation of chloramphenicol therapy.

Ampicillin appears to be an excellent drug for the treatment of acute bacterial meningitis due to *D. pneumoniae*, *N. meningitidis*, and *H. influenzae* in children. It is as safe and as effective as conventional triple therapy and in addition has the following advantages: (1) simplicity of administration, and (2) apparent freedom from hematologic and renal complications encountered with chloramphenicol and sulfonamides, respectively.

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APPENDIX X

[From Post Graduate Medical Journal, December 1964, pp. 119-125]

H. INFLUENZAE MENINGITIS: A CONTROLLED STUDY OF TREATMENT WITH AMPICILLIN

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THE case fatality rate in *Hemophilus influenzae* meningitis has been reduced to 5-10% by present methods of anti-bacterial and supportive therapy. As this rate is still far from optimal, the incidence of both early and late neurological sequelae is appreciable, and the antibiotics presently employed have definite and occasionally serious toxicity, new approaches to therapy must be evaluated.

Preliminary *in vitro* studies performed in our laboratory (Ivler, Thrupp, Leedom, Wehrle and Portnoy, 1963) indicated that 126 strains (118 type B) of *H. influenzae* isolated from cerebrospinal fluid (C.S.F.) were sensitive to ampicillin. Bacteriostatic and bactericidal levels did not differ significantly, and 91% were killed by 0.4 $\mu\text{g./ml.}$ Only one had a bactericidal level as high as 1.6 $\mu\text{g./ml.}$ In addition, sensitivities of meningococci and pneumococci to ampicillin were similar to those to penicillin G. These data, in conjunction with the apparent low toxicity of ampicillin suggested the trial of ampicillin as a single drug treatment for bacterial meningitis, in contrast to control groups treated with conventional therapy. The present report summarizes the experience to date with *H. influenzae* meningitis. Eighteen of these 70 patients were included in a preliminary report (Ivler *et al.*, 1963).

MATERIALS AND METHODS

(1) Selection of Patients: All patients more than two months of age with bacterial meningitis admitted to the Communicable Disease Service of the Los Angeles County General Hospital were included in the ampicillin study. Chart numbers assigned at the hospital central admitting office, and not subject to control of the ward physicians, were used to insure proper randomization. Patients with even (2, 4, 6, etc.) numbers were assigned to the ampicillin group while patients with chart numbers ending 1, 3, 5, etc., were given conventional therapy. During the period considered (June, 1963 to March 1964) a total of 72 patients were admitted with *H. influenzae* meningitis. Of these, 44 with odd chart numbers were assigned to the control group, and 28 with even numbers were eligible for ampicillin therapy. The difference in the size of the two groups was unexpected, although within the limits of chance variation. Two of the 28 patients were excluded from the ampicillin group, one by error in assignment and the other because of concomitant severe facial cellulitis following a dog bite where additional therapy was indicated. These two patients were not tabulated with either group. Most of the patients had received some antibacterial therapy prior to admission, usually subtherapeutic dosages, ineffective drugs, or both.

NOTE.—References at end of article.

No attempt was made to evaluate this, since it was assumed to provide an equal, and probably negligible, effect in both treatment groups.

(2) Administration of antibacterial therapy: Sodium ampicillin was reconstituted in 0.85 per cent NaCl and administered rapidly (15–20 minutes) at four hour intervals in a total daily dose of 150 mg./kg. of body weight. (The first seven patients treated received 100 mg./kg. per day intravenously at six hour intervals). The intravenous route was used invariably for at least the first 48 hours, while after adequate initial clinical response many patients were given the same daily dose by intramuscular injection at four hour intervals during the remainder of the period of treatment.

Chloramphenicol was given by continuous intravenous infusion in a total daily dose of 100 mg./kg. In some patients in whom the diagnosis of *H. influenzae* was not certain on admission, sulfisoxazole and penicillin G (150 mg./kg./day of each drug) were also given until isolation and identification of the organisms were completed.

(3) Duration of therapy: Treatment was continued until the patient was afebrile for at least five days, the spinal fluid contained less than 40 cells per cmm. with few or no polymorphonuclear leukocytes, and the C.S.F. sugar was normal.

(4) Evaluation of response to therapy: Response to therapy was evaluated by the usual clinical criteria, including duration of fever, improvement in neurological status, decrease in peripheral blood leukocyte count with a return of the differential count toward normal, and improvement in C.S.F. finding, including pressure, cell count, percentage polymorphonuclear leukocytes and glucose and protein content.

Subdural taps were performed whenever indicated (Platou, Rinker and Derrick, 1959). In this report the outcome of therapy was evaluated according to the patient's course in the hospital and status at the time of discharge from the hospital. Untoward findings during the course of treatment in the hospital and any neurological abnormalities were recorded. "Delayed resolution clinically, but no sequelae at discharge" is a descriptive category which included patients with one or more findings such as: (a) transients subdural effusions, (b) convulsions persisting beyond the first 24 hours in the hospital, (c) persistence of a positive C.S.F. culture the day following admission to the hospital, (d) persistence or recurrence of C.S.F. pleocytosis, (e) documented persistence of nuchal rigidity or neurological findings such as cranial nerve palsies beyond five days even though resolution has occurred by the time of discharge. An additional "slow response" category incorporated the above plus other patients with no abnormality but fever persisting beyond five days of treatment.

(5) Bacteriological methods: Isolation and identification of the organisms were accomplished by conventional methods utilizing blood and chocolate agar, serum and thioglycollate broth and both aerobic and CO₂ incubation. Quellung was done in C.S.F. if adequate numbers of organisms were present. Bactericidal levels of ampicillin and chloramphenicol were determined using serial tube dilution techniques in GC medium containing 1% supplement B. (Difco).

RESULTS

Bacteriologic confirmation of the diagnosis of *H. influenzae* type B infection was complete in 68 of the 70 patients in the study group. Blood and C.S.F. cultures were both positive in 34 patients and organisms were cultured from the C.S.F. alone in the remaining 34. Two patients admitted with partially treated purulent meningitis had no positive cultures; they are included in this series on the basis of organisms seen of Gram's stain of the C.S.F. The cultural recovery of *H. influenzae* from 68/70 patients supported the assumption that antibiotic therapy given prior to admission had little effect on the course of the illness. To date, 164 strains of *H. influenzae* isolated from C.S.F. have been tested for *in vitro* sensitivity to ampicillin. Ninety-one per cent of the strains were killed by 0.4 µg./ml., and only two had bactericidal end points as high as 1.6 and 3.1 µg./ml. respectively.

The age and sex distribution of the patients studied is indicated in Table I. Two of the patients were more than 15 years of age. It should be noted that 14 of 26 patients in the ampicillin group were two years of age or older, and 13 of 44 patients in the control group were in this age group. This was believed to be an unimportant difference, since the distribution of severity of illness, according to the criteria in Table II, was similar within each age group and apparently

was not related to age. The expected male predominance was found in both study groups.

The duration of illness prior to admission was similar in both groups. In Table II the patients in each group are recorded by severity of illness on admission. There was no difference between the two groups.

The duration of fever after therapy was instituted as indicated in Table III. No significant difference is apparent between the two groups. Sixty-four per cent of the chloramphenicol treated patients were afebrile by the fifth hospital day, while 72% of the ampicillin group were in this category.

The C.S.F. was re-examined within one or two days following admission in 24 ampicillin and 38 control patients. Cultures of these follow-up C.S.F. samples were positive in three of 31 specimens from the ampicillin patients and three of 46 samples from controls. These six positive specimens were all obtained less than 18 hours after the start of therapy; no positive C.S.F. cultures were obtained from either treatment group later than 18 hours after admission. The similarity of response in the two treatment groups is further emphasized in Figs. 1 and 2, in which changes in C.S.F. cell count and glucose are shown during the period of therapy. In addition to the data shown, the rate of decline in percentage of polymorphonuclear cells in the C.S.F. during the period of treatment was similar in the two groups.

TABLE I.—H. INFLUENZA MENINGITIS, AGE AND SEX DISTRIBUTION OF PATIENTS BY THERAPY GROUP

Therapy group and sex	Less than 1 year	1 year	2 to 4 years	5 to 29 years	Total
Control:					
Male.....	10	7	3	3	23
Female.....	9	5	5	2	21
Total.....	19	12	8	5	44
Ampicillin:					
Male.....	7	3	6	0	16
Female.....	2	0	6	2	10
Total.....	9	3	12	2	26

TABLE II.—H. INFLUENZA MENINGITIS, CLINICAL STATUS ON HOSPITAL ADMISSION ACCORDING TO TREATMENT GROUP

Severity group	Findings	Control		Ampicillin	
		Number	Percent	Number	Percent
4+	Coma, shock, semicoma, hypotension ¹	8	18	3	12
3+	Convulsions without coma or shock.....	10	23	7	27
2+	Temperature of 105° R. or more, symptoms 5 days or more, complicating disease, marked lethargy ¹	15	34	9	34
1+	None of above.....	11	25	7	27
	Total patients.....	44	100	26	100

¹ 1 or more of the findings listed.

TABLE III.—H. INFLUENZAE MENINGITIS, DURATION OF FEVER IN HOSPITAL BY TREATMENT GROUP

[Number (percent distribution) of patients with maximum temperature > 100° F.]

Therapy group	Days in hospital						Total
	0-1	2-3	4-5	6-7	8-9	10+	
Control.....	3 (8)	11 (28)	11 (28)	8 (21)	2 (5)	4 (10)	1 39 (100)
Ampicillin.....	6 (24)	3 (12)	9 (36)	1 (4)	2 (8)	4 (16)	2 25 (100)
Total.....	9	14	20	9	4	8	64

¹ 4 fatalities and 1 case with incomplete temperature record excluded.

² 1 fatal case excluded.

TABLE IV.—H. INFLUENZAE MENINGITIS COMPLICATIONS AND SEQUELAE BY TYPE OF TREATMENT

	Control		Ampicillin	
	Number	Percent	Number	Percent
Death.....	4	9	1	4
Neurological residual ¹	5	11	3	12
Severe.....	1	-----	2	-----
Mild or questionable.....	4	-----	1	-----
Subdural effusions.....	4	9	4	15
Required surgery.....	0	-----	2	-----
Mild neurological residual.....	1	-----	1	-----
No sequelae.....	3	-----	1	-----
Seizures persistent ²	1	2	2	8
Delayed resolution clinically ³ but no sequelae at discharge.....	13	30	8	31
Temperature of 100° F. or more for 6 days but without any of the above findings.....	5	11	1	4
Good response (none of above findings).....	18	41	13	54

¹ At hospital discharge.² Some seizures persistent 24 hours or more after admission.³ Tabulation includes patients with slight subdural effusions which cleared without surgery or neurological sequelae.

TABLE V.—H. INFLUENZAE MENINGITIS, STATUS ON DISCHARGE FROM THE HOSPITAL

Age group—Treatment group	No residual satisfactory response	Slight or no residual with minor subdurals or slow response	Serious neurologic residual or death	Total
Less than 12 months:				
Control.....	9	9	1	19
Ampicillin.....	0	6	3	9
Total.....	9	15	4	28
12–23 months:				
Control.....	7	3	2	12
Ampicillin.....	2	1	0	3
Total.....	9	4	2	15
2 or more years:				
Control.....	6	5	2	13
Ampicillin.....	12	2	0	14
Total.....	18	7	2	27
All ages:				
Control.....	22	17	5	44
Ampicillin.....	14	9	3	26
Total.....	36	26	8	70

TABLE VI.—H. INFLUENZAE MENINGITIS (POSSIBLE REACTIONS OR COMPLICATIONS OF THERAPY)

Type of reaction	Control (44 patients)		Ampicillin (26 patients)	
	Number	Percent	Number	Percent
Any possible reaction.....	20	(45)	16	(62)
Phlebitis.....	9	(20)	10	(38)
Skin rash.....	4	(9)	5	(19)
Gastrointestinal.....	3	(7)	1	(4)
Miscellaneous.....	6	(14)	1	(4)
Eosinophilia ¹	3	(7)	1	(4)
Hematologic depression.....	10	(23)	2	(8)
Leukopenia ²	5	-----	0	-----
Rel. granulocytopenia ⁴	5	-----	1	-----
Thrombocytopenia ⁵	2	-----	1	-----
Anemia ⁶	3	-----	1	-----

¹ >10 percent eosinophils in peripheral smear.² 1 patient failed to respond to Ampicillin, and developed mild anemia and thrombocytopenia 14 days after the substitution of chloramphenicol.³ <4,000 per cmm. (or <5,000 if other hematology abnormal).⁴ <15 percent polys and bands.⁵ Marked reduction in platelets on smear.⁶ Drop in hemoglobin of >2 g./100 ml.

Complications seen are recorded in Table IV by type of sequelæ and method of therapy. Again, it is apparent that no significant difference is present between the two groups. A strong association was found with coma, shock and/or convulsions on admission and fatal outcome or serious neurological residual. This was the case in both therapeutic groups. None of the 42 patients admitted without the above serious clinical signs had a fatal outcome or neurological sequelæ of consequence. Among the 28 patients admitted with coma, shock or convulsions, four of 18 treated with chloramphenicol died and one had a serious residual. One of 10 in the ampicillin series died, and an additional two patients had severe residual involvement (hydrocephalus).

The status of the patients at the time of discharge by age group and type of therapeutic response is recorded in Table V. Although minor differences were noted among the various age groups, the numbers were small and of doubtful significance. In the total group, the proportion with entirely satisfactory response was 22 of 44 control patients and 14 of 26 ampicillin patients. These proportions may be regarded as nearly identical.

Possible drug reactions or complications of therapy are listed in Table VI. These findings were not proven to be due to the specific antibiotic therapy in any instance. The high incidence of local phlebitis in both groups accompanied the frequent use of polyethylene, indwelling, venous catheters. Twelve patients with some evidence of hematologic depression are also listed in Table VI, although the findings were minimal in most. Eleven cases accompanied the administration of chloramphenicol. One three-month-old patient treated with ampicillin had a peripheral white blood cell differential count of 15% polymorphonuclears and no bands on the seventh day of therapy. This finding was of doubtful significance in view of the age of the patient, lack of accompanying anemia or leukopenia, and a reticulocyte count of 1.6%. The other patient with hematologic depression included in the ampicillin group was treated initially with ampicillin with prompt sterilization of C.S.F. However, the pleocytosis failed to clear, and subdural effusions and hydrocephalus were noted. The marrow depression appeared two weeks after chloramphenicol had been substituted.

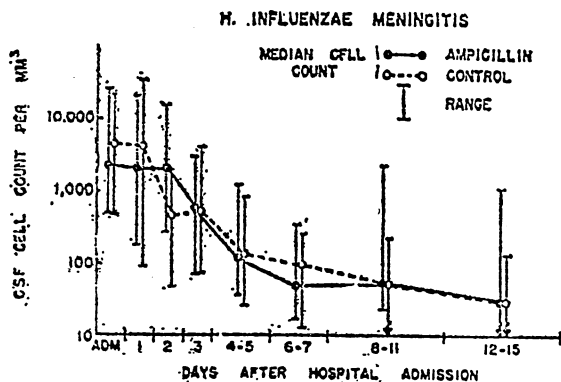


FIGURE 1.—C.S.F. cell counts during the treatment period.

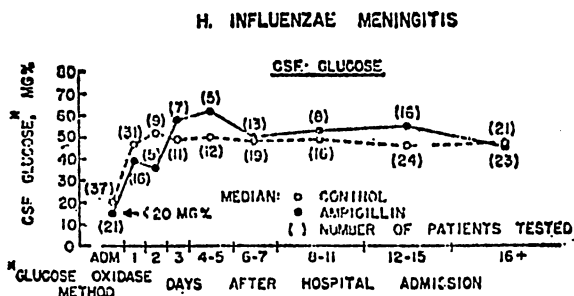


FIGURE 2.—C.S.F. glucose levels during the treatment period.

DISCUSSION

The patients with *H. influenzae* meningitis in this study comprised a group similar to series previously reported (Haggerty and Ziai, 1964). 90% of the patients were between two months and four years old. This age distribution followed the characteristic pattern which, as shown by Fothergill and Wright (1933), reflects inversely the age prevalence of bactericidal serum antibody. Three per cent (two cases) were young adults, a proportion similar to the 2.7% of patients more than 20 years of age recorded in Dolphin and Popham's (1951) review of 915 cases. There was the expected male predominance.

Analysis of the results of therapy with ampicillin and chloramphenicol in these two comparable groups of patients failed to elicit any clear-cut differences. General clinical criteria such as mortality, neurological sequelae, duration of fever, subdural effusions, sterilization of the C.S.F. rates of reduction in the number of cells, per cent polys and protein content in C.S.F. and rise in C.S.F. sugar, were similar in both groups. The C.S.F. cell counts and sugar levels showed no differences on the first and the third days after admission, or afterwards. Among small numbers of observations on the second day, the larger variation in values for the ampicillin patients resulted in differences in distributions of values about the medians for that single day of bordering significance (Figs. 1 and 2). However, in view of the data for the days prior to, and following, this second day of treatment, it is doubtful that these differences were meaningful.

Although all nine ampicillin patients less than one year of age manifested at least some deficiency in response to therapy, nine of 19 controls in this age group had satisfactory responses (Table V). A trend toward fewer unsatisfactory responses with ampicillin than chloramphenicol was observed in patients two or more years of age. As stated previously, neither therapeutic group was weighted with disproportionate numbers of severely ill or moderately ill patients at any age. Disregarding age, the proportion of satisfactory responses in both therapeutic groups was almost identical. The apparent minor differences in response to ampicillin and chloramphenicol by age group would probably disappear if more patients were tested. Consideration of these data emphasizes the difficulty of being certain that every important variable is known in any clinical study.

The one patient in the ampicillin group who died and the two who survived with major residua were all severely ill on admission. Nevertheless the clinical findings in these two survivors were of interest in that C.S.F. pleocytosis with polymorphonuclear predominance persisted in one, and both developed subdural effusions and hydrocephalus eventually requiring neurosurgical correction. None of the patients in the control group required neurosurgery, although it should be noted that four deaths occurred in this group.

Several studies have demonstrated the *in vitro* effectiveness of ampicillin against *H. influenzae* (Rolinson and Stevens, 1961; Klein and Finland, 1963) including type B strains isolated from C.S.F. in our hospital (Ivler *et al.*, 1963). Although ampicillin displayed significantly more activity *in vitro* than penicillin G against C.S.F. *H. Influenzae* isolates, the differences were small and of questionable clinical significance (Ivler *et al.*, 1963). Nevertheless, the overall response of patients with *H. influenzae* meningitis treated with ampicillin was comparable to the results observed with chloramphenicol. These favourable results with ampicillin stand in contrast to the reported experience with penicillin G even when patients treated with the latter drug had meningitis due to *H. influenzae* strains sensitive to penicillin G, and C.S.F. penicillin G levels were maintained by intrathecal therapy (Drysdale, McIntosh and Brodie, 1946; Zinnemann, 1946; Thomson, Bruce and Green, 1947). Perhaps qualitative differences in the activity of ampicillin and penicillin G against *H. influenzae* account for the more effective results with ampicillin.

Ampicillin levels in the C.S.F. samples studied to date have been variable, ranging from 0.1 to 1.0 $\mu\text{g./ml.}$ with average C.S.F.-to-serum ratios of 20 to 30%. These C.S.F. levels seem rather low in view of the overall satisfactory clinical response to ampicillin. Indeed, C.S.F. levels of 0.1 to 1.0 $\mu\text{g./ml.}$ barely approximate the *in vitro* minimum bactericidal concentrations (Ivler *et al.*, 1963) and clinical responses have not correlated well with C.S.F. levels. For example, a C.S.F. sample from an eight month old patient who developed subdural effusion and hydrocephalus contained more than 7.0 $\mu\text{g./ml.}$ of ampicillin, one of the highest levels found in any patient.

The peripheral blood differential count of 15% neutrophils noted in a three month old in the ampicillin group on the seventh day of therapy could not be

considered definitely abnormal. The anemias, leukopenias, granulocytopenias and thrombocytopenias observed in the control patients on chloramphenicol therapy all subsided after the drug was discontinued. One control patient who developed anemia, thrombocytopenia and leukopenia, concurrently developed staphylococcal pneumonia and extensive phlebitis and cellulitis at the site of an intravenous polyethylene catheter. However, as the patient's differential count remained normal, and the lowest total white blood cell count recorded was 3,100 per cmm. the superinfection was not necessarily related to the mild leukopenia.

SUMMARY

Overall results of treatment of *H. influenza* meningitis with ampicillin or chloramphenicol appeared comparable, but no definite advantages were demonstrated in the use of ampicillin other than the freedom from hematologic depression. While one death occurred among the ampicillin group and two additional patients required neurosurgical procedures for correction of hydrocephalus, four control patients died and one had severe neurological residual. Further study, perhaps with higher dosage, is indicated.

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The diagnostic bacteriology was directed by Margaret Parrish and Patricia Hagen, in the Communicable Disease Section of the Microbiology Laboratories, Dr. Robert Clelland, Director, Los Angeles County General Hospital.

Ampicillin assays were performed by Bristol Laboratories, Syracuse, New York.

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APPENDIX XI

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EXPERIENCE WITH AMPICILLIN IN BACTERIAL MENINGITIS

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ABSTRACT

The mortality of bacterial meningitis is 10 to 15% in large contemporary series and prompts continuing search for effective, nontoxic therapeutic agents.

Ampicillin was highly effective in vitro against *Haemophilus influenzae*, *Neisseria meningitidis*, and *Diplococcus pneumoniae*, and, being a penicillin, would be expected to have low toxicity. Therefore, ampicillin as a single drug treatment for bacterial meningitis was contrasted with "conventional" therapy. From 1 July 1963 to 30 April 1965, 541 bacterial meningitis patients over 2 months of age were assigned to ampicillin therapy or to conventional therapy with penicillin, chloramphenicol, or both, according to chart number. Error in drug assignment, fulminant meningococcemia, unusual organisms, or concomitant disease requiring other therapy excluded 88 patients. The severity of illness on admission was comparable in both treatment groups. Overall mortality rates in the ampicillin (A) and control (C) groups were 8.3 and 11.8%, respectively. Case fatality rates varied slightly according to etiological agent, i.e., *H. influenzae* (6.0 with A versus 9.3 with C); *N. meningitidis* (5.3 with A versus 9.1 with C); *D. pneumoniae* (22.0 with A versus 28.7 with C); purulent meningitis, no isolate (0 with A versus 5.7 with C). The overall incidence of neurological residua was 12.5% with A and 10.7% with C. Duration of fever and cerebrospinal fluid abnormalities were comparable. Possible complications of therapy were more frequent in the control group, primarily because of hematological changes with chloramphenicol. The data indicate that ampicillin is effective as a single drug for the three major causes of bacterial meningitis and purulent meningitis of unknown etiology, and also illustrate the difficulties inherent in naming a "regimen of choice" when two effective modes of treatment are compared.

Although serum therapy, sulfonamides, and subsequently the use of various antibiotics have substantially reduced the mortality of bacterial meningitis, the total case fatality rate remains between 10 and 15% in many large series. Current therapeutic recommendations for the most frequent types of bacterial meningitis include one or more of several different antimicrobial agents. Of the drugs most frequently recommended, only benzylpenicillin lacks major pharmacological toxicity. A new 6-amino-penicillanic acid derivative, ampicillin, demonstrated marked bactericidal activity against *Haemophilus influenzae* in vitro and resembled benzylpenicillin in potential toxicity and efficacy against organisms customarily penicillin-sensitive (Ivler et al., 1964). Therefore, it seemed desirable to evaluate this antibiotic in the therapy of *H. influenzae* and other types of acute bacterial central nervous system (CNS) infections.

After treatment of a small number of patients seemed to indicate clinical efficacy and no toxicity, a controlled clinical evaluation of parenteral ampicillin in comparison with groups treated with penicillin or chloramphenicol or both, was started at the Communicable Disease Service of the Los Angeles County General Hospital in 1963. A preliminary report of this study (Ivler et al., 1964) and some of the data concerning patients with *H. influenzae* have been presented previously (Thrupp et al., 1964).

MATERIALS AND METHODS

Selection of patients. The Communicable Disease Service of the Los Angeles County General Hospital is the major referral center for the entire County for patients with CNS infections of all ages and from all socioeconomic groups. Patients were included in the present study in accordance with the following criteria. All patients 2 months of age and older who were admitted to the Communicable Disease Service of the Los Angeles County General Hospital with bacterial meningitis were included in this study. Patients were assigned to the ampicillin or control groups on the basis of hospital chart numbers. Chart numbers were obtained by telephoning the central admitting office, which obviated physician bias in assignment of patients to one group or another. Patients with even chart numbers were assigned to the ampicillin group, and those with odd chart numbers, to the control group.

Administration of antibiotic therapy. One-third of the 24-hr dose of the respective antibiotic was given by rapid intravenous infusion on admission to the service. Sodium ampicillin was given in a daily dose of 150 mg/kg, intravenously, in equally divided doses at 4-hr intervals. Each dose of ampicillin was dissolved in 0.85% sodium chloride and was administered as a rapid infusion. Reconstituted drug was stored in a refrigerator at 4 C for not more than a 24-hr period. After a minimum of 2 or 3 days of intravenous therapy, the antibiotic was given intramuscularly, at the same dosage, on a 4-hr schedule. Control therapy consisted of penicillin G in doses approximating 150 mg/kg for patients with

Neisseria meningitidis or *Diplococcus pneumoniae* infections. For those with *H. influenzae*, chloramphenicol was used as a single drug dosage of 100 mg/kg, for 24 hr. Both of the latter antibiotics were administered by continuous intravenous infusion. As with ampicillin, after 2 or 3 days of therapy, these drugs were given in the same dosage intramuscularly. Control group patients with meningitis of unknown etiology received both aqueous penicillin G at 150 mg/kg and chloramphenicol at 100 mg/kg. As outlined above, the initial 24-hr dosage of ampicillin or penicillin G was therefore approximately 200 mg/kg and for chloramphenicol was 133 mg/kg. Sulfisoxazole was added to the regimen of a few patients in the control group at the beginning of the study. In control patients in whom no organisms were seen on the initial direct examination of the spinal fluid, but who had subsequent isolation of an organism, either penicillin or chloramphenicol was discontinued, depending upon the organism identified.

The response to therapy was evaluated by the usual clinical criteria, including duration of fever, improvement in the mental and neurological status, and improvement in the cerebrospinal fluid (CSF). Treatment was continued until: the patient was afebrile for at least 5 days; the spinal fluid cell count was less than 30 cells, with less than 10% polymorphonuclear cells; the CSF sugar was normal; and the protein approached normal. Subdural taps were performed whenever indicated.

Bacteriological methods. Gram-stained sediment of spinal fluid was examined both by the admitting physician and by laboratory personnel. The quellung test for specific confirmation of *H. influenzae* infections was used if adequate numbers of organisms were present. Isolation and identification of the causative organisms were accomplished by conventional methods, including both aerobic and CO₂ incubation techniques. In vitro data concerning ampicillin, chloramphenicol, and penicillin G sensitivities have been presented previously (Ivler et al., 1964).

TABLE 1.—TOTAL MENINGITIS PATIENTS STUDIED, LOS ANGELES COUNTY GENERAL HOSPITAL, JULY 1963 TO APRIL 1965

Bacterial etiology	Treatment regimen		Patients excluded	Total patients
	Ampicillin	Control		
<i>Haemophilus influenzae</i>	66	107	16	189
<i>Neisseria meningitidis</i>	56	77	23	156
<i>Diplococcus pneumoniae</i>	41	42	22	105
Unknown.....	29	35	9	73
Other organisms.....			18	18
Total cases.....	192	261	88	541

TABLE 2.—IDENTIFICATION OF ORGANISMS FROM MENINGITIS PATIENTS BY TREATMENT GROUPS¹

Etiology and regimen	Source of organisms			Total	Smear ²	Total cases included
	CSF	Blood	CSF plus blood			
<i>Haemophilus influenzae</i> :						
Ampicillin.....	60	35	32	63	3	66
Control therapy.....	94	51	42	103	4	107
<i>Neisseria meningitidis</i> :						
Ampicillin.....	39	7	5	41	5	³ 56
Control therapy.....	55	12	7	60	6	⁴ 77
<i>Diplococcus pneumoniae</i> :						
Ampicillin.....	34	21	20	35	6	41
Control therapy.....	30	17	13	34	8	42
Total.....	312	143	119	336	32	389

¹ Total cases studied 453, 81 percent with known etiology (88 exclusions).

² Direct examination only.

³ Includes 10 clinical diagnoses.

⁴ Includes 11 clinical diagnoses.

RESULTS

Distribution of patients. During the period from 1 July 1963 through 30 April 1965, a total of 541 patients with bacterial meningitis were admitted to the Communicable Disease Service. The distribution of these patients by etiological agent is shown in Table 1. The 88 total exclusions comprise patients who were inadvertently assigned to the inappropriate therapeutic group (43), or were subsequently discovered to have nonpurulent meningitis (7). Those with underlying disease [brain abscess (4) or bacterial endocarditis (7)] were also excluded, as were those with dual infection (1), unusual organisms (10), and those patients known to be hypersensitive to penicillin (6). Within the meningococcal category, those considered by the admitting physician to have fulminant meningococcal disease were also excluded. Five patients who would have received ampicillin and five patients who might have been assigned to the control group were thus excluded. All received penicillin G, and two deaths occurred among these 10 patients, one in each category should they have been included.

Source of organisms. Of the 453 patients suitable for analysis, precise bacterial etiologies were determined in 368, or 81%. Although many of the patients had received at least some antibacterial therapy prior to their admission, this was not a reason for exclusion, since, despite previous antibacterial therapy, the organism was recovered on culture from the great majority of patients, as is noted in Table 2. In 32 instances, organisms were identified on direct examination of spinal fluid or petechiae without subsequent growth in culture. Twenty-one patients with purulent meningitis and a petechial-purpuric rash were included in the meningococcal category on clinical grounds.

Severity of illness. To properly categorize patients for comparative purposes, they were divided into four groups according to the severity of illness at the time of admission to the hospital. Included in the 4+ (severe) category, were patients who were comatose or semicomatose, in definite shock, or with significant hypotension. The 3+ (moderate) category included patients with convulsions, but who were not hypotensive or comatose. The 2+ (mild) category had patients in whom either the temperature was greater than 105 F rectally on admission, or symptoms had been present for more than 5 days; also included were those with a complication already present on admission or with marked lethargy. The 1+ (mild) category was reserved for those patients with none of the above findings but with definite bacterial meningitis. Since the 2+ and 1+ categories were associated with low mortality and few complications, these grades have been combined and are presented for all groups in Table 3. As is apparent, the distribution of severe and lesser grades of illness was essentially the same for the ampicillin and the control groups. The method of randomization was effective, although minor differences in proportions of patients in moderate and severe categories were seen.

In the pneumococcal severe category there was an apparent difference in the assignment of excess patients in the severe group to penicillin therapy. This difference is not statistically significant ($X^2=3.28$; $P=0.077$), and is explained by the difference in age distribution for pneumococcal cases (Table 4). Fewer control patients appear in the 1 to 15-year group, and an excess is apparent in the 30 to 44-year and 60 to 74-year groups. The slightly lower mortality in pneumococcal disease with ampicillin therapy may be explained entirely by the age and severity distributions in this study.

TABLE 3.—TYPES OF MENINGITIS BY SEVERITY ON ADMISSION

Etiology and regimen	Clinical estimate on severity						Total cases
	Severe		Moderate		Mild		
	Number	Percent	Number	Percent	Number	Percent	
Haemophilus influenzae:							
Ampicillin.....	13	20	10	15	43	65	66
Control therapy.....	18	17	20	18	69	65	107
Neisseria meningitidis:							
Ampicillin.....	13	23	10	18	33	59	56
Control therapy.....	23	30	4	5	50	65	77
Diplococcus pneumoniae:							
Ampicillin.....	22	54	3	7	16	39	41
Control therapy.....	31	74	2	5	9	21	42
Unknown:							
Ampicillin.....	3	10	5	17	21	73	29
Control therapy.....	5	14	0	0	30	86	35

TABLE 4.—PERCENTAGE DISTRIBUTION OF MENINGITIS PATIENTS BY AGE AND TREATMENT GROUP

Etiology	Regimen ¹	Age group in years								Total cases
		Less than 1	1-4	5-14	15-29	30-44	45-59	60-74	75 or more	
Haemophilus influenzae.....	A	41	50	9	2	1				66
	C	41	51	5						107
Neisseria meningitidis.....	A	12	39	14	11	9	11	4		56
	C	14	29	22	18	9	4	3		77
Diplococcus pneumoniae.....	A	15	19	12	5	8	17	19	5	41
	C	16	5	5	5	19	19	26	5	42
Unknown.....	A	28	28	14	14	6		10		29
	C	25	20	20	6	17	6	6		35
Total.....		26	35	12	7	7	6	6	1	453

¹ A=ampicillin; C=control therapy.² Percentage of total group.

Therapeutic response. Over 85% of the patients were afebrile or had a temperature lower than 100 F rectally by the 7th day in both the ampicillin and control groups (Table 5). Five *H. influenzae* patients who received ampicillin had subdural effusions, and 3 of these required surgery, whereas 12 of the control group had effusions, and 1 required surgery. The CSF was re-examined 1 or 2 days after admission. No positive cultures were obtained from *H. influenzae* patients later than 24 hr after admission in the ampicillin group, whereas 6, or 5.6% of the 107 patients had positive cultures after more than 24 hr of treatment in the group treated with chloramphenicol. It was somewhat surprising that one and three positive cultures after 24 hr were also seen in meningococcal and pneumococcal categories, respectively, during penicillin G therapy.

The data concerning sequelae and mortality are presented in Table 6. As noted, 4 deaths occurred among 66 patients with *H. influenzae* infection in the ampicillin group, giving a case fatality rate of 6.0%. There were 10 deaths, or 9.3% among 107 patients in the control group. With respect to neurological residua, the figures are similar, since 6 of the 66 patients had neurological residua in the ampicillin group, and 11 of the 107 patients had neurological residua in the chloramphenicol group.

The slight increase in residual rate and decrease in fatal outcome in the meningococcal patients treated with ampicillin can be explained by a single patient recovering with sequelae. This difference is not significant.

TABLE 5.—PERCENTAGE DISTRIBUTION OF COMPLICATIONS OF DISEASE AND RESPONSE TO THERAPY BY TREATMENT GROUP

Etiology	Regimen ¹	Problems observed				Total number of patients
		Persistent fever ²	Subdural effusions		CSF positive at 24 hrs.	
			Total	Require surgery		
Haemophilus influenzae.....	A	19.4	7.6	4.5		66
	C	12.3	11.3	.9	5.6	107
Neisseria meningitidis.....	A	5.3	3.6	1.8		56
	C	11.4	2.6	1.3	1.3	77
Diplococcus pneumoniae.....	A	12.4	7.3			41
	C	26.2	4.7		7.1	42
Unknown.....	A	10.3				29
	C	8.6	2.9			35
Total.....	A	12.5	5.2	2.1		192
	C	13.5	6.5	.8	3.8	261

¹ A=Ampicillin; C=control group.² Temperature >100° F; (R) >7 days.

TABLE 6.—STATUS ON DISCHARGE FROM HOSPITAL BY ETIOLOGY AND TREATMENT GROUP

Etiology and regimen	Category of patients studied						Total number of patients
	No apparent defect		Recovery with sequelae		Fatal outcome		
	Number	Percent	Number	Percent	Number	Percent	
Haemophilus influenzae:							
Ampicillin.....	56	85.0	6	9.0	4	6.0	66
Control groups.....	86	80.4	11	10.3	10	9.3	107
Neisseria meningitidis:							
Ampicillin.....	45	80.4	8	14.3	3	5.3	56
Control groups.....	63	82.0	7	9.1	7	9.1	77
Diplococcus pneumoniae:							
Ampicillin.....	24	58.5	8	19.5	9	22.0	41
Control groups.....	22	52.5	8	9.0	12	28.7	42
Unknown:							
Ampicillin.....	27	93.1	2	6.9	0	0	29
Control groups.....	31	88.6	2	5.7	2	5.7	35
Total:							
Ampicillin.....	152	79.2	24	12.5	16	8.3	192
Control groups.....	202	77.5	28	10.7	31	11.8	261
Grand total.....	354	78.1	52	11.5	47	10.4	453

Both the case fatality rate and the frequency of sequelae upon recovery were extremely high in the pneumococcal category. This can be expected, since many of the older patients were alcoholics and in poor nutritional state, and, at times, substantial delay was encountered before hospitalization. The slightly decreased fatality rate in those receiving ampicillin is without significance, since, as was noted earlier, a slight excess of patients in the older, poor-risk category received penicillin G. The neurological sequelae in this category represented major defects, including mental retardation (1), hearing loss (2), definite weakness or paresis involving one or more extremities (2), expressive aphasia (1), and other similar defects. The types of residual defects noted were similar in both control and ampicillin groups, since three patients in the ampicillin category had definite hearing loss, one a spastic hemiparesis, and others had defects as noted above with penicillin G.

No differences in sequelae or fatality rates were seen among patients in the purulent unknown category. This is particularly interesting in view of the fact that the randomization of the patients in this category yielded almost identical age and severity distribution figures. Patients receiving both chloramphenicol and penicillin G in large doses had similar responses with ampicillin alone.

With respect to the overall figures, 47 deaths occurred among the 453 patients treated for purulent meningitis in the various categories. Although this was a 10.4% case fatality rate, it must be remembered that our Service accepts all age groups, and a substantial portion of our patients come to us with delayed diagnoses, are severe alcoholics, or are persons found in their residence by an interested neighbor who has not seen them for sometime. All patients with detectable heart sounds on admission to the hospital have been included in this report, whether or not respiratory aids were required. It is of particular interest to note that there is no significant difference with regard to either fatality or number and type of sequelae between the ampicillin and control categories.

TABLE 7.—POSSIBLE COMPLICATIONS OF THERAPY

Category considered	Ampicillin		Control		Total	
	Number	Percent	Number	Percent	Number	Percent
Total treated.....	192	100	261	100	453	100
Phlebitis.....	32	16.7	39	15.0	71	15.7
Rash.....	18	9.4	20	7.7	38	8.4
Local.....	4	2.1	5	1.9	9	2.0
Eosinophilia 10 percent.....	20	10.4	18	6.9	38	8.4
Other hematological ¹	7	3.6	23	8.8	30	6.6
Other.....	8	4.2	14	5.4	22	4.9

¹ Depression of reticulocytes <0.1 percent, or marked reduction in platelets on smear, or 4,000 white blood cells/cm, or <15 percent polymorphonucleocytes and bands.

The neurological residua tabulated were those present at the time of discharge from the hospital, and may or may not have persisted. It is possible that in some instances additional defects will be found on careful follow-up study during subsequent years. It is important to note that there do not appear to be significant differences in proportion or severity of residual defects in any category between the study groups.

Evaluation of the side effects of therapy reveal no significant differences in the frequency of phlebitis, rash, eosinophilia >10%, or local reactions (Table 7). There was, however, a substantial difference ($\chi^2=5.26$; $P=<0.05$) in the frequency of signs of hematological toxicity. The most frequent change was a depression of reticulocytes, although granulocytopenia, and thrombocytopenia were also observed. Only 1 of 66 patients who received ampicillin for *H. influenzae* meningitis had a transient depression in granulocytes, whereas 17 of 107 who received chloramphenicol had hematological abnormalities. All of the hematological changes observed have been reversible, although in two patients in the chloramphenicol group granulocytic depression persisted for more than 2 months.

DISCUSSION

During the early period of the development of effective antimicrobial agents, it was apparent, without equivocation, that several caused substantial decreases in mortality and sequelae in bacterial meningitis. At the present time, with numerous effective and relatively safe drugs available, selection of specific antibiotic agents for clinical use becomes more complex. These studies were conducted to determine whether it would be possible to simplify the therapy of acute bacterial meningitis, so that only a single compound could be used with results equivalent in safety and effectiveness to currently accepted therapy. Multiple drug therapy increases the hazards to the patient, as well as the expense of therapy, and, in addition, complicates nursing care. Since *H. influenzae* infection is often difficult to identify on direct examination of the spinal fluid, even by experienced personnel, it has been necessary frequently to administer either tetracycline (with attendant phlebitis with initial intravenous therapy or local reactions on subsequent intramuscular administration) or chloramphenicol (with a definite hematological hazard) to be certain that proper therapy is provided prior to confirmation by culture. It would appear that these studies demonstrating the efficacy of ampicillin offer an escape from this dilemma.

As one of the indices used in determining the response to an antibacterial regimen is the case fatality rate, it should be noted that this was 8.3% for the ampicillin group versus 11.8% in patients treated with conventional antibiotic routines. This difference was not significant, however, and may have been due entirely to the difference in age distribution of the pneumococcal group.

As noted above, all patients with detectable heart sounds on admission were included, whether or not aids to respiration were employed in transit, and whether or not cardiac arrest occurred within minutes. If one adjusts the overall mortality rate to exclude deaths occurring within the 12 hr immediately after admission, the corrected case fatality rate in the ampicillin group is 6.3% and among controls is 9.2%.

With regard to evidence of neurological residua, the rates were also similar in the two groups. Excluding fatalities, the proportions with residua at the time of hospital discharge was 13.6% among ampicillin-treated patients and 12.2% for the control group.

Ampicillin, although appearing to be somewhat more effective than chloramphenicol in vitro (Ivler et al., 1964), did not have a substantially greater clinical therapeutic benefit than chloramphenicol in *H. influenzae* meningitis. It is of interest, however, and consistent with the in vitro data, that six patients with *H. influenzae* meningitis had positive spinal fluid cultures 24 hr or more after initiation of chloramphenicol therapy, whereas none had similar positive cultures in the ampicillin category. The in vitro differences between benzylpenicillin and ampicillin against pneumococci and meningococci, were even less marked, but ampicillin appeared slightly more active (Ivler et al., 1964). It is interesting to note that three patients with pneumococcal meningitis and one with meningococcal meningitis had positive CSF cultures after 24 hr of therapy with benzylpenicillin, whereas none had positive cultures after 24 hr of ampicillin therapy.

While no significant differences were noted between the treatment groups with regard to phlebitis, skin rashes, local reaction, or eosinophilia, 17 patients (16%) who received chloramphenicol alone had evidence of hematological depression. Bone marrow examinations presented the classic picture of chloramphenicol tox-

icity. Fortunately, none of the reactions was permanent, although two patients had persistent and marked hematological depression for more than 2 months.

Although ampicillin is not significantly more effective than penicillin G or chloramphenicol in the treatment of the common types of bacterial meningitis, the advantages of a single drug and the absence of significant toxicity suggest that this agent be considered as the drug of choice for the initial treatment of bacterial meningitis in patients more than 2 months of age. It should be emphasized, however, that, with definite confirmation of the infection as either due to pneumococci or meningococci, penicillin G provides a less expensive and equally effective mode of therapy.

ACKNOWLEDGMENTS

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We thank Pat Hagen for the primary isolation and identification of bacteria.

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APPENDIX XII

EXCERPTS OF AFFIDAVITS SUBMITTED TO THE FOOD AND DRUG ADMINISTRATION FROM VARIOUS PHYSICIANS RE PRESCRIBING OF DRUG THALIDOMIDE BASED ON INFORMATION GIVEN BY DETAIL MEN

D. Scott Bayer, M.D., 2122 West End Avenue, Nashville, Tenn., Obstetrician-Gynecologist, signed an affidavit which states in part, "About November 1, 1960 I was approached by a representative of the Wm. S. Merrell Company . . . regarding the use of Kevadon. This representative told me that Dr. Jere C. Robertson had agreed to use the product in St. Thomas Hospital where he was a resident physician in OB-GYN. . . . This representative told me that the firm just wanted a clinical impression based upon our use and testing or laboratory work were not necessary. . . . Because of the safety representation made by the representative at that time and because it was my understanding that no real clinical experimentation or reporting was required, but that only a clinical impression was wanted, I agreed to sign a statement of investigation for the representative in order to allow Dr. Jere C. Robertson to use the product. . . . It was my understanding that Kevadon would very shortly be available as a prescription item. . . ."

Bernard A. Bercu, M.D., Wayne County General Hospital, Eloise, Michigan, Internist, signed an affidavit stating in part, "The detail man on first visit concerning Kevadon asked me if I would like to try some on patients. I decided to use Kevadon as a sedative for sleep for some of my patients on the basis of the representation made to me by the detailman and the preliminary medical brochure that Kevadon had a very low toxic effect as compared with the other sleep inducing agents such as barbiturates. . . . I have submitted no reports of any kind to Wm. S. Merrell Company or to its representatives concerning Kevadon. I do not consider my use of Kevadon as part of an investigational program to determine safety. I did use it for familiarization. I had not planned any clinical trial. I was not prepared to study the drug. . . ."

Jack B. Brams, M.D., 751 E. 63rd Street, Kansas City, Mo. Internist, signed an affidavit quoted in part, "In October or November 1960 I was approached by Frank Johnson, a detailman for Wm. S. Merrell Company, concerning the drug Kevadon. He presented the drug as a non-barbiturate, non-narcotic, safe sleep

inducing drug. . . . The claims for safety and non-habit forming characteristics of the drug were largely responsible for my using the drug. . . . I submitted no written reports on the use of this drug, and the drug was given to me with this understanding. I did not pretend to do any research on drugs used in my regular practice. My agreement with Mr. Frank Johnson was that I would submit no written report but would give oral reports to him. I made it clear that I was not a research man and that I would want the safety of the drug determined before I would give it to any of my patients. . . . In my opinion this drug was made available to me to familiarize me with its use."

John D. DeMott, M.D., 1440 Professional Bldg., Kansas City, Mo., Psychiatrist, signed an affidavit stated in part, "Just prior to November of 1960 I had discussions with Frank Johnson, detailman for Wm. S. Merrell Company, . . . regarding my use of the drug Kevadon. I also talked to Dr. T. L. Jones, of Wm. S. Merrell Company by phone, concerning this same drug and its use. I decided to try the drug largely because of its claims regarding efficacy and safety which are of great importance in my type of practice. When arrangements were made for my using the drug, I understood that a clinical report was to be submitted after I had used the drug for a period. I signed no particular agreement but drugs were to be supplied to me in the amount that I requested. The drug was supplied to me to allow me to evaluate its effectiveness. . . . I have not submitted any written reports to Wm. S. Merrell Company but I have given verbal reports to the firm's detailman, Frank Johnson concerning the use of the drug. . . . I have received a number of pieces of literature from the home office of Wm. S. Merrell Company and Inspector Souder made copy of this literature as follows:

"1. Dated August 21, 1962 from Thomas L. Jones, M.D. giving a current status report on the use of Kevadon. . . ."

Milton Ende, M.D., 121 S. Market Street, Petersburg, Va. Internist, signed an affidavit stated in part, "The representative contacted me at my office during the latter part of 1960 at which time he offered to supply me with Kevadon for my use as a sedative. The representations made indicated that the drug was safe for use as a sedative. I do not recall any direct claims for the drug other than its safety as a sedative. Information supplied me concerning the drug was of a casual nature with no specific details concerning the drug except that I had obtained the impression from the representative that the drug was completely safe. This drug was represented to me in a manner similar to the manner in which detailmen or medical representatives present me with physicians samples of commonly marketed drugs. I was persuaded to accept the drug for use due to its apparent safety and due to the fact that it was a free sample for which I would not have to charge my patients. . . . I have not submitted any written reports to Merrell Company but may have filled out any investigator statement. I do not recall if this statement was supplied by Merrell Company. . . . In my original contact with the medical representative concerning this drug I was lead to believe that written reports concerning my use of this drug would not be necessary, however, I do not recall any positive statements indicating the need for or non-necessity of written reports and records. . . ."

Ray Firestein, M.D., 416 Sherland Bldg., So. Bend, Indiana, Internist, signed an affidavit which is quoted in part "The detailman stated or else there were statements in the literature supplied by Merrell to the effect that Kevadon had been carefully studied in Europe. I was impressed by the claim that no lethal dose was known for Kevadon. This alone would have made the use of Kevadon highly desirable as a hypnotic. . . . I did not submit any written reports to Wm. S. Merrell regarding my use of Kevadon. I did not consider my use of Kevadon as part of an investigational program to determine safety. I considered that the manufacturer had supplied me with the drugs so that I could familiarize myself with its use. I was not testing safety. . . ."

John V. Hummel, M.D., 273 S. Bellevue, Memphis, Tennessee, Obstetrician and Gynecologist, signed an affidavit which he first wrote out himself and which is quoted in part, "I was first approached about Kevadon in the winter of 1960 when Mr. James M. Walker, representative for the Wm. S. Merrell Company was visiting our office. . . . He was our friend and called on us often. He told us of a new drug called Kevadon that Merrell had and was waiting to get approval before putting this drug on the market. He wanted to know if we would like to have some to try to see if we liked it, how the patients liked it, and so we could be using it by the time it came on the market. He told us the fundamentals of the drug. We said that we would try the drug. He sent us a large folder containing a full account of the drug and stressed how safe it was, that it was of the same strength as the barbiturates and there was no contraindications that I can remember. . . . This was not done as a clinical investigation, but as a friendly personal basis so that we would get an impression of the drug before it was put out on the market as a sleeping pill. . . ."

S. Bruce Kupert, M.D., 303 S. Main Street, Bluffton, Indiana, Obstetrician-Gynecologist, signed an affidavit which is quoted in parts, "I did discuss Kevadon with Mr. Brenner on/or about November 28, 1960. Probably at that time, I was supplied with the Wm. S. Merrell Company's statement of investigator which I signed. Inspectors Glassner and MacIejewski showed me a copy of this signed statement. The phraseology under the section 'Brief description of proposed investigation indicating facilities namely evaluation of above' . . . facilities is not mind. Under the section animal and human experiments appears the type response 'animal.' I had no intention of conducting any animal experiments on Kevadon nor do I have experimental animals available. . . . Regarding the safety of Kevadon, I received the aforementioned letter from Mr. Brennan dated November 19, 1960 which indicated that the drug had no fatal dose, that fatal toxicity was not known. Also, the preliminary medical brochure described above stated that Kevadon was not addicting and was not habit forming; that tolerance had not been a problem; that no withdrawal symptoms had been experienced; that very large dosages had not produced respiratory depressions; that Kevadon had been administered to expectant and nursing mothers and that all of the babies were born or nursed without any abnormality or harmful effects from the medication; that Kevadon resulted in a very low in side effects; that Kevadon produced no measurably impairment of the functions of the vital organs. . . .

"As a result of the representation made to me as described above, I concluded that I would try Kevadon in my practice, because (1) it would not be a hazard in the medicine cabinet in the patient's home in the event of accident ingestion of over-dosage and because of its non-habit forming property. (2) Its reported effectiveness in producing normal sleep and not a deep sleep from which a nursing mother would not be easily aroused to nurse her baby. (3) Because it was as effective as the most active barbiturate. (4) I was told either by the Merrell detailman in the fall of 1960 or by Mr. Brenner on/or about November 28, 1960 that Kevadon was soon to be made commercially available and that it was already being sold in Canada . . . I was not aware at any time of instructions from Wm. S. Merrell Company or its representative that reports from me were unnecessary, similarly I did not have the impression that the reports from me were required. In my use of Kevadon, I was not testing its safety; I was not conducting a basis testing program. I was determining its efficacious application so as to be able to report my experience with its use. . . ."

Richard W. Miller, M.D., 1265 Union Avenue, Memphis, Tennessee, Surgeon, signed an affidavit which is quoted in part, "When first approached, the Merrell representative supplied me with both verbal assurances and literatures attesting to the safety of Kevadon. The majority of this literature comprised reprints of clinical studies, information as to dosage, contraindications, etc. . . . It was my distinct impression that Kevadon was not considered an experimental drug since it had been tested and widely used in Europe and since the literature and verbal assurances of the Merrell representative pointed up the safety of the drug. I definitely feel that the manufacturer sought my participation in this program not to supply clinical evidence but to familiarize myself with Kevadon and to test the patient acceptance of the drug. It was these verbal and written

assurances furnished by the Merrell representative which persuaded me to use Kevadon. . . . When first approached by the Merrell representative with regard to my trying out Kevadon, I made it clear to them that I was not going to keep any records or furnish them with any written reports. I was informed that reports would not be necessary.

I explained that I was not setup to do research or provide clinical data because I deal with paying patients in a private practice. I urged the representative to seek their data from a clinical which had the personnel, equipment and facilities to do justice to a valid research program. It was my impression that reports were not required. . . . To reiterate, I felt that verbal and written assurances on the safety of Kevadon were valid, or else I would never have used the drug. It is my practice to use experimental drugs. The manufacturer never asked that I pay for any Kevadon which I received. With this in mind, I felt that the Wm. S. Merrell Company wanted me to participate in a program which was not to supply data as to the safety and efficacy of Kevadon since such had already been demonstrated in Europe, but to familiarize myself with the drug and test patient acceptance. . . ."

Donald J. Nenno, M.D., 490 McKinley Parkway, Buffalo, New York, Obstetrician-Gynecologist, signed an affidavit quoted in part "Mr. Rose represented Kevadon as being absolutely safe in that according to him it had been proven safe through wide spread use in Europe and was superior to other hypnotic drugs such as barbiturates and that it was impossible to be used for suicidal purposes and was not habit forming. However, Wm. S. Merrell Company advised me not to give the drug before administering anesthesia as the effect of the drug with anesthesia had not been documented even though they were certain it was safe. I accepted the drug on these representations. From our discussion with Mr. Rose, I had no idea that Kevadon was an experimental drug, the safety of which had not been cleared by the U.S. Food and Drug Administration. I thought it was simply for clinical comparison study. I have many drugs offered to me by pharmaceutical companies for my determination if their effects are superior to competitive products on the market. Kevadon was represented to me as just another one in that category. . . . To the best of my knowledge I never signed a clinical investigator statement. Mr. Rose supplied me with the evaluation forms on which the attending nurse could record how the patient felt about the drug. Mr. Rose said that these forms were provided to keep the information on, but it was not necessary to return them. . . ."

R. C. John Pearson, D.O., 3416 S. W. Webster, Seattle, Washington, General Practitioner, signed an affidavit which is quoted in part "The Merrell detailer stated that he had a new sedative preparation named Kevadon. He strongly indicated a human lethal dosage had not yet been determined and even gross amounts consumed in suicidal attempts had not been fatal . . . that this was an important drug since it was a highly effective sedative yet non-toxic. . . . During Mr. Cowles' visit of 11/3/60, I agreed to evaluate Kevadon in my hospital practice to learn if the drug was as effective a sedative as indicated by the detailer and the above brochure. The studies were undertaken on the basis that it was an effective sedative and non-toxic. From Mr. Cowles approach, I considered the use of Kevadon as an opportunity to determine its efficacy and not to determine its safety since I had no facilities for this type of study . . . I gave him my verbal report . . . I do remember receiving a letter dated August 21, 1961 from the Wm. S. Merrell Co. where it states among other things 'Nulsen administered Kevadon to expectant mothers with a sleep problem without effects on the newborn infants.' . . ."

Roy J. Phillip, M.D., 44 W. Main Street, Carbondale, Illinois, Internist, signed an affidavit which is quoted in part, "Mr. Howard informed me his firm had a new sedative, a drug name Kevadon and gave me a brochure on the drug. He informed me to note in this brochure that the drug had no LD50. He also stated that he would have his firm send me an investigator's statement to sign. He made no representations as to safety of the drug and other claims except that I should note or read the information under the safety data. . . . But after reading the brochure I was impressed with the statement under the caption of safety data that LD50 could not be determined. This specifically persuaded me to under-

take the use of this drug as a sedative. . . . That I consider the use of the Kevadon drug as a means to familiarize myself with it and not as part of an investigational program to determine the safety of the drug."

Jere C. Robertson, M.D., 1110 S. Main Street, Hopkinsville, Ky., signed an affidavit which is quoted in part "I was approached by a Wm. S. Merrell detailman and asked if I would like a new type of sleeping pill to use in the clinic known as Kevadon. I remember specifically that the detailman stated that he could take as much as two bottles and not commit suicide. . . . I recall that the detailman emphasized the drug's safety. It was my understanding that the drug Kevadon was due to be marketed momentarily. . . . I believe that the detailman showed me charts and brochures to emphasize the safety and use of Kevadon. Because of this I did not believe it was an experimental drug which required clearance from Dr. D. S. Bayer, Head of the OB-GYN Section of the St. Thomas Hospital. I am almost positive that I did not sign an investigator statement before use of the drug. Any experimental drug or drug for investigational purposes require clearance from Dr. Bayer. I was lead to believe that this drug, Kevadon, was not in that category. No records of any kind were kept on the use of this drug and no reports concerning its use were rendered to the firm as it was my understanding that this was not necessary. I would not have been persuaded to use this drug had it not been for the assurances given me by this detailman that it was completely safe and had been thoroughly tested. . . ."

George P. Rosemond, M.D., 3401 North Broad Street, Philadelphia, Pa., Surgeon, signed an affidavit which is quoted in part, "The Merrell representative told me that this product Kevadon was not yet available for general use. He told me that his firm was interested in obtaining my opinion of the product. He told me that Kevadon had been studied quite extensively in Europe and that its safety had been well established. The latter point of established safety was well stressed. As I recall, he called to my attention to certain statements in a product brochure which stressed the safety of Kevadon. He left a copy of this brochure with me but I no longer have it available. As a result of this initial meeting, I decided to undertake the use of Kevadon tablet as a hypnotic convinced by the detailman that the safety of Kevadon had been well established by oral representations and statements made in the firm's brochure. The detailman had me complete a statement of investigator dated November 2, 1960, . . . a copy of a letter from Wm. S. Merrell Company dated August 21, 1962 addressed to me which states Nulsen administered Kevadon to expectant mothers with a sleeping problem without effects to the newborn infant. I believe I did receive this reference letter although I do not have my original copy. . . . I have not submitted any written or verbal reports covering my use of Kevadon to Wm. S. Merrell Company during the period of my use of the product. I had been told by the detailman during his initial contact that such reports were not necessary. It was my understanding that Kevadon was given to me to familiarize me with the product and was in no way associated with or considered as part of an investigational program. I am familiar with the procedures to be followed for clinical investigations of new drugs. Had I been told by the Merrell detailman that Kevadon was an investigational new drug I would have maintained more adequate records covering its clinical use. . . ."

Herbert F. White, M.D., 4741 Broadway N. E., Knoxville, Tenn., Internist, signed an affidavit which is quoted in part, "Mr. Hurley advised me that Kevadon was an excellent sedative with no side effects which had been used extensively in Europe. I was given to understand that Kevadon would be released in this country for general use very shortly and that Kevadon was the Merrell name for thalidomide. I was lead to understand that the drug had been thoroughly tested and was safe and at this time clinical evaluation was all that was being requested. It was my understanding that Kevadon was not to be considered an experimental drug in the true sense and that controlled experiments with laboratory testing was not required. Mr. Hurley had literature which he showed me during this first presentation which confirmed the above statement on the drug's efficacy. I agreed to use the product because of

the above representations and because I had a number of elderly people in the hospital with a sleep problem on whom I expected to use the drug. . . . I did receive a letter from Wm. S. Merrell dated August 21, 1961 which stated among other things 'Nulsen administered Kevadon to expectant mothers with a sleep problem without effect on the newborn infants.' This letter also requested that I fill out a brief summary report of my clinical experience with Kevadon. I did not complete or return these forms because of the extremely limited use I had made of the drug because I had initially not been asked for any reports and understood that such were not necessary. . . ."

H. Glenn Williams, M.D., 273 South Bellevue, Memphis, Tenn., Obstetrician-Gynecologist, signed an affidavit which is quoted in part "Mr. Walker told me about Kevadon and stressed both the safety of the drug and the fact that it had about the same potency as barbiturates. Mr. Walker also stated that it was almost impossible to take an overdose of Kevadon. He said that his firm wanted physicians with private practices such as mine to try the drug. He said that this was to be done both to acquaint the doctor with Kevadon and to test patient acceptance of the drug. Mr. Walker said that the drug had already been proven safe in Europe and this program which was promotional in nature was to be accomplished prior to the formal release of Kevadon early in 1961. . . . I cannot recall whether or not I signed a Statement of Investigator for Merrell. In any event I made it quite clear that I did not plan to do further research on the drug. . . . To reiterate, I did not furnish the Wm. S. Merrell or their representative with any written reports. I told them from the beginning that I did not have time to keep records. If they still wanted me to try their drug out I would do just that. It was my impression that reports would not be required. I recall at least one instance on an undetermined date where the Merrell representative possibly Mr. James M. Walker asked me informally how I liked the drug. I told him I liked it fine. There was no detailed questioning, and as far as I remember my answer was confined to how I like Kevadon. I do not know whether this impression of Kevadon was to be considered as clinical data. I did not give it as such as I had not agreed to enter into an investigational program. From the beginning it was my impression that Kevadon was not an experimental drug. I was lead to believe from both the clinical reports and by verbal assurances from the Merrell representative that Kevadon was safe. I actually thought the drug had been released by FDA. I even wrote several prescriptions for the drug which bounced, of course. I felt from the very first that the Wm. S. Merrell Company wanted physicians with private practices to become familiar with Kevadon and test patient acceptance. It was my impression that my participation in this program was promotional in nature and was to precede formal introduction of Kevadon to the American market early in 1961. . . ."

Claude H. Workman, M.D., 273 S. Bellevue, Memphis, Tenn., Obstetrician-Gynecologist, signed an affidavit which is quoted in part "When Mr. Walker approached me about Kevadon in late 1960, he told me that the drug was safe. Mr. Walker did not seem to know much else about the drug but he said that he would send me some literature which contained all of the necessary details. To the best of my knowledge Mr. Walker wanted me to try Kevadon to see how I liked it. I interpreted the program to be promotional rather than investigational. To the best of my knowledge I did sign a statement of investigator. I told Mr. Walker that I did not plan to enter into a formal investigation of Kevadon. I was informed that Merrell just wanted me to try the drug. It was my impression that the drug had been proven safe and would be on the market in a few months. . . . During the period in which I was trying Kevadon, I did not submit any written reports to either Wm. S. Merrell Company or to any of their representatives. I do recall giving a verbal report on at least one instance to Mr. James M. Walker, Merrell representative. He asked me informally how I liked the drug, I told him it was the best sedative that I had run across. . . . It is my firm belief that the Wm. S. Merrell asked me to enter into this Kevadon program for promotional investigation reason. . . ."

Appendix XIII

A Study of Pharmaceutical Advertising in Selected
Medical Journals

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LEGISLATIVE REFERENCE SERVICE

March 6, 1969

TO: Senate Subcommittee on Monopoly, Select Committee
on Small Business

FROM: Education and Public Welfare Division

SUBJECT: Study of Pharmaceutical Advertising in Selected
Medical Journals

This is in reply to a request from the Chairman of the Subcommittee asking the Legislative Reference Service to undertake a detailed study of the patterns of pharmaceutical advertising appearing in selected medical journals over the last several years. The Chairman also asked that we ascertain to what degree such advertising constitutes a source of revenue for these journals and the medical organizations which publish them. We were also asked to provide the Subcommittee staff with other materials showing the relationship between the organizations which publish the journals analyzed in this report and the manufacturers who advertise in the journals studied.

1. The Advertising Survey Design

At the direction of the Subcommittee staff, the Legislative Reference Service undertook a survey of the pharmaceutical and other advertising which appears in four medical journals, each of which is published by a different professional association of medical practitioners. The journals selected for the survey were: The Journal of the American Medical Association, published by the American Medical Association; The Journal of Abdominal Surgery, published by the American Society of Abdominal Surgeons; The Annals of Internal Medicine, published by the American College of Physicians; and the American Family Physician, published by the American Academy of General Practice.

The survey period covered a span of five years for each publication, from January 1963 through December 1967. Each issue of each magazine was reviewed by the staff, except for four issues of The Journal of Abdominal Surgery during 1967 and the six issues of the

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American Family Physician for 1963, and one issue of the Journal of the American Medical Association for 1963, which were unavailable for review. The review was made from the collected sets of these journals maintained by the Library of Congress and the National Library of Medicine.

The data contained in this report were obtained from a review of the advertising pages found in each journal and, in part, from a review of the advertising index which each of these journals publishes in each issue. Where the advertising indices were used, careful examination of the particular index was made to assure that the information contained therein accurately reflected advertising copy appearing in the publication. Where the indices were deemed unreliable, a page-by-page review was made of the issues under study. For some journals, a page-by-page review was necessary for every issue.

The advertising copy found in the four journals was studied in sufficient detail in order to obtain information on the firms which advertise in particular issues, the trade-names of the products advertised by these firms, the frequency with which some products appeared, and the volume of advertising copy devoted to the promotion of each product.

Summary data were compiled for each journal, for each year, showing the journal page-to-advertising ratios of the magazine studied, and the distribution of pharmaceutical advertising to other advertising appearing in each magazine throughout the study period. In addition to the summary data, a detailed manufacturer and product survey for each year of each journal is contained in this report to the Subcommittee. In the case of the Journal of the American Medical Association and the Annals of Internal Medicine, the data gathered are so extensive, that additional summary data have been prepared showing the ten leading firms by volume of advertising for each year, the ten most frequently advertised products for each year, and the ten most heavily advertised products for each year, for each of these two journals.

2. The Survey Criteria

Certain criteria were employed in carrying out the survey in order to determine which products would be specifically identified in the study. These criteria were adopted to select out that advertising in the four journals which could not properly be termed "pharmaceutical advertising." Advertising copy not satisfying the criteria used in the study are excluded from the detailed data representations appearing herein, but are accounted for in the aggregate under the term "other journal advertising."

Each page of each journal was classified into one of three categories: journal pages, pharmaceutical advertising, and other journal advertising. Journal pages represent the residual number of pages

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remaining in any particular issue after pharmaceutical and other journal advertising are accounted for. Pages so counted are those devoted to articles, papers, indices, announcements, tables of contents, classified advertising, and other pages not otherwise counted in either of the other two categories.

The term "other journal advertising", is used to account for non-medical trade advertising such as advertising copy promoting soaps, coffee, soft drinks, foods, and other similar products. Also included in this category are advertisements for medical devices and instrumentation, books, educational opportunities and courses, employment opportunities except when they involve placement bureaus, and other service promotions. Institutional promotions, even for manufacturers whose products may be otherwise included in the detailed survey, are also shown in this category.

The term "pharmaceutical advertising" is intended to apply to prescription-legend drug products and to certain non-legend or over-the-counter items, including for example certain antacids, topical preparations, and so on. Vitamin products and certain contraceptive agents are also identified in this category. Persons desiring to limit the detailed data to prescription-legend items only could do so simply by eliminating other products in the detailed analysis and by adding the number of pages for such products to the category of "other journal advertising."

For the purpose of this study, any page which contains a commercial advertisement is considered a page of advertising, rather than a journal page. And, where two or more commercial advertisements are found on the same page, each is counted as a distinct page of advertising. This apportionment of advertising pages, however, does not alter substantially the conclusions from the survey, since the overwhelming majority of commercial advertisements are full-page promotions. To further test the validity of this method, a comparison was made between the results of the American Medical Association's own study of advertising-to-editorial page ratio in their Journal with the results of this survey for the same time period. In a report found in the Journal, the following statement was made:^{1/}

The editorial-to-advertising pages ratio was

^{1/} Journal of the American Medical Association, Vol. 202, No. 1, October 2, 1967.

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55:45 based upon the total of 6,864 pages published during this period [first 6 months of 1967].

Findings from the LRS survey, using the assumptions and criteria set forth above, produce a ratio of 56.2:43.8. We believe, therefore, that the data contained in this report fairly represent the volume and distribution of advertising in the medical journals studied.

3. Organization of Report

The summary and detailed data given in this report are arrayed by the particular journal surveyed. The Journal of the American Medical Association which is the largest of the four publications, in terms of volume of pages and circulation, is discussed in Part I of the report. Parts II, III, and IV are devoted to the Annals of Internal Medicine, the American Family Physician, and the Journal of Abdominal Surgery, in that order.

Each Part in the report begins with summary data covering the entire period of the survey for each journal studied. Among the data summarized are the total pages published for each year, the total journal pages, total advertising pages, total advertising pages classified as pharmaceutical advertising, and the total of other advertising pages. The data are also represented as percentages for each of these categories for each year studied.

Following the summary data, a detailed product survey for each year is given, showing the names of the manufacturers, the trade-names of the products advertised, the frequency of the products advertised, and the volume of copy devoted to each product. In the case of the Journal of the American Medical Association and the Annals of Internal Medicine, special annual summaries are given showing the leading firms which advertise in these two journals, the most frequently advertised products, and the most heavily advertised products appearing in the two journals.

4. Income from Advertising Revenue

The Chairman asked that we attempt to ascertain to what degree advertising revenue constitutes a source of income for the medical associations which publish the four journals surveyed in this study. We have obtained data showing this relationship only for the American Medical Association. Other publications by the remaining three organizations, insofar as they are available for review in the Library of Congress,

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produced no usable data in this area. The staff of the Subcommittee has been advised of this finding, but we understand that some of the data needed by the Subcommittee has been submitted by the organizations themselves. We have, therefore, included in this report only the information on the American Medical Association. Should it be necessary to obtain comparable information for the other three organizations, direct inquiry to the associations probably will be required.

Table 1 on the next page shows the total income and income from advertising of the American Medical Association for the period 1961-1967. Table 2 shows the total income and income from exhibit space sales for the same period. Income from exhibit space sales is included since many of those organizations which purchase such space are pharmaceutical manufacturers who also advertise extensively in the publications of the Association. Table 3 shows the sources of income of the American Medical Association by each source of income, including that obtained from advertising revenue. Table 4 gives the A.M.A.'s financial status for the six-year period 1962-1967.

If there are any questions in connection with this report, please let us know.

Glenn Markus

Joe Licata

Attachment

Table I - Total Income, Income from Advertising, A.M.A., 1961-1967

Table II - Total Income, Income from Exhibit Space Sales, A.M.A.,
1961-1967

Table III - Sources of AMA Income During 1961-1967

Table IV - American Medical Association Financial Position 1962-1967

Survey of Pharmaceutical Advertising in Selected Journals

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TABLE 1

TOTAL INCOME, INCOME FROM ADVERTISING, A.M.A., 1961-1967^{1/}

YEAR	TOTAL INCOME	ADVERTISING INCOME	ADVERTISING AS % ALL INCOME
1961	\$17,589,537	\$ 8,906,993	51.0%
1962	19,524,435	9,017,383	47.0%
1963	22,516,013	10,122,065	45.0%
1964	23,110,239	10,356,640	44.8%
1965	27,772,879	12,770,825	46.0%
1966	27,759,623	13,290,714	47.9%
1967	31,677,215	13,565,106	42.8%

TABLE 2

TOTAL INCOME, INCOME FROM EXHIBIT SPACE SALES, A.M.A., 1961-1967^{1/}

YEAR	TOTAL INCOME	INCOME FROM EXHIBIT SPACE SALES	EXHIBIT INCOME AS % ALL INCOME
1961	\$17,589,537	\$664,753	2.0%
1962	19,524,435	605,104	3.0%
1963	22,516,013	577,092	2.6%
1964	23,110,239	638,471	2.8%
1965	27,772,879	832,341	3.0%
1966	27,759,623	782,680	2.8%
1967	31,677,215	730,646	2.3%

^{1/} From Reports of Annual or Clinical Conventions of the American Medical Association for each year.

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TABLE 3SOURCES OF AMA INCOME DURING 1961-1967^{1/}

	1961 Amount	1962 Amount	1963 Amount	1964 Amount
Advertising.....	\$ 8,906,993 (51)	\$ 9,105,636 (47)	\$10,122,065 (45.0)	\$10,356,640 (44.8)
Subscriptions.....	6,475,289 (37)	2,533,995 (13)	2,713,269 (12.0)	2,279,444 (9.9)
Membership Dues.....	2/	5,483,388 (28)	7,210,680 (32.0)	7,337,043 (31.7)
Directory Report Service...	749,839 (6)	776,615 (4)	822,089 (3.7)	1,054,787 (4.6)
Exhibit Space Sales.....	664,753 (2)	605,104 (3)	577,092 (2.6)	638,471 (2.8)
Investments.....	410,372 (2)	666,320 (2)	597,086 (2.6)	670,760 (2.9)
Miscellaneous Publications.	382,291 ^{3/} (2)	353,377 ^{3/} (2)	473,732 ^{3/} (2.1)	441,384 (1.9)
Other Gross Income.....	4/			331,710 (1.4)
Total.....	\$17,589,537	\$19,524,435	\$22,516,013	\$23,110,239

	1965 Amount	1966 Amount	1967 Amount
Advertising.....	\$12,770,825 (46.0)	\$13,290,714 (47.9)	\$13,565,106 (42.8)
Subscriptions.....	2,316,535 (8.4)	2,436,550 (8.8)	2,726,217 (8.6)
Membership Dues.....	7,446,612 (26.8)	7,508,058 (27.0)	11,547,120 (36.5)
Directory Report Service...	1,241,980 (4.4)	1,451,451 (5.2)	1,538,139 (4.8)
Exhibit Space Sales.....	832,341 (3.0)	782,680 (2.8)	730,646 (2.3)
Investments.....	1,001,338 (3.6)	824,739 (3.0)	589,393 (1.9)
Miscellaneous Publications.	1,862,024 (6.7)	1,144,254 (4.1)	822,386 (2.6)
Other Gross Income.....	301,224 (1.1)	321,177 (1.2)	158,208 (.5)
Total.....	\$27,772,879	\$27,759,623	\$31,677,215

^{1/} From Reports of Annual or Clinical Conventions of the American Medical Association for each year.

Figures in parentheses are percentages of total income.

^{2/} Amount of Income from Membership Dues included in Subscriptions.^{3/} Shown only as "miscellaneous income" for the years 1961-1963.^{4/} No "other income" reported for 1961-1963.

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TABLE 4AMERICAN MEDICAL ASSOCIATION FINANCIAL POSITION 1962-1967^{1/}

	<u>1962</u>	<u>1963</u>	<u>1964</u>
ASSETS			
Cash.....	\$ 600,973	\$ 109,794	\$ 117,989
Accounts and notes receivable.....	876,274	844,605	953,021
Inventories and prepaid expenses.....	691,316	741,584	890,900
Building and equipment.....	4,489,752	5,237,299	7,420,071
Investments and other assets.....	8,367,660	10,636,581	8,688,685
TOTAL.....	\$15,025,975	\$17,569,863	\$18,070,666
LIABILITIES			
Accounts Payable.....	\$ 967,623	\$ 1,112,914	\$ 1,650,682
Income Received but not yet earned.....	1,684,823	1,721,021	1,920,765
TOTAL.....	\$ 2,652,446	\$ 2,833,935	\$ 3,571,447
NET WORTH.....	\$12,373,529	\$14,735,928	\$14,499,219
* * * * *			
	<u>1965</u>	<u>1966</u>	<u>1967</u>
ASSETS			
Cash.....	\$ 271,206	\$ 353,652	\$ 234,524
Accounts and notes receivable.....	856,402	1,151,498	1,150,304
Inventories and prepaid expenses.....	1,704,330	1,550,382	1,498,944
Building and equipment.....	8,946,458	9,275,467	9,260,808
Investments and other assets.....	6,424,119	7,095,887	11,102,365
TOTAL.....	\$18,202,515	\$19,426,886	\$23,246,945
LIABILITIES			
Accounts Payable.....	\$ 1,844,057	\$ 1,715,381	\$ 1,909,609
Income Received but not yet earned.....	2,051,124	2,030,126	2,325,726
TOTAL.....	\$ 3,895,181	\$ 3,745,507	\$ 4,235,335
NET WORTH.....	\$14,307,334	\$15,681,379	\$19,011,610

^{1/} From Reports of Annual or Clinical Conventions of the American Medical Association for each year.

SURVEY OF PHARMACEUTICAL ADVERTISING IN SELECTED JOURNALSTABLE OF CONTENTS

Part I	<u>The Journal of the American Medical Association</u>	pages
1.	Summary Data: 1963-1967.....	1
2.	<u>Year: 1963</u>	
	a. 10 Leading Firms, by Advertising Volume	2
	b. 10 Most Frequently Advertised Drugs	2
	c. 10 Most Heavily Advertised Drugs	2
	d. Detailed Product Data	3
3.	<u>Year: 1964</u>	
	a. 10 Leading Firms, by Advertising Volume	15
	b. 10 Most Frequently Advertised Drugs	15
	c. 10 Most Heavily Advertised Drugs	15
	d. Detailed Product Data	16
4.	<u>Year: 1965</u>	
	a. 10 Leading Firms, by Advertising Volume	27
	b. 10 Most Frequently Advertised Drugs.....	27
	c. 10 Most Heavily Advertised Drugs	27
	d. Detailed Product Data	28
5.	<u>Year: 1966</u>	
	a. 10 Leading Firms, by Advertising Volume	40
	b. 10 Most Frequently Advertised Drugs	40
	c. 10 Most Heavily Advertised Drugs	40
	d. Detailed Product Data	41

6. <u>Year: 1967</u>	pages
a. 10 Leading Firms, by Advertising Volume	52
b. 10 Most Frequently Advertised Drugs	52
c. 10 Most Heavily Advertised Drugs	52
d. Detailed Product Data	52
Part II <u>The Annals of Internal Medicine</u>	
1. <u>Summary Data: 1963-1967</u>	62
2. <u>Year: 1963</u>	
a. 10 Leading Firms, by Advertising Volume	63
b. 10 Most Heavily Advertised Drugs	63
c. Detailed Product Data	64
3. <u>Year: 1964</u>	
a. 10 Leading Firms, by Advertising Volume	71
b. 10 Most Heavily Advertised Drugs	71
c. Detailed Product Data	72
4. <u>Year: 1965</u>	
a. 10 Leading Firms, by Advertising Volume	79
b. 10 Most Heavily Advertised Drugs	79
c. Detailed Product Data	80
5. <u>Year: 1966</u>	
a. 10 Leading Firms, by Advertising Volume	87
b. 10 Most Heavily Advertised Drugs	87
c. Detailed Product Data	88

6. Year: 1967

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Part III The American Family Physician

- 1. Summary Data: 1963-1967 104
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Part IV The Journal of Abdominal Surgery

- 1. Summary Data: 1963-1967 120
- 2. Year: 1963 121
- 3. Year: 1964 122
- 4. Year: 1965 123
- 5. Year: 1966 124
- 6. Year: 1967 125

JOURNAL OF AMERICAN MEDICAL ASSOCIATION

SUMMARY DATA

Advertising, 1963 through 1967

Volume in Pages

Year	Total Pages Magazine	Total Pages Journal	Total Pages Advertising	Total Pages Drugs Advertising	Total Pages Other Advertising
1963*	12,418	6,548	5,870	4,526	1,344
1964	12,702	6,863	5,839	4,650	1,189
1965	13,438	7,244	6,194	5,149	1,045
1966	14,286	7,664	6,622	5,354	1,268
1967	<u>13,332</u>	<u>7,501</u>	<u>5,831</u>	<u>4,964</u>	<u>867</u>
Total...	66,176	35,820	30,356	24,643	5,713

Percentages

Year	Percent Total Pages	Percent Journal Pages	Percent Advertising Pages	Drug Advertising as Percent All Advertising	Other Advertising as Percent All Advertising
1963*	100.0%	52.7%	47.3%	77.1%	22.9%
1964	100.0%	54.0%	46.0%	79.6%	20.4%
1965	100.0%	53.9%	46.1%	83.1%	16.9%
1966	100.0%	53.6%	46.4%	80.8%	19.2%
1967	<u>100.0%</u>	<u>56.2%</u>	<u>43.8%</u>	<u>85.1%</u>	<u>14.9%</u>
Total...	100.0%	54.1%	45.9%	81.1%	18.9%

*Based on review of 51 of 52 issues published in 1963.

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION
SUMMARY DATA
 1963*

10 Leading Firms, by Volume of Advertising

<u>RANK</u>	<u>FIRM</u>	<u>NO. DRUG ADVERTISING PAGES</u>
1	Wallace Laboratories	524
2	Merck, Sharpe, & Dohme	457
3	Warner-Chilcott	239
4	Abbott Laboratories	192
5	Lederle Laboratories	174
6	Upjohn	163
7	Wyeth Laboratories	158
8	Burroughs-Wellcome	157
9	Lilly	145
10	Pfizer	144

10 Most Frequently Advertised Drugs

<u>RANK</u>	<u>DRUG</u>	<u>NO. ISSUES IN WHICH ADVERTISED</u>
1	Deprol (Wallace)	50
2	Miltown (Wallace)	50
3	Meprospan (Wallace)	48
4	Appertrol (Wallace)	40
5	Soma (Wallace)	38
6	Capla (Wallace)	34
7	Aldomet (Merck)	33
8	Miltrate (Wallace)	33
9	Tepanil (National)	33
10	Orinase (Upjohn)	31

10 Most Heavily Advertised Drugs

<u>RANK</u>	<u>DRUG</u>	<u>NO. PAGES ON WHICH ADVERTISED</u>
1	Peritrate (Warner-Chilcott)	97
2	Aldomet (Merck)	96
3	Miltown (Wallace)	93
4	Deprol (Wallace)	89
5	Diuril/Hydrodiuril (Merck)	67
6	Capla (Wallace)	64
7	Orinase (Upjohn)	64
8	Orenzyme/Parenzyme (National)	54
9	Meprospan (Wallace)	49
10	Darvon (Lilly)	48

*Based on a review of 51 of 52 issues published in 1963.

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

1963*

COMPANY	PRODUCT	NO. ISSUES	NO. PAGES
<u>Abbott Laboratories</u>			
	1. Compoicillin-VK	8	16
	2. Desbutal	11	21
	3. Desoxyn	12	24
	4. Enduron	2	8
	5. Enduron/Eutonyl	2	10
	6. Erythocin	13	28
	7. Eutonyl	8	28
	8. Nembutal	4	8
	9. Norisodrine	10	14
	10. Placidyl	3	3
	11. Quelidrine	2	2
	12. Radio pharmaceuticals	9	9
	13. Selsun	3	3
	14. Surbex-T	13	13
	15. Various	1	1
	16. Vi-Daylin	2	4
		Total...	192
<u>Arch Laboratories</u>			
	1. Dicarbosil	10	Total... 10
<u>Armour</u>			
	1. Acthar	6	6
	2. Chymar	10	10
	3. Chymoral	12	26
	4. Listica	4	5
	5. Thyroid	4	6
		Total...	53
<u>Ayerst Laboratories</u>			
	1. Gristactin	6	12
	2. Mesulfin	1	2
	3. Premarin	6	10
	4. Thiosulfil	5	14
		Total...	38
<u>Breon Laboratories</u>			
	1. Bronkometer	12	12
	2. Bronkotabs	11	11
		Total...	23

* Based on review of 51 of 52 issues published in 1963.

COMPANY	PRODUCT	NO. ISSUES	NO. PAGES
<u>Bristol Laboratories</u>			
	1. Kantrex	4	Total... 8
<u>Burroughs-Wellcome</u>			
	1. Aerosporin	8	8
	2. Antepar	20	20
	3. Cardilate	7	10
	4. Cardilate-P	7	8
	5. Empirin	12	15
	6. Lanoxin	12	24
	7. Leukeran	11	12
	8. Mantadil	6	6
	9. Migral	4	4
	10. Myleran	11	12
	11. Marezine	23	23
	12. Perazil	3	3
	13. Purinethol	11	12
			Total... 157
<u>CIBA Pharmaceutical</u>			
	1. Esidrex/Esidrex-K	19	30
	2. Doriden	23	34
	3. Ismelin	11	24
	4. Serpasil	21	23
	5. Vioform	12	13
			Total... 124
<u>Davies, Rose, Hoyt</u>			
	1. Digitalis	3	3
	2. Quinidine sulfate	3	3
			Total... 6
<u>Dome</u>			
	1. Come-dab	4	4
	2. Cort-Dome	6	6
	3. Cor-Tar-Quin/others	3	3
	4. Neo-Domeform	2	2
			Total... 15
<u>Desitin Chemical</u>			
	1. Desitin ointment	11	Total... 12

COMPANY	PRODUCT	NO. ISSUES	NO. PAGES
<u>Eaton Laboratories</u>			
	1. Furacin	27	29
	2. Furadantin	21	25
	3. Tricofurcn	12	<u>12</u>
		Total...	66
<u>Endo Laboratories</u>			
	1. Coumadin	26	43
	2. Hycodan	10	10
	3. Numorphan	22	22
	4. Percodan	10	10
	5. Valpin/Valpin-PB	16	<u>24</u>
		Total...	109
<u>Flint, Eaton, & Co.</u>			
	1. Synthroid	9	Total... 9
<u>Geigy</u>			
	1. Butazolidin	10	10
	2. Persantin	6	<u>18</u>
		Total...	28
<u>Glenbrook Laboratories</u>			
	1. Bayer Aspirin	7	7
	2. Philips Milk of Magnesia	6	<u>6</u>
		Total...	13
<u>Hynson, Westcott, & Dunning</u>			
	1. Bromosulphalein	4	4
	2. Lactinex	1	1
	3. Lutrexin	6	<u>6</u>
		Total...	11
<u>Holland-Rantos</u>			
	1. Nylmerate	6	Total... 6
<u>Ives Laboratories</u>			
	1. Cyclospasmol	16	19
	2. Isordil	12	<u>16</u>
		Total...	35
<u>Johnson & Johnson</u>			
	1. Liquiprin	5	Total... 5

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY 4879

COMPANY	PRODUCT	NO. ISSUES		NO. PAGES	
<u>Key Pharmaceuticals</u>	1. Nitroglyn	7	Total...	7	
<u>Lakeside Laboratories</u>	1. Imferon	14	Total...	14	
<u>Leeming, Thomas</u>	1. Metamine	8	Total...	8	
<u>Lederle Laboratories</u>	1. Achromycin	16		25	
	2. Aristocort	14		28	
	3. Bamadex	10		15	
	4. Declomycin	20		40	
	5. Ferro-Sequels	10		10	
	6. Hydromox	14		28	
	7. Orimune	4		8	
	8. Pathibamate	11		21	
			Total...	175	
<u>Lilly, Eli</u>	1. Anhydron/w/K, KR	2		8	
	2. Darvon	26		48	
	3. Haldron	12		40	
	4. Ilosone	16		18	
	5. Novrad	5		17	
	6. Quintess	2		2	
	7. V-Cillin-K	9		12	
			Total...	145	
<u>Lloyd</u>	1. Doxidan	4	Total...	7	
<u>Mallinkrodt Chemical</u>	1. Codeine	12	Total...	12	
<u>Mead Johnson</u>	1. Beta-Chlor	13		15	
	2. Mucomyst	1		3	
	3. Quibron	9		18	
	4. Vasodilan	16		16	
			Total...	52	
<u>McNeil Laboratories</u>	1. Butisol	14	Total...	27	

COMPANY	PRODUCT	NO. ISSUES	NO. PAGES
<u>Merck, Sharpe, & Dohme</u>			
	1. Aldomet	33	96
	2. Aldomet/Rubeovax	1	2
	3. Aldoril	11	21
	4. Aramine	7	14
	5. Benemid/Colbenemid	5	20
	6. Codeine	1	1
	7. Cuprimine	4	4
	8. Decadron	21	34
	9. Decagesic	25	30
	10. Diuril/Hydrodiuril	20	67
	11. Diupres	13	17
	12. Elavil	13	26
	13. Hydropres	15	20
	14. Mephyton/Aquamephyton	9	11
	15. Periactin	7	7
	16. Redisol/Alpharedisol	16	16
	17. Respihalel some w/ Xylocaine	24	47
	18. Rubeovax/Gammagee	11	19
	19. Urecholine	5	5
		Total...	457
<u>Merrell, Wm. S.</u>			
	1. Bentyl	4	8
	2. Tenuate	13	13
		Total...	21
<u>National Drug</u>			
	1. Orenzyme/Parenzyme	27	54
	2. Parenzyme	3	6
	3. Tepanil	33	41
	4. Vaccines (various)	13	13
		Total...	114
<u>Organon</u>			
	1. Hexadrol	6	6
		Total...	6
<u>Ortho</u>			
	1. Ortho-Novum	4	4
		Total...	4

COMPANY	PRODUCT	NO. ISSUES	NO. PAGES
<u>Parke-Davis</u>			
	1. Benadryl	10	20
	2. Chloromycetin	25	44
	3. Dilantin	9	17
	4. Elase	1	1
	5. Norlutate	9	9
	6. Pitocin	12	12
	7. Povan	4	4
	Total...		107
<u>Pfizer, Chas.</u>			
	1. Diabinese	22	44
	2. Renese	16	32
	3. Terramycin	21	44
	4. Vistaril	12	24
	Total...		144
<u>Pittman-Moore</u>			
	1. Jefron	9	16
	2. Novahistine DH	7	11
	3. Novahistine Elixir	2	4
	4. Novahistine LP	7	11
	5. Novahistine Melet	2	4
	6. Novahistine Singlet	3	5
	Total...		51
<u>Plough, Inc.</u>			
	1. Silain/Sibel	2	2
	2. St. Joseph's Aspirin	12	12
	Total...		14
<u>Polythress, Wm. P.</u>			
	1. Mudrane	14	15
	2. Trocinate	4	4
	3. Synirin	1	1
	4. Solfoton	7	7
	Total...		27
<u>Purdue-Frederick</u>			
	1. Cardioquin	4	4
	2. Paremycin	5	5
	3. Senokot	16	16
	Total...		25

4882 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

COMPANY	PRODUCT	NO. ISSUES	NO. PAGES
<u>Radium Chemical</u>	1. Radium	12	Total... 12
<u>Riker Laboratories</u>	1. Medihaler-Duo	11	22
	2. Norflex	8	16
	3. Rauwiloid	2	4
	4. Ulo	4	7
			Total... 49
<u>Robins, A. H.</u>	1. Ambar	3	3
	2. AllBee w/C	6	6
	3. Dimetane	10	13
	4. Donnatal	12	15
	5. Naclex	4	8
	6. Robaxin	11	18
	7. Robaxisal	3	5
	8. Robinul/Robinul-PH	7	11
	9. Skelaxin	5	10
			Total... 89
<u>Roche Laboratories</u>	1. Alurate	1	1
	2. Gantrisin	6	6
	3. Gantanol	1	4
	4. Librium	17	26
	5. Mestinon	2	4
	6. Madribon	2	4
	7. Roniacol	1	1
	8. Taractin	11	11
	9. Tigan	4	4
	10. Valium	2	10
			Total... 71
<u>Roerig, J. B. & Company</u>	1. Atarax	7	15
	2. Antivert	14	14
	3. Enarax	7	15
	4. Marax	12	12
	5. Tao	12	32
			Total... 88

COMPANY	PRODUCT	NO. ISSUES	NO. PAGES
<u>Rorer, Wm. H.</u>			
	1. Ananase	13	22
	2. Maalox	5	5
		Total...	27
<u>Sandoz Pharmaceutical</u>			
	1. Cafergot/Cafergot-PB	6	6
	2. Fiorinal	4	4
	3. Mellaril	19	19
	4. Sansert	26	26
		Total...	55
<u>Schering Corporation</u>			
	1. Celestone	4	8
	2. Chlorthimeton	16	16
	3. Coricidin	7	7
	4. Fulvicin	6	9
	5. Meticorten	2	2
	6. Naqua	9	9
	7. Naquival	9	9
	8. Rela	10	10
		Total...	70
<u>Searle, G. D.</u>			
	1. Aldactazide/Aldactone	6	6
	2. Dramamine	6	6
	3. Enovid	9	14
	4. Flagyl	8	14
	5. Lomotil	10	10
	6. Nilevar	1	1
	7. Pro-Banthine	23	23
		Total...	74
<u>Schmid, Julius</u>			
	1. Imolin	5	5
	2. Vagesic	8	8
		Total...	13
<u>Sherman Laboratories</u>			
	1. Elixophyllin	9	13

4884 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

COMPANY	PRODUCT	NO. ISSUES	NO. PAGES
<u>Smith, Kline, & French</u>			
	1. Compazine		9
	2. Dexedrine	6	6
	3. Parnate	18	18
	4. Stoxil	4	8
	5. Thorazine	12	12
	6. Various	2	2
		Total...	55
<u>Squibb</u>			
	1. Delautin	7	12
	2. Delestrogen	6	12
	3. Deluteval	3	6
	4. Feramel	3	3
	5. Fungizone	5	5
	6. Kenalog	2	2
	7. Mycolog	6	6
	8. Mystecclin	10	10
	9. Naturetin	8	12
	10. Noctec	6	6
	11. Pentids	6	6
	12. Prolixin	15	17
	13. Rautrax-N	10	10
	14. Raudixin	4	4
	15. Theratuss	8	10
	16. Theragran	7	19
		Total...	140
<u>Strassenburgh Laboratories</u>			
	1. Biphetamine/Ionamin	12	22
	2. Biphetamine-T	5	6
	3. Metropine	4	8
	4. Omnituss	12	16
	5. Tussionex	9	9
		Total...	61
<u>Stuart</u>			
	1. Dialose	2	2
	2. Mulvidren	3	3
	3. Mylanta	14	14
	4. Mylicon	3	3
		Total...	22

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY 4885

COMPANY	PRODUCT	NO. ISSUES		NO. PAGES	
<u>Syntex</u>					
	1. Synalar	12	Total...	25	
<u>Trent Pharmaceuticals</u>					
	1. Tocosamine	12	Total...	12	
<u>Upjohn</u>					
	1. Didrex	1		1	
	2. Depo-Medrol	5		11	
	3. Depo-Provera	13		13	
	4. Medrol Veriderm	16		47	
	5. Medrol	7		12	
	6. Orinase	31		64	
	7. Provera	15		15	
			Total...	163	
<u>U.S. Vitamin & Pharmaceutical</u>					
	1. Arlidin	8		8	
	2. Aquasol	4		4	
	3. Dexemeth	8		13	
	4. DBI-TD	10		10	
	5. Emivan	6		6	
			Total...	41	
<u>Towne</u>					
	1. Various	2	Total...	2	
<u>Wallace Laboratories</u>					
	1. Appertrol	40		40	
	2. Capla	34		64	
	3. Caplaril	8		32	
	4. Deprol	50		89	
	5. Meprospan	48		49	
	6. Milpath	28		31	
	7. Milprem	18		18	
	8. Miltown	50		93	
	9. Miltrate	33		33	
	10. Soma	38		42	
	11. Soma Compound	17		17	
	12. Somacort	16		16	
			Total...	524	

4886 COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

COMPANY	PRODUCT	NO. ISSUES	NO. PAGES
<u>Wampole</u>	1. Vo-Sol	11	Total... 11
<u>Warner-Chilcott</u>	1. Amphocortrin	6	18
	2. Colymycin	16	36
	3. Gelusil	17	22
	4. Mandelamine	12	24
	5. Papase	15	30
	6. Peritrate	26	97
	7. Tedral	6	12
		Total...	239
<u>White Laboratories</u>	1. Aspergum	22	22
	2. A & D	23	23
	3. Cod Liver Oil Tabs	14	14
	4. Disophrol	1	2
	5. Gitaligin	24	24
		Total...	85
<u>Winthrop</u>	1. Creamalin	2	2
	2. Isuprel	9	9
	3. Neo-Synephrine	6	6
	4. Mebaral	5	5
	5. Telepaque	1	1
	6. Trancogesic	11	11
	7. Trancopal	6	6
	8. Winstrol	11	11
	9. WTZ	1	1
		Total...	52
<u>Wyeth Laboratories</u>	1. Bicillin	10	19
	2. Cyclamycin	7	14
	3. Equagesic	13	23
	4. Equanil	12	35
	5. Equanitrate	8	8
	6. Mepergan	5	7
	7. Pen-Vee-K	8	11
	8. Polymagna	3	3
	9. Phenergan	3	3
	10. Prozine	1	1
	11. SMA	10	18
	12. Sparine	8	13
	13. Zactirin	3	3
		Total...	158

COMPANY	PRODUCT	NO. ISSUES	NO. PAGES
<u>Wynn Pharmacal</u>			
	1. Aminophylline	2	2
	2. Histadur	6	6
	3. Numa	8	8
	4. Quinaglute	22	22
		Total...	38

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Summary Data196410 Leading Firms, by Volume of Advertising

<u>Rank</u>	<u>Firm</u>	<u>No. Drug Advertising Pages</u>
1	Wallace Laboratories	585
2	Merck, Sharpe, & Dohme	522
3	Warner-Chilcott	267
4	Upjohn	214
5	Roche Laboratories	189
6	CIBA	154
7	Schering Corporation	152
8	Abbott Laboratories	148
9	Burroughs-Wellcome	145
10	Lederle Laboratories	145

10 Most Frequently Advertised Drugs

<u>Rank</u>	<u>Drug</u>	<u>No. Issues in which Advertised</u>
1	Miltown (Wallace)	52
2	Meprospan (Wallace)	51
3	Deprol (Wallace)	50
4	Soma/Soma Compound (Wallace)	49
5	Diuril/Hydrodiuril	37
6	Neggram (Winthrop)	34
7	Valium (Roche)	34
8	Elavil (Merck)	32
9	Vioform (CIBA)	31
10	Miltrate (Wallace)	29

10 Most Heavily Advertised Drugs

<u>Rank</u>	<u>Drug</u>	<u>No. Pages on which Advertised</u>
1	Soma/Soma Compound (Wallace)	129
2	Diuril/Hydrodiuril (Merck)	119
3	Miltown (Wallace)	110
4	Deprol (Wallace)	100
5	Peritrate (Warner-Chilcott)	97
6	Neggram (Winthrop)	79
7	Valium (Roche)	68
8	Elavil (Merck)	67
9	Celestone (Schering)	61
10	Thyroid (Armour)	61

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COMPANY	PRODUCT	NO. ISSUES	NO. PAGES
<u>Abbott Laboratories</u>	1. Desbutal	10	21
	2. Desoxyn	9	18
	3. Enduron/Eutonyl	3	13
	4. Eutonyl	10	30
	5. Erythocin	16	32
	6. Nembutal	11	11
	7. Radio pharmaceuticals	6	6
	8. Selsun	2	2
	9. Surbex-T	12	12
	10. Triosorb	3	3
		Total...	148
<u>Arch Laboratories</u>	1. Dicarbisol	12	Total... 12
<u>Armour Pharmaceuticals</u>	1. Chymoral	3	6
	2. Thyroid	15	61
		Total...	67
<u>Astra Pharmaceutical Products, Inc.</u>	1. Xylocaine	3	Total... 6
<u>Ayerst Laboratories</u>	1. Mesulfin	7	14
	2. Penbritin*	4	18
	3. Premarin	16	17
	4. Spartocin	3	9
	5. Thiosulfil Forte	3	6
		Total...	64
<u>Bristol Laboratories</u>	1. Polycillin	15	Total... 41

*Distributed by Ayerst for Beecham Laboratories, Inc.

COMPANY	PRODUCTS	NO. ISSUES	NO. PAGES
<u>Burroughs Wellcome and Co., Inc.</u>			
	1. Antepar	12	12
	2. Aerosporin	10	10
	3. Alkeran	7	7
	4. Cardilate	13	13
	5. Cardilate-P	9	9
	6. Cortisporin	3	3
	7. Empirin	5	5
	8. Lanoxin	13	22
	9. Leukeran	10	10
	10. Mantadil	5	5
	11. Marezine	20	20
	12. Myleran	10	10
	13. Migral	2	2
	14. Neosporin	4	4
	15. Perazil	3	3
	16. Purinethol	10	10
		Total...	145
<u>CIBA Pharmaceutical</u>			
	1. Esidrex/Esidrex-K	17	34
	2. Doriden	7	7
	3. Pyribenzamine	13	13
	4. Ritalin	19	26
	5. Serpasil	26	34
	6. Vioform	31	40
		Total	154
<u>Davies, Rose-Hoyt and Co.</u> (Division of Kendall)			
	1. Quinidine/Digitalis	2	2
	2. Quinidine sulfate	1	1
		Total...	3
<u>Dome Chemicals, Inc.</u>			
	1. Domol	1	1
	2. Cort-Dome	7	7
	3. Cor-Tar-Quin	2	2
	4. Domeboro	2	2
		Total...	12